10 November 2022
EMA/CHMP/931431/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/II/0012

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation	Definition
AC	Adjudication Committee
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	Applied Radioactivity
ASCO-CAP	American Society of Clinical Oncology-College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUClast	area under the serum concentration-time curve up to last quantifiable time
AUCss	area under the serum concentration-time curve at steady state
BC	breast cancer
BOR	best overall response
BSV	between subject variability
BSC	best supportive care
Cavg	average concentration
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLcr	creatinine clearance
CLDXd	clearance of DXd
CLT-DXd	clearance of intact T-DXd
Cmax	maximum serum concentration
Cmax,ss	maximum serum concentration at steady state
CMH	Cochran-Mantel-Haenszel
Cmin	minimum serum concentration
Cmin,ss	minimum serum concentration at steady state
CPS	combined positive score
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAR	drug-to-antibody ratio
DCO	data cut-off
DCR	disease control rate
Deruxtecan	drug-linker in T-DXd composed of cleavable tetrapeptide linker and released drug
DoR	duration of response
DXd	the released drug in T-DXd; topoisomerase I inhibitor derivative of exatecan
EC50	Concentration of the test substance dissolved in test medium that results in a 50% reduction in the measured endpoint
ECHA	European Chemicals Agency
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-dimension 5-level (of severity) assessment
E-R	exposure-response
ERA	Environmental Risk Assessment
EU	European Union

FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FL-DP1	frozen liquid drug product 1
Foc	Fraction of Organic Carbon
Fpen	Market penetration factor
GC	gastric cancer
GEJ	gastroesophageal junction
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ICI	immune checkpoint inhibitor
ICR	independent central review
IHC	immunohistochemistry
ILD	interstitial lung disease
IQR	interquartile range
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	Intent-to-Treat
IV	intravenous
Kd	Adsorption distribution coefficient
KM	Kaplan-Meier
Koc	Organic carbon normalized adsorption coefficient
LOEC	Lowest Observed Effect Concentration
LV	left ventricular
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder drug product
MAA	Marketing Authorisation Application
mAb (of T-DXd)	monoclonal antibody (anti-HER2 component of T-DXd)
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MSI	microsatellite instability
Nab	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NE	not estimable
NOEC	No Observed Effect Concentration
NSCLC	non-small cell lung cancer
OECD	Organisation for Economic Co-operation and Development
ORR	objective response rate
OS	overall survival
PBT	Persistent, Bioaccumulative and Toxic
PD-1	programmed cell death receptor 1
PD-L1	programmed cell death ligand 1
PEC	Predicted Environmental Concentration
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Japan Pharmaceutical and Medical Devices Agency
PNEC	Predicted No Effect Concentration
PopPK	population pharmacokinetics
pp	percentage points
PRO	patient reported outcome
PT	preferred term
PTX	paclitaxel
Q3W	every 3 weeks
QoL	quality of life
QTc	QT interval corrected for heart rate

QTcF	QT interval corrected for heart rate using Fridericia's formula
Ram	ramucirumab
RDI	relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RES	Response Evaluable Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SoC	standard of care
SOC	system organ class
SoD	sum of diameters
t1/2	terminal elimination half-lifeT-DM1 trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum serum concentration
ToGA	traztuzumab for gastic cancer
TPC	treatment of physician's choice (irinotecan or paclitaxel)
TTR	time to response
US	United States
V1, T-DXd	intact T-DXd central volume of distribution
V2,T-DXd	intact T-DXd peripheral volume of distribution
VDXd	DXd volume of distribution
vs.	versus

Not all abbreviations have been used

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 12 October 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include monotherapy treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen for Enhertu based on final results from studies DS8201-A-U205 (DESTINY Gastric02) and DS8201-A-J202 (DESTINY Gastric01); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, changes regarding the dosing recommendation for corticosteroid treatment and the protection of the infusion bag from light have been introduced. Version 1.1 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	12 October 2021
Start of procedure:	30 October 2021
CHMP Rapporteur Assessment Report	17 December 2021
PRAC Rapporteur Assessment Report	3 January 2022
CHMP Co-Rapporteur Critique	5 January 2022
PRAC members comments	5 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	7 June 2022
PRAC Rapporteur Assessment Report	30 May 2022
PRAC members comments	1 June 2022
Updated PRAC Rapporteur Assessment Report	7 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur Assessment Report	17 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	17 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	4 November 2022
SAG experts meeting to address questions raised by the CHMP	3 November 2022
Opinion	10 November 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease

In most cases stomach (gastric) cancer (GC) starts in the lining of the stomach, growing slowly over the course of several years and causing few if any symptoms. Most patients (up to 95 percent) develop adenocarcinoma and are typically classified based on anatomic location (cardia/proximal, arising in the region adjoining the GEJ, or non-cardia/distal, arising in the lower portion of the stomach) and histologic type (diffuse, with undifferentiated tumour cells, or intestinal, with well-differentiated tumour cells).

[1]Overexpression or amplification of the HER2 gene or protein is reported in approximately 20% of patients with gastric adenocarcinoma, with higher rates of HER2 positivity seen in patients with intestinal histology than those with diffuse histology.

State the claimed therapeutic indication

The wording of the proposed indication is:

ENHERTU as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

The proposed dose of ENHERTU is 6.4 mg/kg every 3 weeks (Q3W) administered as an intravenous (IV) infusion over 90 minutes. [2, 3] Patients who tolerate the first 90-minute infusion can receive subsequent infusions over 30 minutes. Treatment may be continued until symptomatic disease progression or unacceptable toxicity.

Epidemiology, risk factors, screening tools/prevention

GC is the fourth most commonly diagnosed cancer [4,5](5.6% of all newly diagnosed cancers) and the third most common cause of cancer-related deaths worldwide. In Western, Southern and Northern Europe in 2020, there were an estimated 70,522 new cases of GC and 46,979 patients died of GC. The rates of GC are 2-fold higher in men than in women. The incidence of GC varies significantly among geographic regions, with the highest rates reported in Eastern Asia (including Japan and South Korea where it is amongst the most commonly diagnosed cancers in men), Central and Eastern Europe, and South America, while rates in Western Europe, Northern Europe, and North America are lower. Most patients present with inoperable advanced or metastatic disease requiring palliative treatment, although early detection is more common in Asia than in other regions. 5-year survival for advanced or metastatic gastric cancer is around 5–20%, with median overall survival being less than 1 year.

The major risk factors for developing gastric cancer include male gender, H. pylori infection, increasing age, smoking, and alcohol consumption. Other risk factors include salt in diet, positive family history, and pernicious anaemia. The risk of gastric cancer is nearly six times higher for H. Pylori-infected than for uninfected individuals; however, whilst around 60% of the world's population are infected with H. Pylori, less than 0.5% will develop gastric adenocarcinoma.[6]

It is recognized that GC is difficult to treat at an advanced stage when it is no longer curable and survival outcomes are poor. Compared with the Asian countries that have national screening programs which starts at approximately 40 years of age allowing early detection of the disease, patients in Western countries with a low incidence are more often diagnosed at the advanced stage and have a worse prognosis.

[1] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric cancer. Version 4.2021. 03 Aug 2021.
[2] ENHERTU (fam-trastuzumab deruxtecan-nxki). Full Prescribing Information, Revised:12/2019 (United States). [Cited 24 Aug 2021]. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf.
[3] ENHERTU (fam-trastuzumab deruxtecan-nxki). Full Prescribing Information, Revised: 01/2021 (United States). [Cited 24 Aug 2021]. Available at: https://daiichisankyo.us/prescribing-informationportlet/getPIContent?productName=Enhertu&inline=true
[4] World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2020. Stomach Cancer. [Cited 24 Aug 2021]. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf.
[5] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71(3):209-49.
[6] Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterology Rev. 2019; 14(1):26-38.

Aetiology and pathogenesis

There are three types of adenocarcinoma[7]:

Non-cardia (Distal) Stomach Cancer: This type of stomach cancer may be related to long periods of inflammation and irritation in the lower part of the stomach. It is often associated with chronic infection of bacteria called Helicobacter pylori and is more common in developing countries than in other parts of the world.

Proximal Stomach Cancer: This type of stomach cancer starts in the first (proximal) part of the stomach and may extend into the gastroesophageal junction (where the oesophagus joins the stomach). This cancer is more common in the western part than in other parts of the world, and tends to start in people who are obese or have gastro-oesophageal reflux disease.

Diffuse Stomach Cancer: This aggressive cancer grows rapidly in the cells of the stomach wall. It does not form a mass or a tumour, so it can be challenging to diagnose. It tends to start in younger people with a family history of the disease where a mutation in the adhesion molecule E Cadherin can be the cause (also associated with breast cancer) or a related genetic syndrome.

Clinical presentation, diagnosis and stage/prognosis

The symptoms of gastric cancer are frequently vague and non-specific, with patients often unfortunately presenting at an advanced stage. The common presenting symptoms include dyspepsia (particularly if new onset or not responsive to simple PPI treatment), dysphagia, early satiety, vomiting, or melena. Non-specific cancer symptoms (anorexia, weight loss, or anaemia) are markers of late stage disease. On examination, clinical signs are usually absent, especially in the early stages, however an epigastric mass may be felt in late stage disease. Troisier sign is the presence of a palpable left supraclavicular node (Virchow node) and is considered a sign of metastatic abdominal malignancy (typically gastric). Other signs of metastatic disease include hepatomegaly, ascites, jaundice, or acanthosis nigricans.

The primary investigation of any suspected gastric cancer is an urgent upper GI endoscopy (OGD), allowing for the direct visualisation of any malignancy present and subsequent biopsies taken as needed.

Biopsies [8]from suspected gastric malignancies should be sent for:

- Histology – for classification and grading of any neoplasia present.
- CLO test – for the presence of H. Pylori.
- HER2/neu protein expression – this will allow for targeted therapies if present.

For staging and in order to plan treatment, all patients need a CT Chest-Abdomen-Pelvis and a staging laparoscopy (to look for peritoneal metastases), the most commonly used staging system for gastric cancers is TNM staging.

[7] Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterology Rev. 2019; 14(1):26-38.
[8] Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: Guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017; 35(4):446-64.

5-year relative survival rates for GC

These numbers are based on people diagnosed with cancers of the stomach between 2010 and 2016.[9]

SEER stage	5-year relative survival rate
Localized	70%
Regional	32%
Distant	6%
All SEER stages combined	32%

Management

The current standard of care (SoC) for metastatic GC in the first-line setting based on guidelines in the EU, US, and Japan is a combination of chemotherapy with a fluoropyrimidine agent (fluorouracil, capecitabine, or S-1 [EU and Japan]) and a platinum agent (oxaliplatin or cisplatin). The oral fluoropyrimidine regimen S-1 (tegafur [a prodrug of 5-fluorouracil]/gimeracil/oteracil) is approved in the EU and Japan in this indication, but not in the US.

Based on the ToGA study[10], for patients with HER2-positive disease, the SoC in the EU, US and Japan is the fluoropyrimidine + platinum combination with the addition of the anti-HER2 monoclonal antibody (mAb) trastuzumab.

Second line treatment: Based on the REGARD and RAINBOW trials, the SoC in the EU is ramucirumab (a mAb targeting vascular endothelial growth factor receptor 2) in combination with paclitaxel. These trials included patients regardless of HER2 expression. Other treatment options in the second-line or subsequent therapy setting include single-agents docetaxel, paclitaxel, irinotecan and FOLFIRI (folinic acid, fluorouracil, and irinotecan). Regimens recommended in third-line or beyond are irinotecan, taxanes, pembrolizumab if PD-L1 expression by CPS ≥1, and the trifluridine/tipiracil regimen.

Locally advanced or metastatic HER2-positive gastric adenocarcinoma remains an incurable disease. Once patients have progressed after a first-line regimen that includes an anti-HER2 therapy, the disease outcomes are poor. Currently, there is no approved targeted anti-HER2 therapy in the EU for the treatment of metastatic HER2-positive gastric adenocarcinoma in the second-line setting and beyond, which constitutes an unmet medical need.

[9] John S, Broggio J. Office for National Statistics. Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018. [Cited 24 Aug 2021]. Available at:ttps://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018

[10] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a Phase 3, open-label, randomised controlled trial. Lancet. 2010; 376(9742):687-97.

2.1.2. About the product

The active substance in ENHERTU, trastuzumab deruxtecan, is made up of two active components which are linked together:

- Trastuzumab, a monoclonal antibody that has been designed to attach to HER2, which is found in large quantities on some cancer cells. By attaching to HER2, trastuzumab activates cells of the immune system, which then kill the cancer cells. Trastuzumab also stops HER2 from stimulating the growth of cancer cells.

- Deruxtecan, a toxic substance that kills cells when they attempt to divide and grow. It becomes active once the trastuzumab component has attached to HER2 and enters the cancer cell. Deruxtecan blocks an enzyme called topoisomerase I, which is involved in copying cell DNA and is needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and they eventually die.

Trastuzumab deruxtecan is currently approved as monotherapy for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received one or more prior anti-HER2 based regimens. The recommended dose for HER2-positive BC is 5.4 mg/kg once every 3 weeks (Q3W).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice from the CHMP was not sought concerning the clinical development of Enhertu in the GC/GEJC setting.

A pre-submission meeting with the Rapporteurs was held on 30 August 2021.

2.1.4. General comments on compliance with GCP

The MAH claims that the studies are conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

2.2. Non-clinical aspects

New non-clinical data have been submitted in this application, which is considered acceptable.

Results from 11 nonclinical studies with human biomaterials were previously submitted and are not described further. An additional nonclinical study (Study TCRM-DMPK-2020-19) was conducted after the initial BC application. This additional study using cryopreserved hepatocytes supported that the released drug (DXd), at concentrations of up to 30 nmol/L, did not show any induction potential or effect on the metabolic activity of cytochrome P450 (CYP)3A4, CYP1A2, or CYP2B6.

However, a new environmental risk assessment report was submitted to reflect the new intended indication.

2.2.1. Introduction

Trastuzumab deruxtecan (herein referred to as T-DXd) has been approved in the EU for use as a monotherapy indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received 2- or more prior anti-HER2-based regimens (EMEA/H/C/005124). Daiichi Sankyo Europe is submitting this type II

variation to register T-DXd, as a monotherapy indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen. An Environmental Risk Assessment (ERA) has been undertaken for T-DXd in accordance with the EMA Guidance (CHMP 2006: EMEA/CPMP/SWP/4447/00 and CHMP 2016: EMA/CHMP/SWP/44609/2010).

2.2.2. Ecotoxicity/environmental risk assessment

Tabulated summary:

Substance (INN/Invented Name): DXd (as MAAA-1181d; released drug of T-DXd)			
CAS-number (if available): N/A			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107** (1075.00204)	pH 5 = 1.92 pH 7 = 1.80 pH 9 = 1.28	< 4.5: **not B** < 4.5: **not PBT**
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	If Fpen=0.01 0.0565 (default)	µg/L	Refined PEC < 0.01 µg/L **No Phase II assessment required**
Breast cancer refined $PEC_{surfacewater}$	If Fpen=0.000288 1.40×10^{-3} (refined)	µg/L	
Gastric cancer refined $PEC_{surfacewater}$	If Fpen=0.000190 1.07×10^{-3} (refined)	µg/L	
Combined (total) $PEC_{surfacewater}$	0.00247	µg/L	
Other concerns (e.g. chemical class)			None
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water Solubility	**OECD 105** (1075.00203)	7.52 mg/L	
Dissociation Constant (pKa)	**OECD 112** (1075.00201)	N/A	*Study not possible due to low water solubility and other physical chemical properties*

Summary

T-DXd is an Antibody Drug Conjugate (ADC) composed of an anti-HER2 mAb covalently conjugated to a drug-linker, deruxtecan. The drug-linker is composed of a cleavable maleimide tetrapeptide and the released drug, DXd. DXd is a potent topoisomerase I inhibitor. The three components of T-DXd, mAb, tetrapeptide linker, and drug (DXd), will be examined individually within this assessment. The three components are designed to dissociate from one another once bound to the HER2 positive target cell in patients and therefore they will be excreted separately and can be treated as separate molecules within the environmental risk assessment.

Both the mAb and the tetrapeptide linker are considered to be naturally occurring molecules (i.e., they are polypeptides or proteins), which are not expected to remain either stable or biologically active in the environment for any significant period of time because of their high susceptibility to rapid chemical (e.g., oxidation, deamidation, proteolysis, beta elimination and disulfide scrambling) and physical (e.g., denaturation (protein unfolding), aggregation, precipitation, and surface adsorption) degradation, as well as biodegradation by a wide range of microflora, and various physical removal mechanisms.

Degradation may be easily triggered from exposure to uncontrolled ambient environmental conditions (e.g., due to desiccation, suboptimal pH or temperature, and light exposure).

The mAb and the tetrapeptide linker molecules are considered to be non-hazardous, biodegradable products. As such, the environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline (CHMP 2006: EMEA/CHMP/SWP/4447/00), ERA studies are not required.

The active pharmaceutical ingredient DXd is a topoisomerase I inhibitor and is released from the mAb and linker portion of T-DXd upon binding to the target cell. Therefore, the environmental risk assessment considers this molecule in isolation.

The calculated refined $PEC_{surfacewater}$ is below the Phase I action limit (0.01 µg/L); therefore, the risk assessment for T-DXd ceases at Phase I. No Phase II environmental risk assessment is required, see below for details.

Screening for Persistence, Bioaccumulation and Toxicity

The monohydrate form of DXd (named MAAA-1181d) was used for all experimental testing but is referred to as DXd throughout this assessment. This is not considered to impact the risk assessment to any significant extent. No molar conversion of the monohydrate form is considered necessary within this risk assessment.

The octanol-water distribution coefficient, Log Dow, of DXd was determined across an environmentally relevant pH-range. The log Dow values were in the range 1.28 to 1.92, and since they are <4.5, no further screening for persistence, bioaccumulation and toxicity is necessary.

Calculation of Predicted Environmental Concentration (PEC)

Approved indications

T-DXd is approved as a monotherapy indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received 2 or more prior anti-HER2-based regimens.

Extensions and New indications

Daiichi Sankyo Europe is submitting this type II variation (extension of indication) to register T-DXd, as a monotherapy indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen. The maximum recommended dose of T-DXd is 6.4 mg/kg, given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Default PEC Calculation

On average, the target number of drug-linker (deruxtecan) to 1 antibody molecule is 8. The molecular weight of deruxtecan is 1034.05 and the molecular weight of the mAb is approximately 150,000 Da. Therefore, the total molecular weight of T-DXd is approximately 158,000 Da. On average 8 molecules of the active drug (DXd at 493.484 Da) are present on each molecule (8 × 493.484 = 3947.872 Da), thus DXd represents approximately 2.5% of the total dose of T-DXd (3947.872 ÷ 158 000 = 2.5%).

The maximum recommended dose of T-DXd taken in one day is 6.4 mg/kg; which is given once every 3 weeks for gastric cancer indications. Breast cancer indications require a lower dose and therefore are sufficiently covered assuming a worst-case daily dose of 6.4 mg/kg. Average body weight in Europe has been estimated to be approximately 70.8 kg (Walpole et al 2012).

The maximum daily dose is calculated based on the maximum recommended dose which can be taken in one day (6.4 mg/kg) and the average weight of a European adult (6.4 mg/kg × 70.8 kg). A reduction

is then applied to this maximum daily dose based on the percentage of total dose representing the active drug (2.5%); equivalent to 11.3 mg per day.

In line with the conservative nature of the assessment, no consideration is given to the posology of the dose only being given once every 3 weeks. The calculation conservatively assumes the maximum daily dose is taken every day by all patients; this equates to an approximate 21-fold over estimate in the PEC. For example, the average daily dose taken by a patient receiving one dose per week would be equivalent to: 11.3 mg (maximum daily dose) ÷ 21 days (3 weeks) = 0.53 mg / day

$$PEC_{Surfacewater} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

where;

DOSEai = maximum daily dose consumed per inhabitant = 11.3 mg × inh^{-1} × d^{-1}

Fpen = market penetration factor (default) 0.01

WASTEWinhab = amount of wastewater per inhabitant per day = 200 L × inh^{-1} × d^{-1}

DILUTION = dilution factor = 10

$$PEC_{surfacewater} = \frac{11.3 \times 0.01}{200 \times 10}$$

$$PEC_{surfacewater} = 5.65 \times 10^{-5}\ mg/L$$

$$PEC_{surfacewater} = 0.0565\ \mu g/L$$

The default $PEC_{surfacewater}$ is above the PEC action limit for triggering a full ERA. As mentioned previously the PEC based on maximum daily dose is approximately 21-fold higher than if based on the actual dose regime recommended (once every 3 weeks). A PEC accounting for the actual dosing regimen would clearly be below the trigger (≤0.01 μg/L); however, the PEC has subsequently been refined utilising prevalence data on the stated indication(s).

Refined PEC Calculation

The disease prevalence has been used to estimate the refined $PEC_{surfacewater}$ for each individual indication. The total $PEC_{surfacewater}$ is then calculated as the sum of all the $PEC_{surfacewaters}$ for each indication.

Breast Cancer

The Globocan database estimates Belgium to be the European Member State with the highest prevalence of breast cancer; 1-year prevalence is 191.8 per 100 000 females (Globocan 2018; Appendix 2). The prevalence data is available on a 'per female' only; the prevalence rate therefore was adjusted to that of the total population assuming a 1:1 male: female ratio. As such, the single year prevalence for breast cancer in Belgium is estimated to be 191.8 per 200 000 to account for the equivalent numbers of males in the total population; equivalent to 95.9 per 100 000 total population. In addition, HER2-positive breast cancers have been demonstrated to account for approximately 20% and not more than 30% of all breast cancer sub-types (Wolff et al., 2013; Slamon et al., 1987; Hudis 2007).

The worst-case Fpen used for dose calculation is therefore proposed to be refined to (30% × 0.000959) 0.000288. The maximum daily dose is calculated based on the maximum recommended dose which can be taken in one day (5.4 mg/kg) and the average weight of a European adult (5.4 mg/kg × 70.8 kg). A reduction is then applied to this maximum daily dose based on the percentage of total dose representing the active drug (2.5%); equivalent to 9.56 mg per day.

In line with the conservative nature of the assessment, no consideration is given to the posology of the dose only being given once every 3 weeks. The calculation conservatively assumes the maximum daily dose is taken every day by all patients; this equates to an approximate 21-fold over estimate in the PEC. For example, the average daily dose taken by a patient receiving one dose per week would be equivalent to: 9.56 mg (maximum daily dose) ÷ 21 days (3 weeks) = 0.45 mg / day

$$PEC_{Surfacewater} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

where;

DOSEai = maximum daily dose consumed per inhabitant = 9.56 mg × inh^{-1} × d^{-1}

Fpen = 0.000288 (highest EU prevalence of HER2-positive breast cancer)

WASTEWinhab = amount of wastewater per inhabitant per day = 200 L × inh^{-1} × d^{-1}

DILUTION = dilution factor = 10

$$PEC_{surfacewater} = \frac{9.56 \times 0.000288}{200 \times 10}$$

$$PEC_{surfacewater} = 1.4 \times 10^{-6}\ mg/L$$

$$PEC_{surfacewater} = 1.4 \times 10^{-3}\ \mu g/L$$

Gastric Cancer

The Globocan database estimates Lithuania to be the European Member State with the highest prevalence of gastric cancer; 1-year prevalence is 19.0 per 100 000 (Globocan 2018; Appendix 3). The worst-case Fpen used for dose calculation is therefore proposed to be 0.000190.

The maximum daily dose is calculated based on the maximum recommended dose which can be taken in one day (6.4 mg/kg) and the average weight of a European adult (6.4 mg/kg × 70.8 kg). A reduction is then applied to this maximum daily dose based on the percentage of total dose representing the active drug (2.5%); equivalent to 11.3 mg per day.

In line with the conservative nature of the assessment, no consideration is given to the posology of the dose only being given once every 3 weeks. The calculation conservatively assumes the maximum daily dose is taken every day by all patients; this equates to an approximate 21-fold over estimate in the PEC. For example, the average daily dose taken by a patient receiving one dose per week would be equivalent to: 11.3 mg (maximum daily dose) ÷ 21 days (3 weeks) = 0.53 mg / day

$$PEC_{Surfacewater} = \frac{DOSEai \times Fpen}{WASTEWinhab \times DILUTION}$$

where;

DOSEai = maximum daily dose consumed per inhabitant = 11.3 mg × inh^{-1} × d^{-1}

Fpen = 0.000190 (highest EU prevalence of gastric cancer)

WASTEWinhab = amount of wastewater per inhabitant per day = 200 L × inh^{-1} × d^{-1}

DILUTION = dilution factor = 10

$$PEC_{surfacewater} = \frac{11.3 \times 0.000190}{200 \times 10}$$

$$PEC_{surfacewater} = 1.07 \times 10^{-6}\ mg/L$$

or

$$PEC_{surfacewater} = 1.07 \times 10^{-3}\ \mu g/L$$

Combined PECsurfacewater

The total or combined PECsurfacewater is calculated as the sum of all the refined PECsurfacewater values for each indication as detailed below.

Breast cancer $PEC_{surfacewater} = 1.4 \times 10^{-3}$ µg/L

+

Gastric cancer $PEC_{surfacewater} = 1.07 \times 10^{-3}$ µg/L

=

$PEC_{surfacewater} = 2.47 \times 10^{-3}$ µg/L (0.00247 µg/L)

The refined PECsurfacewater is below the PEC action limit of 0.01 µg/L for triggering a full Phase II ERA. No Phase II ERA is therefore required or presented.

2.2.1. Discussion on non-clinical aspects

The active pharmaceutical ingredient DXd is a topoisomerase I inhibitor and is released from the mAb and linker portion of T-DXd upon binding to the target cell. Therefore, the environmental risk assessment considers this molecule in isolation. This is accepted, since the rest of the molecule can be considered of protein nature, which is susceptible to rapid degradation in the environment.

The disease prevalence was used to estimate the refined $PEC_{surfacewater}$ for each individual indication. The total $PEC_{surfacewater}$ is then calculated as the sum of all the $PEC_{surfacewater}$ for each indication.

Hence, without considering the posology of administration once every 3 weeks, the sum of the two $PEC_{surfacewaters}$ is

$PEC_{surfacewater} = 2.47 \times 10^{-3}$ µg/L (0.00247 µg/L)

Which is below the action limit of 0.01 µg/L and no further environmental risk assessment should be required.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, Trastuzumab deruxtecan is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1.2: Clinical Studies Included in the Application

Study Number, Phase, and Status	DCO	Study Title Total Number of Subjects (Location in Module 5)	Test Products and Dosage Regimen
DS8201-A-J202 (Study J202) Phase 2 Completed[a]	*Primary efficacy analysis*: 08 Nov 2019 *Update DCO:* 03 Jun 2020	A Phase 2, multicenter, open-label study of DS-8201a in subjects with HER2-positive advanced gastric or GEJ adenocarcinoma (DESTINY-Gastric01) N = 233 subjects (see Module 5.3.5.1 DS8201-A-J202 CSR) (see Module 5.3.5.1 DS8201-A-J202 Abbreviated CSR)	T-DXd, IV infusion Q3W, 6.4 mg/kg *Primary Cohort* (HER2-positive [IHC 3+ or IHC 2+ /ISH-positive] and pretreated): 188 subjects randomized 2:1 to T-DXd (n = 126) or TPC (n = 62; 55 irinotecan, 7 PTX) *Exploratory Cohorts* (treatment-naïve for anti-HER2 therapy; nonrandomized): • Exploratory Cohort 1 (HER2 IHC 2+ /ISH-negative): 21 subjects • Exploratory Cohort 2 (HER2 IHC 1+) 24 subjects

Study Number, Phase, and Status	DCO	Study Title Total Number of Subjects (Location in Module 5)	Test Products and Dosage Regimen
DS8201-A-U205 (Study U205) Phase 2 Completed[a]	*Primary efficacy analysis*: 09 Apr 2021	A Phase 2, open-label, single-arm study of T-DXd (DS-8201a) in HER2-positive, unresectable or metastatic gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen (DESTINY-Gastric02) N = 79 subjects (see Module 5.3.5.2 DS8201-A-U205 CSR)	T-DXd, IV infusion Q3W, 6.4 mg/kg 79 subjects treated

DS8201-A-J101 (Study J101) Phase 1 Completed[a]	*Primary efficacy analysis*: 01 Feb 2019 *Update DCO*: 01 Aug 2019 (outputs only no report)	Phase 1, 2-part, multicenter, nonrandomized, open-label, multiple dose first-in-human study of DS-8201a in subjects with advanced solid malignant tumors N = 292 subjects, including 44 subjects with metastatic HER2-positive gastric or GEJ adenocarcinoma in Part 1 and Part 2b of the study: 19 assigned to 5.4 mg/kg and 25 assigned to 6.4 mg/kg (see Module 5.3.3.2 DS8201-A-J101 CSR)	T-DXd, IV infusion Q3W *Part 1, Dose Escalation*: (27 subjects treated) 0.8 mg/kg, 1.6 mg/kg, 3.2 mg/kg, 5.4 mg/kg, 6.4 mg/kg, 8.0 mg/kg **Included 3 subjects with HER2-positive gastric or GEJ cancer treated either at 5.4 mg/kg (n = 2) or 6.4 mg/kg (n = 1)** *Part 2, Dose Expansion:* (262 subjects treated) • Part 2a (HER2-positive breast cancer): 103 subjects • **Part 2b (HER2-positive gastric or GEJ cancer): 41 subjects, of which 17 were treated at 5.4 mg/kg and 24 at 6.4 mg/kg** • Part 2c (HER2-low breast cancer): 40 subjects • Part 2d: HER2-positive solid tumors other than breast and gastric: 60 subjects • Part 2e: HER2-positive breast cancer: 21 subjects

2.3.2. Pharmacokinetics

Introduction

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody and topoisomerase I inhibitor conjugate (ADC molecule) approved for the treatment of unresectable or metastatic HER2-positive breast cancer (T-DXd dose 5.4 mg/kg) who have received two or more prior anti-HER2-based regimens.

The present application concerns approval of T-DXd as 2L monotherapy (T-DXd dose 6.4 mg/kg) for treatment of patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior anti-HER2-based regimen.

A summary of the studies and analyses conducted as part of the clinical pharmacology program is provided in this section. The clinical pharmacology package for the initial BC application included five studies (Studies J101, J102, A103, A104, and U201). The package included in the current application includes data from two additional Phase 2 studies in subjects with HER2-positive advanced GC or gastroesophageal junction (GEJ) adenocarcinoma (Studies J202 and U205). A list and brief descriptions of the seven studies that were conducted to evaluate the clinical pharmacological properties of T-DXd are shown in **Table 1.1**. In each study, serum concentrations of three analytes (intact antibody-drug conjugate T-DXd, total anti-HER2 antibody, and the topoisomerase I inhibitor DXd) were measured to characterize the PK of T-DXd. A randomised, 2-arm, open-label Phase 3 Study U306 is currently enrolling subjects with HER2-positive GC who have received a prior trastuzumab containing regimen (2L setting). This study started enrolment in 2021, therefore there are no data to present from this study.

Table 1.1: List of Clinical Pharmacology Studies

Document No. Location Data Cut-Off Date	Short Study Title	Study Title	Subjects	Region	Dose Regimen
J101 Module 5.3.3.2 01 Feb 2019	J101	Phase 1, two-part, multicenter, non-randomized, open-label, multiple-dose first-in-human study of T-DXd, in subjects with advanced solid malignant tumors	Part 1: Subjects with advanced BC and gastric or GEJ adenocarcinoma Part 2a: Subjects with HER2-positive BC previously treated with T-DM1 Part 2b: Subjects with HER2-positive gastric or GEJ adenocarcinoma previously treated with trastuzumab Part 2c: Subjects with BC with low HER2 expression Part 2d: Subjects with HER2-expressing solid cancers, except BC and gastric or GEJ adenocarcinoma or subjects with HER2 mutation Part 2e: Subjects with HER2-expressing BC	North America, Asia	T-DXd, IV infusion Q3W Part 1, Dose Escalation: 0.8 mg/kg, 1.6 mg/kg, 3.2 mg/kg, 5.4 mg/kg, 6.4 mg/kg, 8.0 mg/kg Part 2, Dose Expansion: • Part 2a: HER2-overexpressing BC (5.4 mg/kg and 6.4 mg/kg) • Part 2b: HER2-overexpressing gastric or GEJ cancer (5.4 mg/kg and 6.4 mg/kg) • Part 2c: HER2-low BC (5.4 mg/kg and 6.4 mg/kg) • Part 2d: HER2-expressing solid tumors other than breast and gastric (6.4 mg/kg only)

					• Part 2e: HER2-expressing BC (6.4 mg/kg only)
J102 Module 5.3.4.2 05 Dec 2018	J102	Phase 1, multicenter, open-label, multiple-dose study of T-DXd to assess the effect on the QT interval and pharmacokinetics in subjects with HER2-expressing, metastatic and/or unresectable BC	Subjects with metastatic or unresectable HER2-expressing BC	Asia	T-DXd, 6.4 mg/kg IV infusion Q3W
A103 Module 5.3.3.2 14 Sep 2018	A103	Phase 1, multicenter, open-label study of T-DXd to assess safety and pharmacokinetics in subjects with HER2-positive advanced and/or refractory gastric, GEJ adenocarcinoma, or BC	Taiwanese subjects with HER2-positive advanced and/or refractory gastric adenocarcinoma, GEJ adenocarcinoma, or BC	Asia	T-DXd, 6.4 mg/kg IV infusion Q3W
A104 Module 5.3.3.4 26 Sep 2018	A104	Phase 1, multicenter, open-label, single sequence crossover study to evaluate drug-drug interaction potential of OATP1B/CYP3A inhibitor on the pharmacokinetics of T-DXd in subjects with HER2-expressing advanced solid malignant tumors	Subjects with unresectable or metastatic HER2-expressing advanced solid cancers	Asia	T-DXd, 5.4 mg/kg IV infusion Q3W Cohort 1: Ritonavir + T-DXd Cohort 2: Itraconazole + T-DXd

U201 (DESTINY-Breast01) Module 5.3.5.2 21 Mar 2019	U201	Phase 2, multicenter, open-label study of T-DXd, an anti-HER2 ADC for HER2-positive, unresectable and/or metastatic BC subjects previously treated with T-DM1	Subjects with unresectable or metastatic HER2-positive BC previously treated with T-DM1	North America, Asia, Europe	T-DXd, IV infusion Q3W Part 1, PK stage: Randomized 1:1:1 5.4 mg/kg 6.4 mg/kg 7.4 mg/kg Part 1, Dose-finding stage: Randomized 1:1 5.4 mg/kg 6.4 mg/kg Part 2a and b: All subjects received T-DXd at RP2D determined to be 5.4 mg/kg
J202 (DESTINY-Gastric01) Module 5.3.5.1 03 Jun 2020	J202	Phase 2, multicenter, open-label study of T-DXd in subjects with HER2-expressing advanced gastric or GEJ adenocarcinoma	Subjects with locally advanced or metastatic HER2-expressing gastric or GEJ adenocarcinoma Primary Cohort: • HER2-overexpressing • Progression on a trastuzumab • Randomized 2:1 ➢ T-DXd group ➢ Physician's choice group Exploratory Cohort 1: • HER2 IHC 2+/ISH-negative • Treatment naïve with T-DXd Exploratory Cohort 2: • HER2 IHC 1+ • Treatment naïve with T-DXd	Asia	T-DXd, 6.4 mg/kg IV infusion Q3W

U205 (DESTINY-Gastric02) Module 5.3.5.2 09 Apr 2021	U205	Phase 2, open-label, single-arm study of T-DXd in HER2-positive, unresectable or metastatic gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen	Subjects with unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen	North America , Europe	T-DXd, 6.4 mg/kg IV infusion Q3W

ADC = antibody-drug conjugate; BC = breast cancer; GC = gastric cancer; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2.; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; OATP1B/CYP3A = organic anion transporting polypeptide/cytochrome P450 3A; Q3W = every 3 weeks; RP2D = recommended Phase 2 dose; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Methods

In addition to the studies listed above, population pharmacokinetic (PopPK) and exposure-response (E-R) analyses were used to further characterize the clinical pharmacology profile of T-DXd. The PopPK analysis developed for the initial BC application with data from five studies was updated with data from Study J202, and was further updated with inclusion of data from Study U205 (**Table 1.1 – List of Clinical Pharmacology Studies**).

Results from the updated analysis including Study U205 are presented in this document.

Bioanalysis

The same bioanalytical methods used to quantify the three moieties from T-DXd and to detect and confirm anti-T-DXd, or ADA in human serum, in the initial breast cancer application, were also used for bioanalysis conducted in studies J202 and U205. ADA positive samples were further analysed using a new validated cell-based assay for detection of NAb against T-DXd.

The NAb method performance is summarised below:

Table 1.3: Method Summary for the Detection of Neutralizing Antibodies Against T-DXd in Human Serum ([redacted] Project RIRM2 – Method VSDCBA 82)

Analyte	Neutralizing antibodies against trastuzumab deruxtecan		
Precision [a]		HPC	LPC
	Concentration	4.00 µg/mL	2.00 µg/mL
	Inter-assay (%CV)	37.0	6.59
	Intra-assay (%CV)	0.842	7.34
Screening assay cut point(s)	≥ 1.15 (NHS); ≥ 1.10 (BCS) (upper bound 99% limit of prediction interval)		
Specificity/Matrix Interference	Unspiked: Ten out of ten individuals were negative (NHS and BCS) LPC: Ten out of ten individuals were reactive (NHS and BCS)		
Sensitivity	1.41 µg/mL		
Cell Passage Limit	Passages 4 to 27		
Drug Tolerance [b]	LPC: up to 50.0 µg/mL excess trastuzumab deruxtecan HPC: up to 100 µg/mL excess trastuzumab deruxtecan		
Lipemia Interference	Five out of six unspiked, and six out of six samples spiked at the LPC and HPC levels met acceptance criteria.		
Hemolysis Interference	1%, 5% and 10% hemolysis levels tested. For each level, six out of six unspiked, spiked at LPC, and spiked at HPC met acceptance.		
Stability Freeze/Thaw	Eight cycles thawed at room temperature		
Thawed Matrix Stability	12 hours at room temperature and 24 hours at 2 to 8 °C		
Clinical Studies [c,d]	DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201, DS8201-A-J202, and DS8201-A-U205.		

%CV = percent coefficient of variation; BCS – breast cancer human serum; HPC – high positive control for screening assay; LPC – low positive control for screening assay; NHS – normal human serum

[a] Statistics for intra-assay precision was determined by PC samples in one validation run. Statistics for inter-assay precision was determined by PC samples from 24 validation runs.

[b] Drug tolerance demonstrated in validation is higher than mean Ctrough concentrations, which are 5.5, 9.2, 8.8, and 11.8 µg/mL for 5.4, 6.4, 7.4 and 8.0 mg/kg dose levels, respectively. Data source - Table 3.1 of initial breast cancer application CTD 2.7.2.

[c] For clinical studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, and DS8201-A-U201, breast cancer specific cut point was applied for sample analysis. For clincial studies DS8201-A-J202, DS8201-A-204, and DS8201-A-205, normal human serum cut point was applied for sample analysis.

[d] NAb sample analysis reports for DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201 studies (which were not included in the original CSRs) can be found in the Combined NAb Assay Sample Analysis Report for DS-8201a Studies. For all other studies (DS8201-A-J202 and DS8201-A-U205) NAb sample analysis reports can be found in respective CSRs.

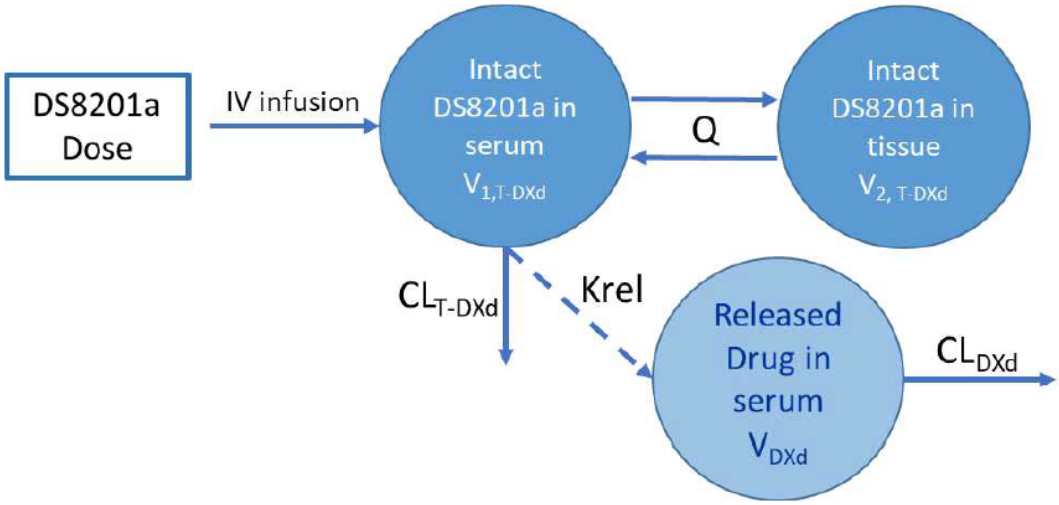
Source: Method Validation Report RIRM2 and RIRM2 Amendment 1, Combined NAb Assay Sample Analysis Report for DS-8201a Studies.

Population PK analysis

NONMEM (version 7.4.3) for nonlinear mixed-effects analysis (ICON, Hanover, MD, US) with FOCEI was used for PopPK modelling. Xpose 4 (version 4.6.1) and PsN (version 4.8.1) was used for model diagnostics and covariate testing. R (version 4.0.2 or higher) was used for data exploration and simulations.

A previous PopPK analysis for trastuzumab deruxtecan (T-DXd, intact ADC) was based on data from Studies J101, J102, A103, A104, U201 and J202 served as the starting point for model development. In this model the time-course of intact T-DXd concentrations, adjusted for the drug-antibody ratio of 8 and molar mass, was the input to the released drug model (Fig 3-1).

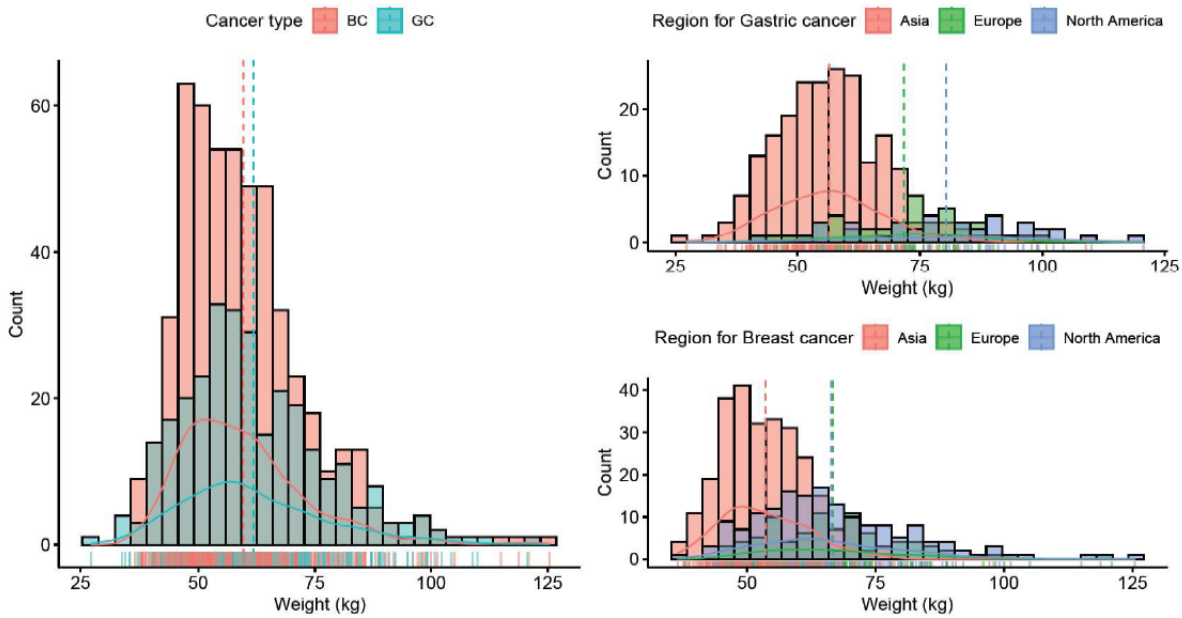
Figure 3-1 Structural model schematic



Abbreviations: $CL_{T\text{-}DXd}$ = elimination clearance of T-DXd; CL_{DXd} = elimination clearance of DXd; IV = intravenous; Krel = release rate constant; Q = distributional clearance; $V_{1,\ T\text{-}DXd}$ = T-DXd central volume of distribution; $V_{2,\ T\text{-}DXd}$ = T-DXd peripheral volume of distribution; V_{DXd} = DXd volume of distribution.

An updated dataset with additional dose and PK observations from subjects with gastric cancer from studies J101 and J202 and new data from Study U205 (conducted in US/European patients) was used to re-estimate model parameters including covariate effects. Study U205 contributed a total of 779 T-DXd and 778 DXd (only the topoisomerase I inhibitor) PK-evaluable samples from 76 subjects enrolled at study sites in USA and Europe. A total of 6 outlier concentrations in Study U205 were identified using a |CWRES|>5 criterion and excluded from covariate testing. No further data exclusions were conducted. The final combined T-DXd PopPK model were estimated using 14852 T-DXd and 14933 DXd PK samples collected from 884 subjects. Figure 4-5 shows the distribution of weights in the data set.

Figure 4-5 Distribution of weight among cancer type and regions



Abbreviations: BC = breast cancer; GC = gastric cancer.
Note: Dashed lines present the means of the subpopulations. Solid lines represent the density distributions for each subpopulation.
Source: weight_region_poptype_distributions.pdf, 2021-06-17-ds8201a-205-intact.r

The prior model was fit to the updated dataset with re-estimation of parameters for T-DXd and covariate effects using the T-DXd PK data only. Then, using both the T-DXd and DXd data, DXd parameters and corresponding covariate effects were re-estimated with fixed estimates for T-DXd, including the fixed and random-effects terms. The final model for T-DXd was the same as the base model and comprised a two-compartment model with linear elimination. Numerous covariates appeared correlated (e.g., sex, cancer type, and body weight; age, body weight and creatinine clearance). Cancer type on CLT-DXd was retained in the base model (run331) while sex was not tested as a covariate. The PK of DXd was described by a one-compartment model with a two-component, time-varying release rate from T-DXd. The release rate (Krel) was modelled to decrease over time based on a term for constant reduction after Cycle 1 (FPC1) and a term for gradual decline per cycle (FPC2). Covariate effects included in the final model are shown in **Table 4-7 and 4-9** for intact T-DXd and DXd, respectively.

Table 4-7 Overview of covariate analysis for the T-DXd model

Steps	Covariate Effects
Initial covariates from PopPK analysis included in gastric cancer BLA	$CL_{T\text{-}DXd}$: baseline tumor size, albumin, body weight, race-country, cancer type $V_{1,T\text{-}DXd}$: body weight, cancer type $V_{2,T\text{-}DXd}$: race-country
Exploratory covariate analysis	$CL_{T\text{-}DXd}$: sex $V_{1,T\text{-}DXd}$: sex
Final covariate model	$CL_{T\text{-}DXd}$: baseline tumor size, albumin, body weight, race-country, cancer type $V_{1,T\text{-}DXd}$: body weight, cancer type $V_{2,T\text{-}DXd}$: race-country

Abbreviations: BLA = biologics license application; $CL_{T\text{-}DXd}$ = T-DXd clearance; PopPK = population pharmacokinetics; $V_{1,T\text{-}DXd}$ = T-DXd central volume of distribution; $V_{2,T\text{-}DXd}$ = T-DXd peripheral volume of distribution.

Source: 2021-21-05-ds8201-205-gof.R, Intact_key models_withrerun.csv

Table 4-9 Overview of covariate analysis for the DXd model

Steps	Covariate Effects
Initial covariates from previous BLA PopPK analysis	CL_{DXd}: body weight, total bilirubin, AST, itraconazole co-administration, ritonavir co-administration effect, cancer type (gastric cancer, other cancer types compared to breast cancer) V_{DXd}: formulation, age, BSA, cancer type (other cancer types compared to gastric cancer and breast cancer)
Full covariate model	CL_{DXd}: body weight, total bilirubin, AST, itraconazole co-administration, ritonavir co-administration effect and cancer type (gastric cancer, other cancer types compared to breast cancer), race-country (Asian vs non-Asian) and line of therapy V_{DXd}: formulation, age, BSA, cancer type (other cancer types compared to gastric cancer and breast cancer) and race-country (Asian vs non-Asian)
Backward elimination	CL_{DXd}: race-country (Asian vs non-Asian) and line of therapy removed
Final covariate model	CL_{DXd}: body weight, total bilirubin, AST, itraconazole co-administration, ritonavir co-administration effect and cancer type (gastric cancer, other cancer types compared to breast cancer) V_{DXd}: formulation, age, BSA, cancer type (other cancer types compared to gastric cancer and breast cancer) and race-country (Asian vs non-Asian)

Abbreviations: BLA = biologics license application; CL_{DXd} = DXd clearance; PopPK = population pharmacokinetics; V_{DXd} = DXd volume of distribution.
Source: key_models_RD.csv

Model parameters were estimated with good precision (RSE <30%) except for the effect of "Other cancer" on CL,T-DXd, CL,DXd and V1,T-DXd. Shrinkage ranged up to 35%. BSV terms were included on CLDXd, VDXd, Krel, and FPC1. RUV was modelled with a proportional error structure. The RUV was estimated to be 30% with 6.6% shrinkage. Final model parameters for T-DXd and DXd are shown in **Tables 4-6 and 4-10**. A sensitivity analysis of the final T-DXd PopPK model (run542) including CWRES outliers (run542s) was performed and found no large shifts in model parameters.

Table 4-6 Parameters of the T-DXd base model (run331)

Parameter	T-DXd Base Model (run331)					Typical Value Estimate Previous Analysis without Study U205 (RSE %)
	Estimate		Between-subject Variability			
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)	
Clearance ($CL_{T\text{-}DXd}$, L/d)	0.422	1.39	24.51	2.70	6.23	0.420 (1.43)
Central volume of distribution ($V_{1,T\text{-}DXd}$, L)	2.78	0.791	15.7	2.79	5.58	2.78 (0.780)
Distribution clearance ($Q_{T\text{-}DXd}$, L/d)	0.201	1.55	30.6	4.58	28.4	0.198 (1.58))
Peripheral volume of distribution ($V_{2,T\text{-}DXd}$, L)	5.05	4.38	71.7	4.60	24.3	4.98 (4.68)
Albumin (g/L) on $CL_{T\text{-}DXd}$	-0.566	10.9	-	-	-	-0.601 (11.0)
Asian from Japan on $CL_{T\text{-}DXd}$	-0.106	14.8	-	-	-	-0.0952 (18.2)
Tumor size (mm) on $CL_{T\text{-}DXd}$	0.0642	17.9	-	-	-	0.0638 (19.0)
Body weight (kg) on $CL_{T\text{-}DXd}$	0.436	9.92	-	-	-	0.460 (10.2)
Gastric cancer on $CL_{T\text{-}DXd}$	0.158	15.4	-	-	-	0.154 (19.0)
Other cancer (not breast or gastric) on $CL_{T\text{-}DXd}$	0.06361	54.5	-	-	-	0.0566 (61.7)
Body weight (kg) on $V_{1,T\text{-}DXd}$	0.533	5.09	-	-	-	0.552 (5.36)
Gastric cancer on $V_{1,T\text{-}DXd}$	0.153	9.09	-	-	-	0.178 (8.75)
Other cancer (not breast or gastric) on $V_{1,T\text{-}DXd}$	0.0468	44.6	-	-	-	0.0456 (45.4)
Asian from Japan on $V_{2,T\text{-}DXd}$	-0.168	28.9	-	-	-	-0.156 (32.6)
Residual unexplained variability						
Proportional residual error SD	0.151	0.380	-	-	-	0.151 (0.39)
Additive residual error SD (ng/mL)	1223	2.24	-	-	-	1220 (2.41)
Covariance of $CL_{T\text{-}DXd}$ and $V_{1,T\text{-}DXd}$	0.0205	4.08	-	-	-	0.0204 (8.50)

Abbreviations: CV = coefficient of variation; RSE = relative standard error; SD = standard deviation; SE=standard error; sqrt = square root.

Notes: RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are calculated as 100×(SE/variance estimate)/2. CV% for the between-subject variability estimates

Table 4-10 Parameters of the DXd final model (run542)

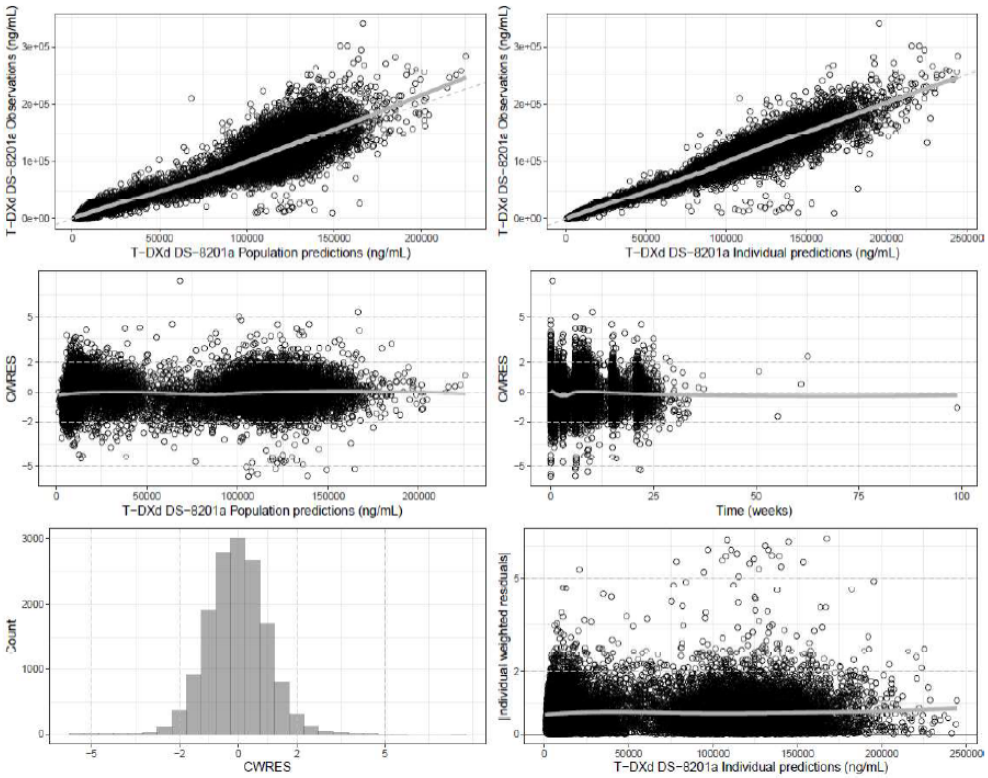
Parameter	Final DXd Model (run542)				
	Estimate		Between-subject Variability		
	Typical Value	RSE (%)	Magnitude (%CV)	RSE (%)	Shrinkage (%)
DXd clearance (CL_{DXd}, L/h)	18.5	3.78	27.2	5.18	35.2
DXd volume of distribution (V_{DXd}, L)	Fixed 17*BSA	-	41.2	4.18	23.0
Release rate (K_{rel}, 1/h)	0.0150	3.40	36.4	4.01	18.5
Fraction of K_{rel} at Cycle>1 (FPC1)	0.799	1.43	24.6	3.37	18.5
Exponent of cycle effect on K_{rel} (FPC2)	-0.143	4.51	-	-	-
Ritonavir on CL_{DXd}	-0.116	14.9	-	-	-
Itraconazole on CL_{DXd}	-0.105	21.1	-	-	-
AST (U/L) on CL_{DXd}	-0.230	11.1	-	-	-
Total bilirubin (µmol/L) on CL_{DXd}	-0.174	16.7	-	-	-
Body weight (kg) on CL_{DXd}	0.465	14.4	-	-	-
Gastric cancer on CL_{DXd}	-0.157	18.0	-	-	-
Other cancer (not breast or gastric) on CL_{DXd}	-0.133	38.1	-	-	-
Age (y) on V_{DXd}	0.503	15.9	-	-	-
FL-DP2 formulation on V_{DXd}	0.309	19.9	-	-	-
FL-DP1 formulation on V_{DXd}	-0.171	21.5	-	-	-
Other cancer (not breast or gastric) on V_{DXd}	-0.245	24.4	-	-	-
Non-Asian on V_{DXd}	-0.177	17.4	-	-	-
Residual unexplained variability					
Proportional residual error SD	0.302	0.435	-	-	-

Abbreviations: AST = aspartate aminotransferase; BSA = body surface area; CV = coefficient of variation; FL-DP1 = frozen liquid drug product 1; FL-DP2 = frozen liquid drug product 2; RSE = relative standard error; SD = standard deviation; SE=standard error; sqrt = square root.

Notes: RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are calculated as 100×(SE/variance estimate)/2. CV% for the between-subject variability estimates are based on the estimated variances. Shrinkage (%) is calculated as 100×(1-SD(ETA)/sqrt(variance). Overall residual unexplained variability shrinkage was estimated to be 6.61%.

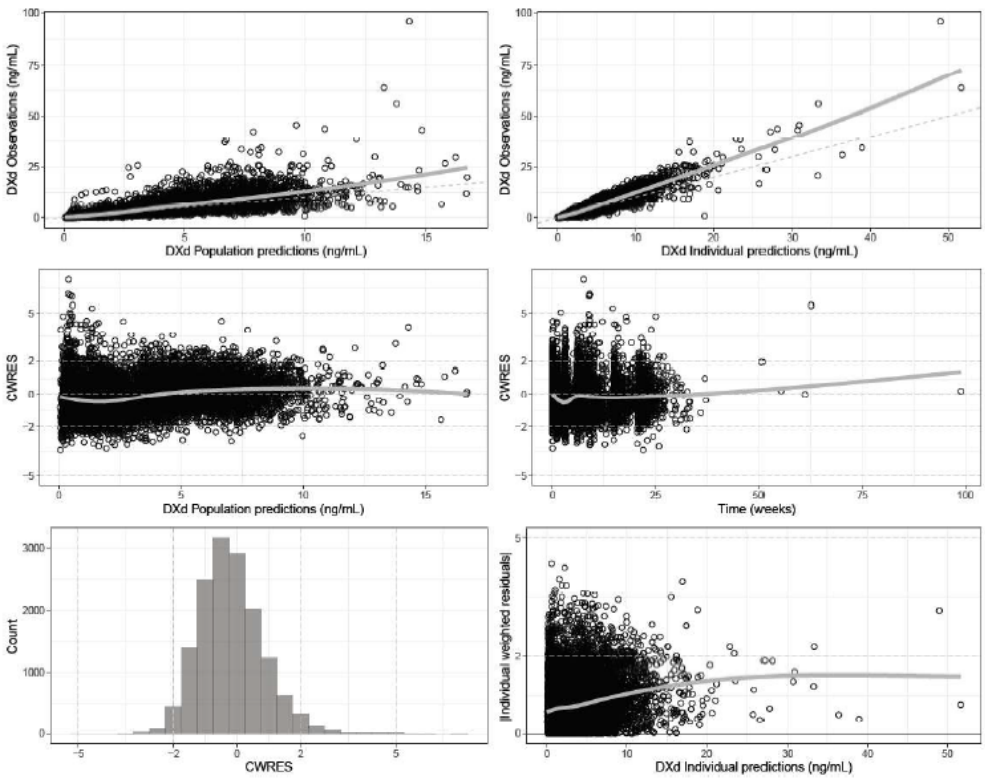
Source: payload-DXd-update-final-542-nmtable.csv, 2021-07-ds8201a-205-payload.r

Figure 4-8 Goodness-of-fit diagnostics of the T-DXd base model (run331)



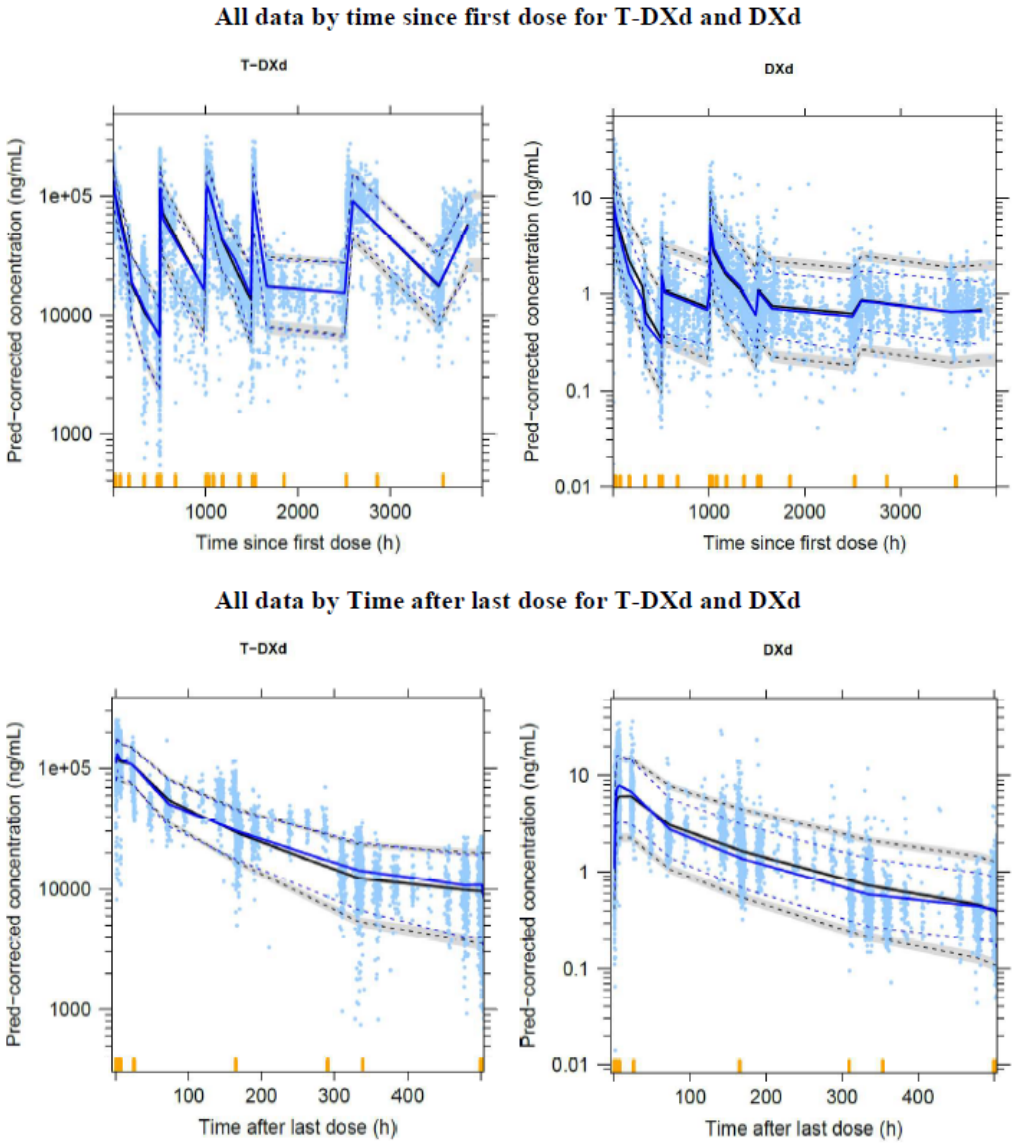
Abbreviations: CWRES = conditional weighted residual.
Note: The dots represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.
Source: gof-INonly-final-331-all.pdf, 2021-21-05-ds8201-205-gof.R

Figure 4-13 Goodness-of-fit diagnostics of the DXd final model (run542)



Abbreviations: CWRES = conditional weighted residuals.
Note: The circles represent observations, the black dashed lines represent identity lines, and gray curves represent loess smoothers.
Source: gof-PAY-FINAL-combined-542-all.pdf, 2021-21-05-ds8201-205-gof.R

Figure 4-15 Prediction-corrected VPC for the T-DXd and DXd PopPK model (run542), all data

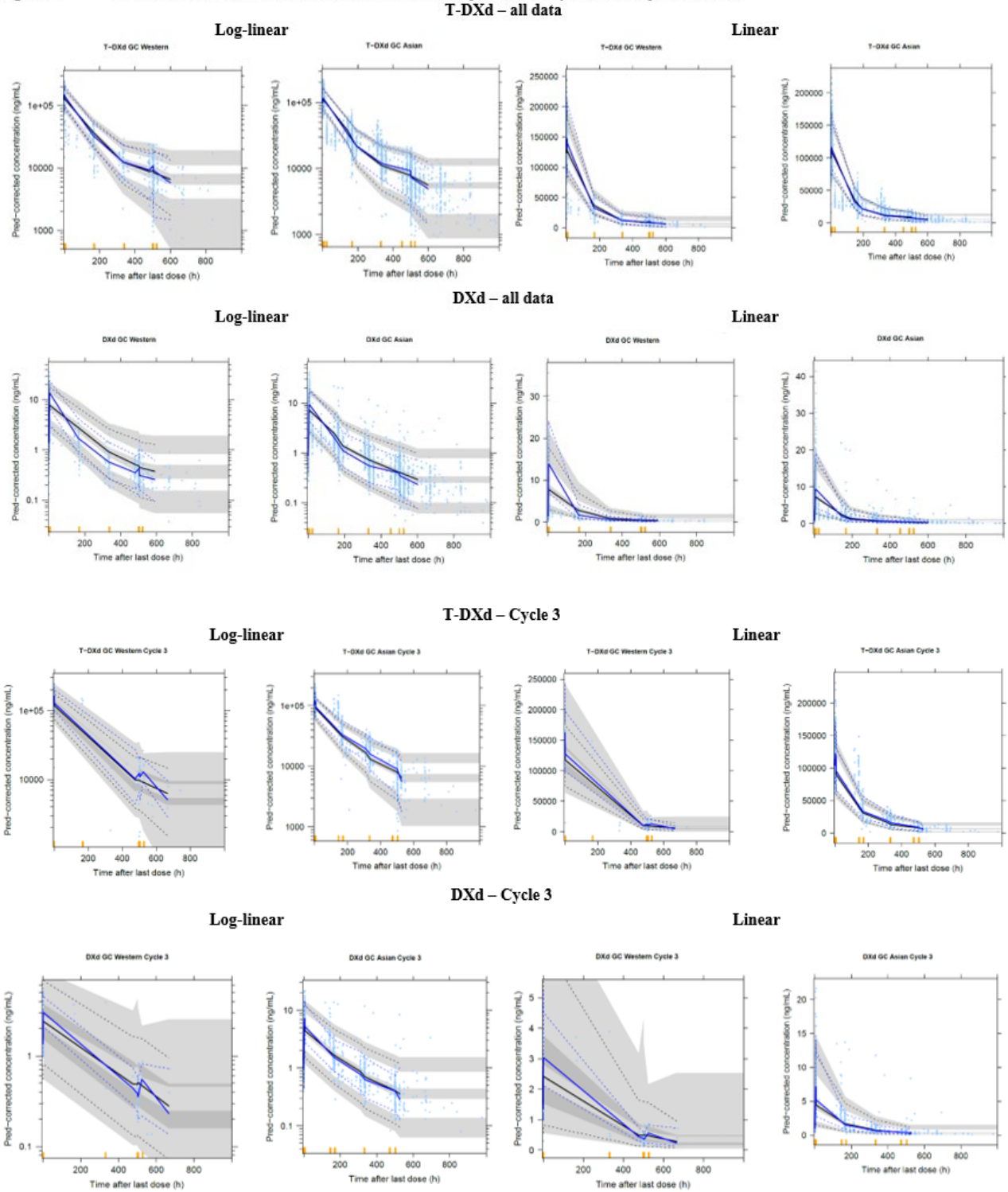


Abbreviations: PopPK = population pharmacokinetics; pred-corr = prediction-corrected; VPC = visual predictive check.

Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.

Source: VPC-TIME-both-all-data542.pdf, VPC-TAD-both-all-data-542.pdf, 2021-21-05-ds8201-205-gof.R

Figure 1: Prediction-corrected VPC for the T-DXd and DXd PopPK model, by Race in subjects with GC



Abbreviations: GC = gastric cancer; PopPK = population pharmacokinetics; pred-corrected = prediction-corrected; VPC = visual predictive check.
Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% prediction interval for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.
Source: VPC-TAD-RD-GC-RACE542.pdf, VPC-TAD-RACE-GC-C3-542.pdf, 2022-01-10-ds8201-205-EUresponse.R

Covariate effects on exposure estimates

In the previous model all covariates had effects contained within the 0.8 to 1.25 exposure ratios with the exceptions of high values of albumin for T-DXd which increased Cmin by 33% and gastric vs. breast

cancer for T-DXd at 6.4 mg/kg Q3W. For DXd, high values of baseline AST increased AUC and Cmin by 27%. In the updated model, post hoc DXd exposure estimates of subjects dosed at 6.4 mg/kg Q3W T-DXd showed differences based on cancer type but not by sex, region and race-country. Presence of ADA was tested for T-DXd and line of therapy was tested for both T-DXd and DXd. None had significant effect.

Subpopulation analyses of DXd exposures performed under proposed regimens based on T-DXd exposure differences, 5.4 mg/kg Q3W T-DXd for breast cancer and 6.4 mg/kg Q3W T-DXd for gastric cancer, showed greater DXd exposure in the 6.4 mg/kg Q3W T-DXd gastric cancer group at Cycle 1 (up to 41% higher), but comparable exposures between the two groups at steady state (geometric mean ratio 1.12 to 1.22).

Exposure-response analyses

The initial exposure-safety analysis used data from four Phase 1 studies (Studies J101, J102, A103, and A104) and two Phase 2 studies (Studies U201 and J202). Models were updated with data from U205 (Table 3-3).

Table 3-3: Study U205 SDTM/ADaM datasets

Category	Description (Label)	Selected Information
General Datasets	Subject-level data (ADSL)	Demographics, populations, endpoints
	Concomitant medications (ADSL, CM)	Prior therapy
	Demographics (ADSL, DM)	Age, sex, race, country
	Disposition (AE)	Discontinuations due to AEs
	Medical history (MH)	Cancer type
	Tumor type (TU)	Cancer type
	Questionnaires (QS)	ECOG PS
	Vital signs (VS)	Weight
	Supplemental demographics (SUPPDM)	Identifiers for study populations
	Chemistry labs (LB)	Hepatic and renal function parameters, HER2ECD, HER2 status
Exposure-Efficacy Analysis	Tumor response (ADRS2)	Confirmed ORR
	Survival (ADTTE)	PFS, DoR
Exposure-Safety Analysis	Adverse events (ADAE, AE)	AE listings
	Adverse events (SUPPAE)	Special AEs of interest (ILD, LVEF decrease)
	Cardiovascular (CV)	LVEF change (ECHO)
	Chemistry labs (LB)	Neutropenia, thrombocytopenia, anemia

Abbreviations: ADaM = analysis data model; AE = adverse event; DoR = duration of response; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HER2 = human epidermal growth factor receptor 2; HER2ECD = human epidermal growth factor receptor 2 extracellular domain; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic; SDTM = standard data tabulation model.

R (version 4.0.5) was used for the exposure-efficacy/safety modeling, as well as for data explorations prior to and/or after modeling and simulations. Exploratory plots were used to assess whether to perform detailed modeling of each efficacy or safety endpoint. Covariates that were not significant ($p>0.05$ using z-test) were removed followed by a forward inclusion at $p<0.05$ and a backward elimination at $p<0.01$ using the likelihood ratio test. The covariates were tested on the intercept and the slope of logistic ER relationships or on the slope of Cox regression models.

No statistically significant relationships between increasing T-DXd or DXd exposures and either PFS or DoR was detected over the range of exposures for the 6.4 mg/kg Q3W dose in Study U205. No covariate relationships were explored.

Table 5-55: Grade ≥2 LVEF decrease (ECHO) final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade≥2 LVEF decrease (ECHO)	Intercept	-3.37	0.514	15
		Slope	0.0104	0.00306	29
		Tumor location GEJ	-1.91	0.757	40
		Tumor location missing	0.376	0.247	66
		Asian from Japan	0.200	0.211	106
		Asian not from Japan	-0.800	0.387	48

Abbreviations: ECHO = echocardiogram-based; GEJ = gastroesophageal junction; LVEF = left ventricular ejection fraction; RSE = relative standard error.
Note: Asian race covariate had a relatively high RSE but was included in the base model as part of the race-country covariate.
Source: es.analysis.r

Table 5-61: Any Grade ILD final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd AUC steady state (µg/mL×day)	Any Grade ILD	Slope	0.00181	0.000332	18
		Creatinine clearance (mL/min)	-0.00842	0.00318	38
		Asian from Japan	0.375	0.191	51
		Asian not from Japan	-0.752	0.439	58

Abbreviations: AUC = area under the concentration-time curve; ILD = interstitial lung disease; RSE = relative standard error.
Source: es.analysis.r

Table 5-62: Grade ≥3 ILD final model parameters

Exposure-Response Model		Parameter	Estimate	Standard Error	RSE (%)
Exposure Metric	Safety Endpoint				
T-DXd peak conc steady state (µg/mL)	Grade ≥3 ILD	Slope	0.0257	0.00585	23
		Albumin (g/L)	-0.140	0.0428	31

Abbreviations: ILD = interstitial lung disease; RSE = relative standard error.
Source: es.analysis.r

Interpretation of model covariates, both presence in the model and in direction of effect, may be complex because of the correlation between covariates, multiplicity of testing, sample size of subgroups, and unknown covariate status for some of the patients.

Stratifying modelled event rates in gastric cancer by region (Asia, USA, Europe) showed more than 15% higher rates in Asia for Grade ≥3 AE, Grade ≥3 anaemia and Grade ≥3 neutropenia. Model-predicted safety event rates also showed this difference between Asians and Non-Asians and may be related to clinical practice. However, USA and European subjects had comparable AE rates across all endpoints, although the numbers of subjects in this comparison is small.

Bridging analysis

A virtual second-line or later HER2-positive gastric cancer Western population was created from real-world (RW) data. Individual longitudinal information in HER2+ gastric cancer patients in the US was extracted from electronic health records of healthcare provider sites by a third-party vendor. Patients receiving one or more line of therapy were included in the RW dataset. For patients receiving more lines of therapy, baseline time was defined as the start time of the last received therapy. Covariates were taken from the visit corresponding to the baseline time, or nearest available visit, or indicated as missing. Per real-world patient, 50 virtual patients were simulated using the population PK model to obtain PK exposures for intact antibody and released drug. Each virtual patient utilized the corresponding covariates of the real-world patient, except for imputed covariates. Missing covariates were sampled from other patients in the RW dataset, or from the bridging population (Table 1.1 – Summary of Subject Populations used for Bridging). The real-world population included 49 HER2-positive gastric cancer patients, of which 25 patients were identified as second-line or later and included in the Western RW dataset. The inclusion criteria were: patients diagnosed with gastric cancer, HER2-positive and received trastuzumab. Therefore, the virtual PK population included 1250 subjects.

The PK model parameters were used to compute the exposure metrics Cmin, Cmax and AUC at Cycle 1 and at steady-state (Cycle 9). Exposure metrics obtained in Japan and the virtual Western population were compared. For time-to-event exposure metrics, dose regimens and endpoint times were randomly sampled from the bridging population in Table 1.1 – Summary of Subject Populations used for Bridging. These regimens incorporated dose interruptions, dose reductions and treatment discontinuations. For each efficacy or safety endpoint, 1000 trial simulations were conducted. Each trial simulation used the RW dataset sample size, by sampling the virtual population with replacement. Each trial simulation also incorporated uncertainty in the exposure-response models by sampling parameters from the variance-covariance matrix of the parameter estimates of the exposure-response models. Trial simulations were also conducted in the Japan gastric cancer bridging population as outlined in Table 1.1 for comparison. Each trial simulation provided an event probability. Across the 1000 trial simulations, 1000 probabilities were obtained to derive the 90% confidence intervals. Sensitivity analyses were conducted to elucidate the covariates accounting for differences between Japan and Western populations and illustrated using forest plots.

Table 1.1: Summary of Subject Populations used for Bridging

Previous Analysis	Original population	N in original analysis [2]	Exclusions	Bridging population	N in bridging population
Exposure-efficacy	HER2-positive gastric cancer	160	Dose other than 6.4 mg/kg (N=19) Dose of 6.4 mg/kg but not in Japan (N=24)	Japan, HER2-positive gastric cancer subjects received 6.4 mg/kg	117
Exposure-safety	HER2-expressing solid tumors	808	Dose other than 6.4 mg/kg (N=348) Dose of 6.4 mg/kg but not in Japan (N=136) Dose of 6.4 mg/kg, Japan, but not gastric cancer (N=166)	Japan, HER2-expressing gastric cancer subjects received 6.4 mg/kg	158

Abbreviations: N = number of subjects, HER2 = human epidermal growth factor receptor 2.
Notes: HER2-expressing includes HER2-positive, HER2-low or HER2 status unknown. Exclusions from the exposure-efficacy and the exposure-safety bridging population include 5 gastric-cancer subjects from Western countries who received a dose of 5.4 mg/kg.
Source: DS-8201a E-R report in gastric cancer and other solid tumors ([2]).

The PK simulations results from the virtual bridging analysis indicated that in HER2-positive second-line-or-later subjects with GC receiving 6.4 mg/kg T-DXd Q3W, PK exposures of intact T-DXd and DXd are generally comparable between Western and Japanese subjects with GC. Based on the exposure-efficacy simulations, there was a similar incidence of ucORR in Western subjects relative to Japanese subjects;

however, the incidence of cORR in Western subjects was lower relative to that in Japanese subjects. The results from exposure-safety simulations suggested that any grade ILD was lower in the Japan population, and ILD3 rates in Japan and Western populations were comparable. The incidence of other TEAEs was comparable, with the exception of Grade ≥3 neutropenia, which was lower in Western subjects relative to Japanese subjects.

The bridging analysis enabled projections of efficacy/safety rates for the 6.4 mg/kg Q3W T-DXd regimen in Western subjects, prior to the availability of results from Study U205. In general, the efficacy and safety data from Study U205 agreed with the results of the virtual bridging analysis, thereby confirming the extrapolation of the results from the Asian patients with GC to Western patients with GC.

ADME

The absorption, distribution, metabolism, and excretion characteristics of T-DXd (and each individual component) are well characterized based on a series of nonclinical studies using human biomaterials as described in the initial BC application, and based on data from clinical studies J101, J102, A103, A104, and U201.

PopPK modelling, based on a dataset updated with GC data, suggested that T-DXd clearance increased with body weight, baseline tumor size, and having GC or other cancers (relative to BC).

Following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance of trastuzumab deruxtecan in population pharmacokinetic analysis was calculated to be 0.42 L/day. In patients with locally advanced or metastatic gastric or GEJ adenocarcinoma, trastuzumab deruxtecan clearance was 16% higher than in patients with metastatic HER2-positive breast cancer. The clearance of DXd based on population pharmacokinetic analysis was estimated to be 446 L/day and 401 L/day for patients with metastatic HER2-positive breast cancer and locally advanced or metastatic gastric or GEJ adenocarcinoma, respectively.

As for DXd, the model identified body weight, total bilirubin, AST, coadministration of itraconazole or ritonavir, and having GC or other cancers as significant covariates on the clearance of DXd.

Exposure data in GC or GEJ patients compared with BC data

Serum T-DXd

The cycle 1 PK data (calculated using noncompartmental methods) for T-DXd in subjects with GC and BC were integrated across six studies (J101, J102, A103, U201, J202, and U205) and PK parameters are presented by dose for subjects with HER2-positive GC and BC in **Table 3.1**. The PK exposure parameters for T-DXd in cycle 1 at 6.4 mg/kg for subjects with GC were similar to those at 5.4 mg/kg for subjects with BC.

Table 3.1: Summary of T-DXd Pharmacokinetic Parameters: Integrated Analysis of Cycle 1 Pharmacokinetic Data in Subjects with Gastric or Breast Cancer

Dose	PK Parameter (unit)				
	Cmax (µg/mL)	Tmax (h)[a]	AUClast (µg · d/mL)	AUC21d (µg · d/mL)	Ctrough (µg/mL)
5.4 mg/kg GC					
N	19	19	19	19	19
Mean	113	2.03	524	522	5.34
(Std Dev)	(28.5)	-	(165)	(164)	(2.60)
Min/Max	-	1.58 / 4.08	-	-	-
6.4 mg/kg GC					
N	226	226	226	211	218
Mean	133	3.17	629	631	5.52
(Std Dev)	(36.4)	-	(188)	(181)	(3.11)
Min/Max	-	0.00 / 572.16	-	-	-
5.4 mg/kg BC					
N	232	232	232	190	215
Mean	124.15	2.167	544.68	572.6	5.5
(Std Dev)	(32.61)	-	(163.42)	(167.1)	(5.13)
Min / Max	-	0.02 / 166.7	-	-	-
6.4 mg/kg BC					
N	122	122	122	115	116
Mean	165.23	2.07	740.9	756.5	9.246
(Std Dev)	(50.96)	-	(212.27)	(205.1)	(20.02)
Min / Max	-	0.02 / 7.05	-	-	-

AUC21d = area under the serum concentration-time curve from time zero to Day 21; AUClast = area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration; BC = breast cancer; Cmax = maximum serum concentration; Ctrough = trough serum concentration; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; Tmax = time to reach peak serum concentration.

[a] Values are presented as N / mean (Std Dev) except for Tmax, which shows N / median (range).

Source: Module 5.3.5.3 SCP TFLs Table 1.1.1; initial Gastric Cancer BLA Table 3.1.

Serum total anti-HER2 antibody

The Cycle 1 PK data for total anti-HER2 antibody in subjects with HER2-positive cancer were integrated across six studies (J101, J102, A103, U201, J202, and U205) and PK parameters (calculated using noncompartmental methods) are presented by dose for subjects with HER2-positive GC and BC **Table 3.2**.

Table 3.2: Summary of Total Anti-HER2 Antibody Pharmacokinetic Parameters: Integrated Analysis of Cycle 1 Pharmacokinetic Data in Subjects with Gastric or Breast Cancer

Dose	PK Parameter (unit)				
	Cmax (µg/mL)	Tmax (h)[a]	AUClast (µg · d/mL)	AUC21d (µg · d/mL)	Ctrough (µg/mL)
5.4 mg/kg GC					
N	19	19	19	19	19
Mean	105	2.02	683	681	11.8
(Std Dev)	(36.4)	-	(533)	(533)	(20.1)
Min / Max	-	1.55 / 6.82	-	-	-
6.4 mg/kg GC					
N	226	226	226	209	217
Mean	125	2.32	726	716	9.77
(Std Dev)	(37.7)	-	(319)	(299)	(10.0)
Min / Max	-	0.00 / 572.16	-	-	-
5.4 mg/kg BC					
N	232	232	232	196	211
Mean	125.34	2.00	712.96	772.1	13.2
(Std Dev)	(35.07)	-	(320.58)	(370.98)	(13.26)
Min / Max	-	0.02 / 310.66	-	-	-
6.4 mg/kg BC					
N	122	122	122	118	116
Mean	160.98	2.00	910.5	937.4	15.80
(Std Dev)	(60.68)	-	(357.46)	(359.8)	(20.959)
Min / Max	-	0.02 / 22.15	-	-	-

AUC21d = area under the serum concentration-time curve from time zero to Day 21; AUClast = area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration; BC = breast cancer; Cmax = maximum serum concentration; Ctrough = trough serum concentration; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; Std Dev = standard deviation; Tmax = time to reach peak serum concentration.

[a] Values are presented as N / mean (Std Dev) except for Tmax, which shows N / median (range).

Source: Module 5.3.5.3 SCP TFLs Table 1.1.2; initial Gastric Cancer BLA Table 3.2.

Serum DXd

The cycle 1 PK data for DXd in subjects with HER2-positive cancer were integrated across six studies (J101, J102, A103, U201, J202, and U205) and PK parameters are presented by dose for subjects with HER2-positive GC and BC in **Table 3.3**.

Table 3.3: Summary of DXd Pharmacokinetic Parameters: Integrated Analysis in Subjects with Gastric Cancer or Breast Cancer

Dose	PK Parameter (unit)				
	Cmax (ng/mL)	Tmax (h)[a]	AUClast (ng · d/mL)	AUC21d (ng · d/mL)	Ctrough (ng/mL)
5.4 mg/kg GC					
N	19	19	19	18	19
Mean	9.30	6.92	43.3	43.3	0.404
(Std Dev)	(6.86)	-	(42.5)	(43.2)	(0.400)
Min / Max	-	3.78 / 24.07	-	-	-
6.4 mg/kg GC					
N	226	226	226	186	217
Mean	12.3	6.77	48.7	47.2	0.306
(Std Dev)	(5.59)	-	(23.4)	(19.2)	(0.269)
Min / Max	-	1.61 / 572.16	-	-	-
5.4 mg/kg BC					
N	232	232	232	109	226
Mean	8.187	6.792	31.729	33.334	0.263
(Std Dev)	(5.722)	-	(17.658)	(16.551)	(0.250)
Min / Max	-	0.24 / 166.51	-	-	-
6.4 mg/kg BC					
N	122	122	122	103	115
Mean	10.453	6.840	43.69	43.61	0.351
(Std Dev)	(9.343)	-	(32.364)	(31.395)	(0.244)
Min / Max	-	0.34 / 191.47	-	-	-

AUC21d = area under the serum concentration-time curve from time zero to Day 21; AUClast = area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration; BC = breast cancer; Cmax = maximum serum concentration; Ctrough = trough serum concentration; DXd = released drug; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; Std Dev = standard deviation; Tmax = time to reach peak serum concentration.

[a] Values are presented as N / mean (Std Dev) except for Tmax, which shows N / median (range).

Source: Module 5.3.5.3 SCP TFLs Table 1.1.3; initial Gastric Cancer BLA Table 3.3.

Dose proportionality and time dependencies

Not addressed in the present application.

Special populations

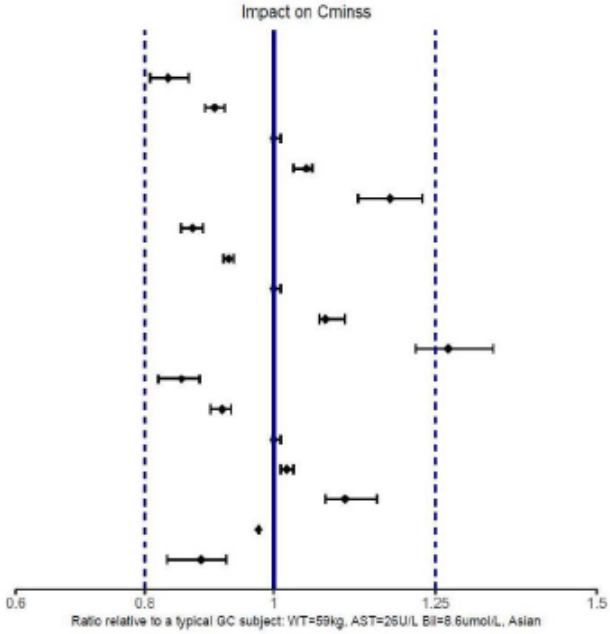
A popPK analysis performed with an analysis dataset pooled from five studies (J101, J102, A103, A104, and U201) for the initial BC application was updated with inclusion of data from study J202 and U205. This analysis explored the exposures among subpopulations of interest, including tumor type, sex, race-country, region, hepatic function, and renal function.

Covariate Effect on DXd Pharmacokinetics

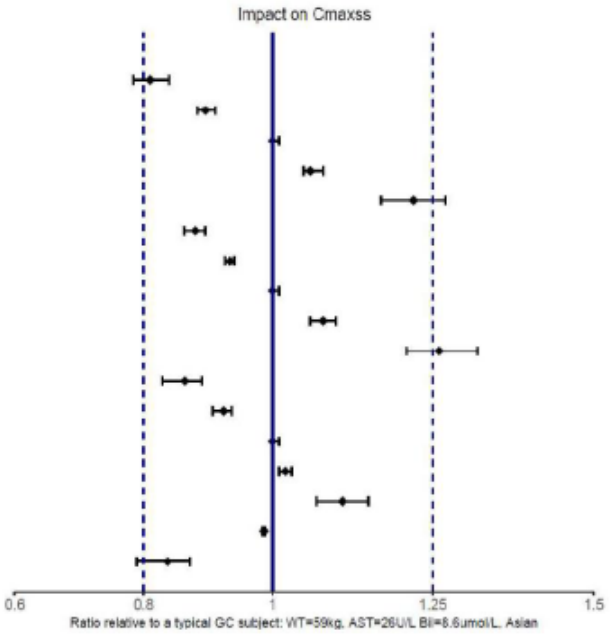
The effect of each significant covariate included in the final model on the AUCss of DXd after administration of T-DXd at 6.4 mg/kg Q3W was evaluated by forest plots (**Figure 3.8**). A typical subject who was administered T-DXd lyophilized drug product was a 65-year-old Asian subject with GC, body weight 59 kg, total bilirubin 8.6 µmol/L, and AST 26 U/L. The magnitude of all covariate effects on DXd exposure (Cmax,ss, Cmin,ss, and AUCss) was contained within a 0.8 to 1.25 ratio interval except for effects of extreme values of AST and body weight.

Figure 3.8: Forest Plot of Covariate Effect on the Exposure of DXd at Steady State

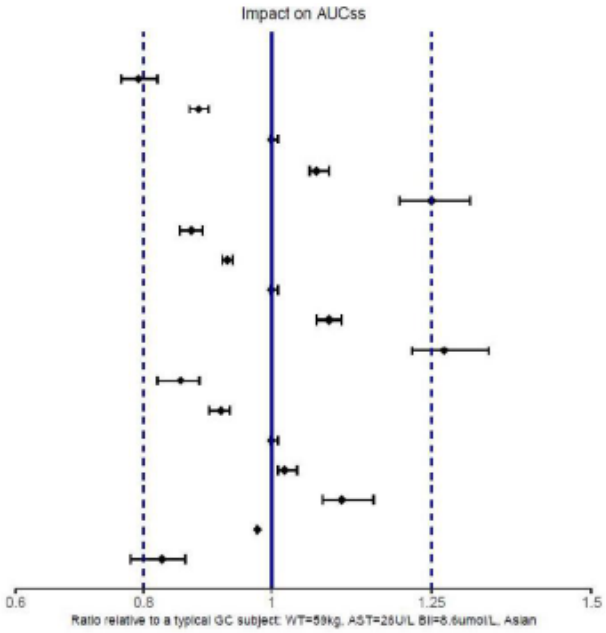
Covariate	Percentile	Value	Ratio [95% CI]
Body weight (kg)	5%	42	0.836 [0.808, 0.868]
	25%	50	0.908 [0.893, 0.924]
	50%	58	1 [0.998, 1.01]
	75%	68	1.05 [1.03, 1.06]
	95%	88	1.18 [1.13, 1.23]
AST (U/L)	5%	16	0.874 [0.856, 0.89]
	25%	21	0.93 [0.922, 0.938]
	50%	29	1 [0.998, 1.01]
	75%	41	1.08 [1.07, 1.11]
	95%	82	1.27 [1.22, 1.34]
Total bilirubin (umol/L)	5%	4	0.857 [0.821, 0.885]
	25%	6	0.92 [0.902, 0.934]
	50%	8	1 [0.998, 1.01]
	75%	11	1.02 [1.01, 1.03]
	95%	18	1.11 [1.08, 1.16]
Race−country		Non−Asian	0.976 [0.976, 0.977]
Cancer type		Breast cancer	0.887 [0.835, 0.926]



Covariate	Percentile	Value	Ratio [95% CI]
Body weight (kg)	5%	42	0.81 [0.784, 0.839]
	25%	50	0.896 [0.883, 0.911]
	50%	58	1 [0.999, 1.01]
	75%	68	1.06 [1.05, 1.08]
	95%	88	1.22 [1.17, 1.27]
AST (U/L)	5%	16	0.88 [0.863, 0.896]
	25%	21	0.934 [0.926, 0.941]
	50%	29	1 [0.999, 1.01]
	75%	41	1.08 [1.06, 1.1]
	95%	82	1.26 [1.21, 1.32]
Total bilirubin (umol/L)	5%	4	0.864 [0.829, 0.891]
	25%	6	0.924 [0.907, 0.937]
	50%	8	1 [0.999, 1.01]
	75%	11	1.02 [1.01, 1.03]
	95%	18	1.11 [1.07, 1.15]
Race−country		Non−Asian	0.987 [0.985, 0.989]
Cancer type		Breast cancer	0.837 [0.789, 0.872]



Covariate	Percentile	Value	Ratio [95% CI]
Body weight (kg)	5%	42	0.792 [0.765, 0.822]
	25%	50	0.886 [0.872, 0.902]
	50%	58	1 [0.998, 1.01]
	75%	68	1.07 [1.06, 1.09]
	95%	88	1.25 [1.2, 1.31]
AST (U/L)	5%	16	0.875 [0.857, 0.892]
	25%	21	0.931 [0.923, 0.939]
	50%	29	1 [0.998, 1.01]
	75%	41	1.09 [1.07, 1.11]
	95%	82	1.27 [1.22, 1.34]
Total bilirubin (umol/L)	5%	4	0.858 [0.822, 0.887]
	25%	6	0.921 [0.903, 0.935]
	50%	8	1 [0.998, 1.01]
	75%	11	1.02 [1.01, 1.04]
	95%	18	1.11 [1.08, 1.16]
Race−country		Non−Asian	0.978 [0.978, 0.978]
Cancer type		Breast cancer	0.829 [0.76, 0.865]



AST = aspartate aminotransferase; AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration; GC = gastric cancer; Lyo-DP = lyophilized drug product.
Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimate and 90% confidence interval, respectively. A typical subject is defined as a 65-year-old Asian subject with GC, baseline weight of 59 kg, AST of 26 U/L, total bilirubin of 8.6 μmol/L. For DXd race-country categories Asian from Japan and Asian not from Japan were grouped together and are displayed here against the non-Asian group.
Source: Module 5.3.3.5 Population PK Report (PMx x008) Figure 4-14

Pharmacokinetic interaction studies

Clinical data

No new drug drug interaction studies have been conducted.

Immunogenicity

Anti-drug antibodies (ADAs) against T-DXd were evaluated in subjects from Studies J202 and U205, and these data were combined with the data from the studies included in the initial BC application to provide an integrated immunogenicity assessment across the seven clinical studies (J101, J102, A103, A104, U201, J202, and U205). Immunogenicity data are summarized across all studies in **Table 4.2**.

Immunogenicity data are summarized at baseline and post-treatment, which includes the incidence of treatment-emergent ADA-positive results. Across the clinical studies, 892 subjects were tested for ADAs against T-DXd, and the median duration of immunogenicity assessment was 25 weeks (range of median values across studies: 15.1 weeks to 39.0 weeks). In general, the rate of baseline and post-baseline ADA-positive immunogenicity was low with 4.5% and 2.4% prevalence, respectively. The rate of treatment-emergent ADAs (defined as subjects who were ADA-negative at baseline and became ADA-positive post-treatment; or subjects who were ADA-positive at baseline and post-treatment, but had an increase in ADA titer from baseline to posttreatment; or subjects who had missing ADA data at baseline and were ADA-positive posttreatment) continued to be low, with 1.8% subjects (16/892) having treatment-emergent ADAs. No apparent difference was noted in the incidence of treatment-emergent ADAs across different tumor types. None of the treatment-emergent ADA-positive subjects had neutralizing antibody (NAb)-positive samples. No obvious effect of immunogenicity on PK, efficacy, or

safety was observed. No apparent impact of ADA positivity on systemic concentrations of T-DXd was noted. The population PK analysis confirmed lack of an impact of ADA status on the CLT-DXd.

Table 4.2: Summary of Clinical Immunogenicity Data for T-DXd

Statistic		Clinical Study							Overall
		J101	J102	A103	A104	U201	J202	U205	
Baseline assessment									
Total number of subjects assessed		289	51	12	40	253	169	78	892
ADA-positive at baseline[a]	n (%)	5 (1.7)	3 (5.9)	0	1 (2.5)	13 (5.2)	13 (7.7)	5 (6.7)	40 (4.5)
NAb-positive at baseline[a]	n (%)	0	0	0	0	1 (0.4)	0	0	1 (0.1)
Post-baseline assessment									
Total number of subjects assessed		289	51	12	40	253	169	78	892
ADA-positive post-baseline[b]	n (%)	1 (0.3)	1 (2.0)	0	0	5 (2.0)	12 (7.2)	2 (2.6)	21 (2.4)
NAb-positive post-baseline[b]	n (%)	0	0	0	0	0	0	0	0
ADA-positive at baseline and post-baseline[c]	n (%)	1 (0.3)	1 (2.0)	0	0	3 (1.2)	1 (0.6)	0	6 (0.7)
NAb-positive at baseline and post-baseline[c]	n (%)	0	0	0	0	0	0	0	0
Treatment-emergent ADA-positive[b]	n (%)	0	0	0	0	3 (1.2)	11 (6.6)	2 (2.6)	16 (1.8)
Treatment-induced ADA-positive[b]	n (%)	0	0	0	0	2 (0.8)	11 (6.6)	2 (2.6)	15 (1.7)
Treatment-boosted ADA-positive[b]	n (%)	0	0	0	0	1 (0.4)	0	0	1 (0.1)
Treatment-emergent Nab-positive[b]	n (%)	0	0	0	0	0	0	0	0

ADA = anti-drug antibody(ies); n = number of subjects; NAb = neutralizing antibody(ies); T-DXd = trastuzumab deruxtecan.

[a] Denominator for percentages is the n with baseline immunogenicity data.

[b] Denominator for percentages is the n with post-baseline immunogenicity data.

[c] Denominator for percentages is the number of subjects with baseline and post-baseline immunogenicity data.

Source: Module 5.3.5.3 SCP TFLs Table 2.1.1.

2.3.3. Pharmacodynamics

Mechanism of action

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody linked to topoisomerase I inhibitor molecules (ADC molecule). DXd acts as a cytotoxic payload.

Primary and secondary pharmacology

Exposure-response analyses

Exposure-efficacy analysis

For the E-R analysis for efficacy, data from subjects with HER2-positive GC were analysed separately using an integrated dataset from Studies J101 and J202 and a dataset from Study U205. For the

integrated analysis of Studies J101 and J202, 160 subjects were included, with the median age being 66 years and male subjects accounting for 74%; the study subjects were from Japan (82%), non-Japan Asia (South Korea) (15%), and non-Asia (3%). For the analysis of Study U205, 76 subjects were included, with the median age being 61.5 years and male subjects accounting for 72.4%.

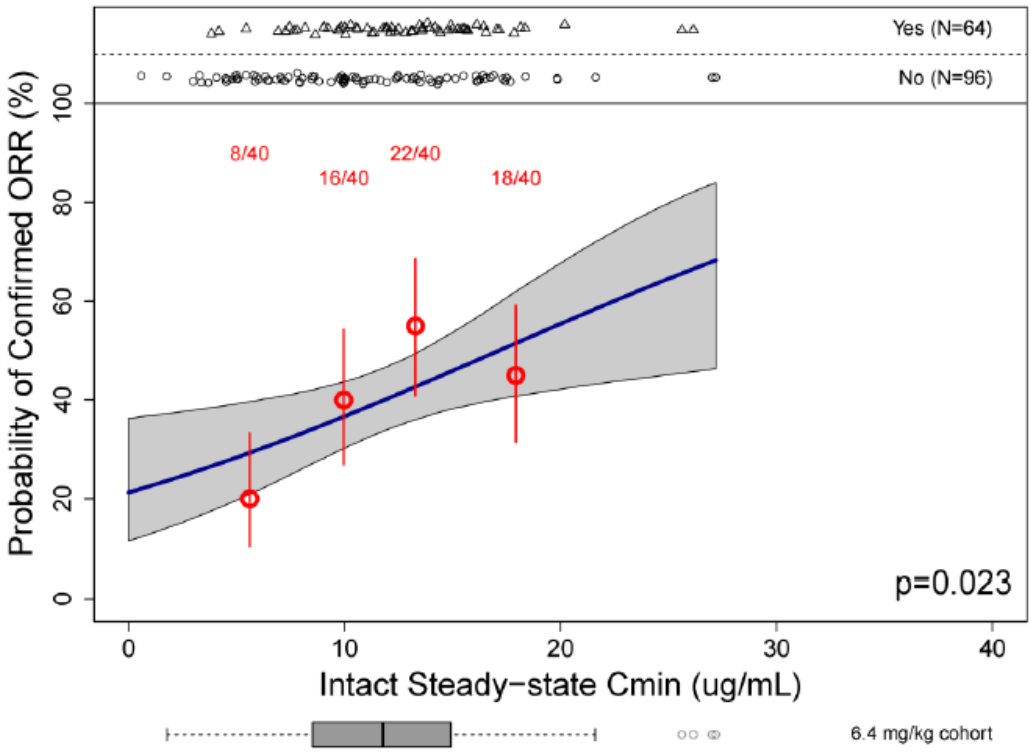
The exposure indicators investigated were the AUC, Cmax, and Cmin of T-DXd and DXd in Cycle 1 and at steady state, and Cavg during the period up to the development of the efficacy event under analysis. The efficacy endpoints were cORR, DoR, and PFS in subjects with HER2-positive GC.

None of the T-DXd or DXd exposure metrics had a statistically significant relationship with the primary efficacy endpoint of ucORR.

In the integrated analysis of Studies J101 and J202, the analysis of cORR by logistic regression showed that cORR was statistically significantly higher in subjects with higher Cmin,ss of T-DXd (P = 0.023; **Figure 3.13**).

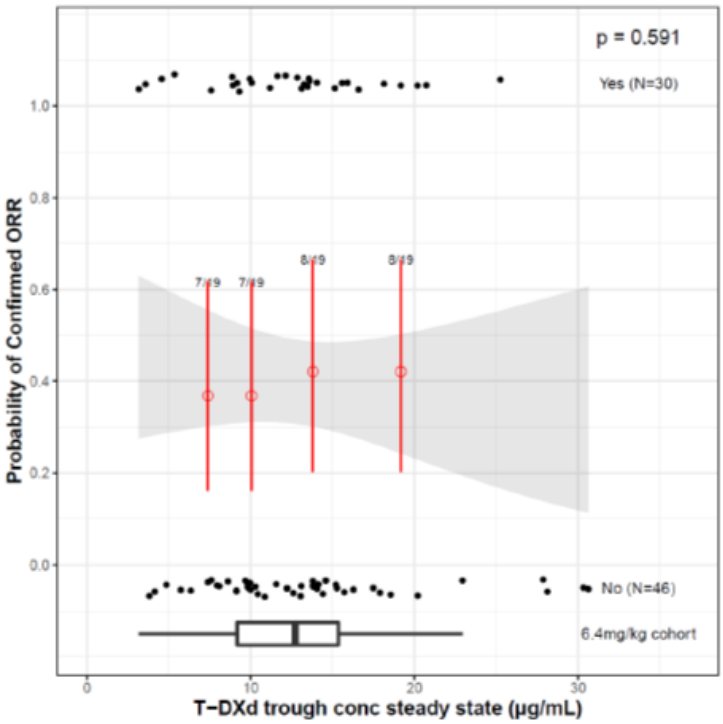
In the analysis of Study U205, cORR by logistic regression showed that cORR was not statistically significantly higher in subjects with higher Cmin,ss of T-DXd (P = 0.591; **Figure 3.14**).

Figure 3.13: Relationship Between Exposure and Confirmed Objective Response Rate: Study J101 and Study J202



CI = confidence interval; Cmin = minimum concentration; cORR = confirmed objective response rate; Intact = intact T-DXd; N = number of subjects; ORR = objective response rate.
Note: Yes and No refer to if subjects experienced or did not experience objective response. Subjects are stratified into exposure quartiles. Red points are mean exposure and cORR per quartile. Vertical red bars are 90% CIs of the cORR. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The plot shows data for all dose groups. Horizontal boxplots below the plot show the exposure distribution for the 6.4 mg/kg dose group. The *P* value is for the slope of the logistic regression fit.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx006 Figure 4-4.

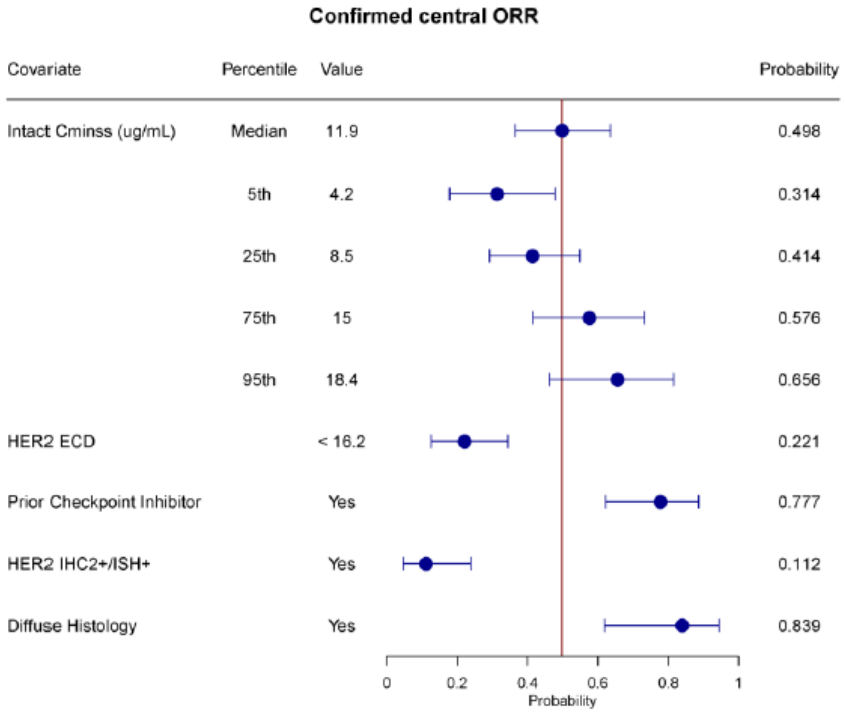
Figure 3.14: Relationship Between Exposure and Confirmed Objective Response Rate: Study U205



CI = confidence interval; conc = concentration; N = number of subjects; ORR = objective response rate.
Note: Yes and No refer to if subjects experienced or did not experience an objective response. Subjects are stratified into exposure quartiles. Red points are ORR per exposure quartile plotted at the mean exposure per quartile. Vertical red bars are 90% CIs of the ORR. Gray band represents the 5th to 95th percentile CI of a linear logistic regression fit. The *P* value is the significance level for the slope of the logistic fit using a z-test. Horizontal boxplots below the plot show the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-2.

A Forest plot of the covariate effect on cORR as predicted from the E-R relationships is shown in **Figure 3.15.**

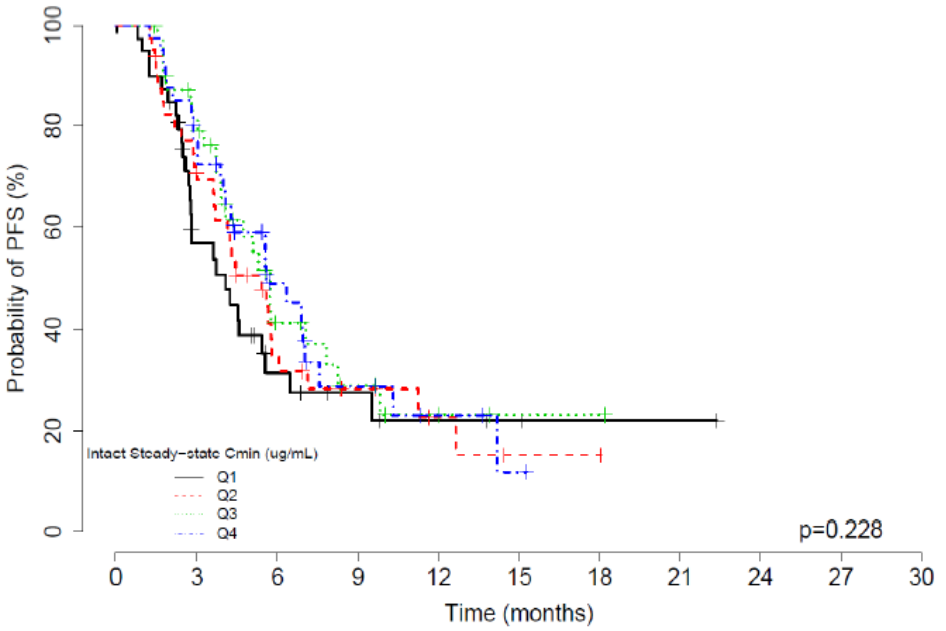
Figure 3.15: Forest Plot of Confirmed Objective Response Rate: Study J101 and Study J202



Cmin,ss = steady-state minimum concentration; HER2ECD = extracellular domain of HER2; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Intact = intact T-DXd; ISH = in situ hybridization; ORR = objective response rate.
Note: Dot and horizontal line corresponds to the probability estimate and 90% confidence interval, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a GC subject with HER2 IHC 3+, HER2ECD ≥16.2 ng/mL, intestinal histology, no prior checkpoint inhibitor use, and the indicated median exposure.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx006 Figure 4-5

There were no statistical trends for PFS (P = 0.725; **Figure 3.17**) or DoR (P = 0.164; **Figure 3.19**) with increasing T-DXd exposures over the range of exposures for the 6.4 mg/kg Q3W dose. In the integrated analysis of Studies J101 and J202, PFS was longer in subjects with higher T-DXd Cmin,ss, but there was no statistically significant E-R relationship (P = 0.228; **Figure 3.16**).

Figure 3.16: Kaplan-Meier Curve for Progression-Free Survival Stratified by Interquartile Ranges of Exposure: Study J101 and Study J202



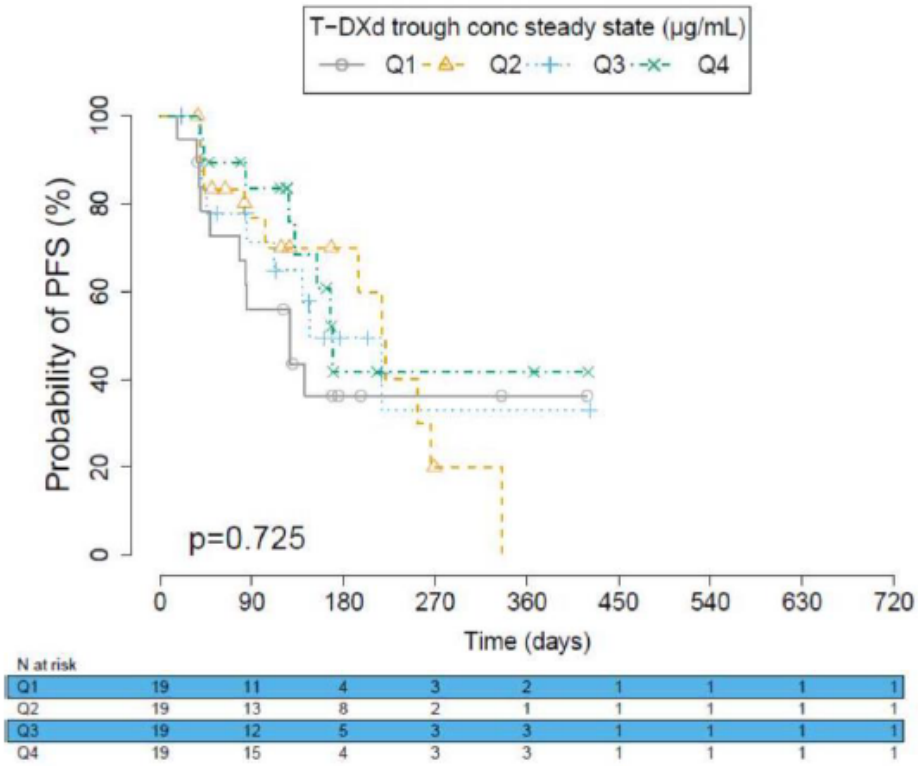
No. at Risk

Q1	40	22	9	6	4	3	2	2	1	1	1
Q2	40	28	12	7	4	2	2	1	1	1	1
Q3	40	31	12	7	4	2	2	1	1	1	1
Q4	40	33	14	7	4	2	1	1	1	1	1

Cmin = minimum concentration; Intact = intact T-DXd; PFS = progression-free survival; Q = quartile.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx006 Figure 4-7

In the analysis of Study U205, there were no statistically significant relationships between the probability of PFS and increasing T-DXd Cmin,ss (P = 0.725; **Figure 3.17**).

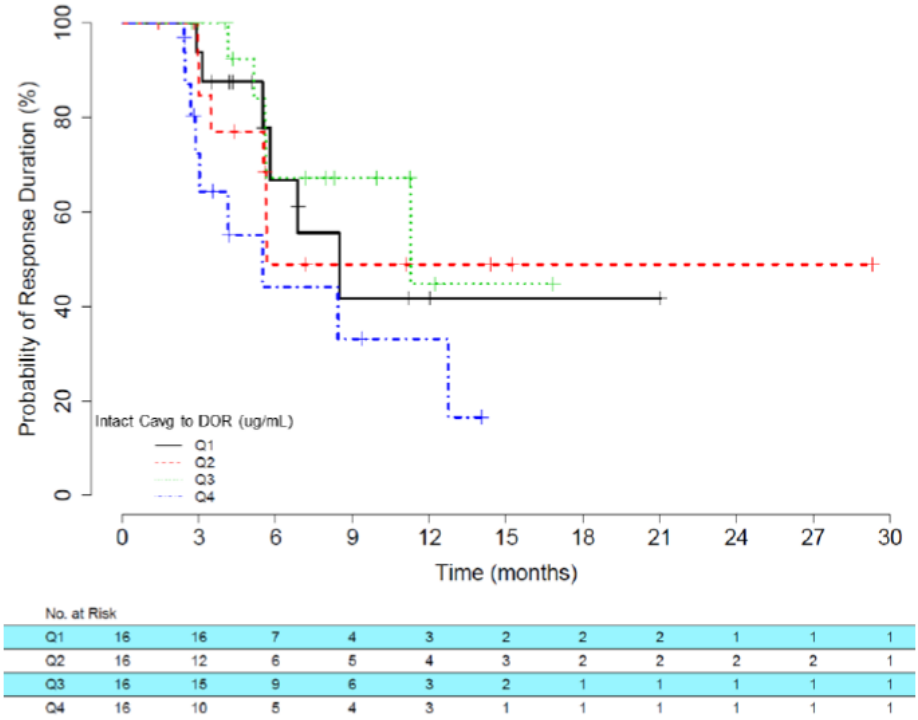
Figure 3.17: Kaplan-Meier Curve for Progression-Free Survival Stratified by Interquartile Ranges of Exposure: Study U205



conc = concentration; N = number of subjects; PFS = progression-free survival; Q = quartile.
Note: *P* value is significance level of log-rank test of the survival distributions by quartile.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-4.

In the integrated analysis of Studies J101 and J202, there was no E-R relationship with any exposure indicator and DoR. In the analysis of Study U205, there was no statistically significant relationship between DoR and increasing exposures of T-DXd (P = 0.164). **Figure 3.18** and **Figure 3.19** show an exploratory Kaplan-Meier curve for DoR stratified by the interquartile ranges of Cavg of T-DXd for the integrated analysis of Studies J101 and J202 and the analysis of Study U205, respectively.

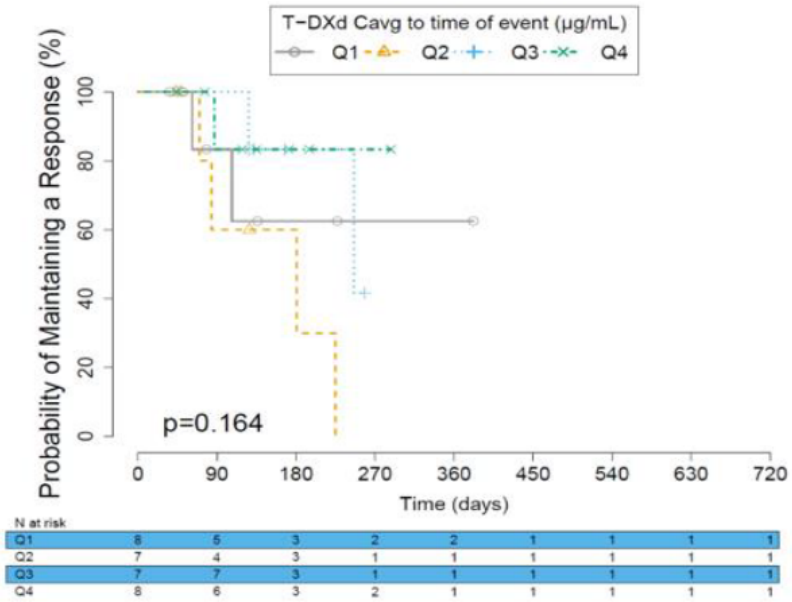
Figure 3.18: Kaplan-Meier Curve for Duration of Response Stratified by Interquartile Ranges of Exposure: Study J101 and Study J202



No. at Risk											
Q1	16	16	7	4	3	2	2	2	1	1	1
Q2	16	12	6	5	4	3	2	2	2	2	1
Q3	16	15	9	6	3	2	1	1	1	1	1
Q4	16	10	5	4	3	1	1	1	1	1	1

Cavg = average serum concentration; DoR = duration of response; Intact = intact T-DXd; Q = quartile; T-DXd = trastuzumab deruxtecan.
Note: No *P* value is noted because there was no exposure-DoR relationship.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx006 Figure 4-6.

Figure 3.19: Kaplan-Meier Curve for Duration of Response Stratified by Interquartile Ranges of Exposure: Study U205



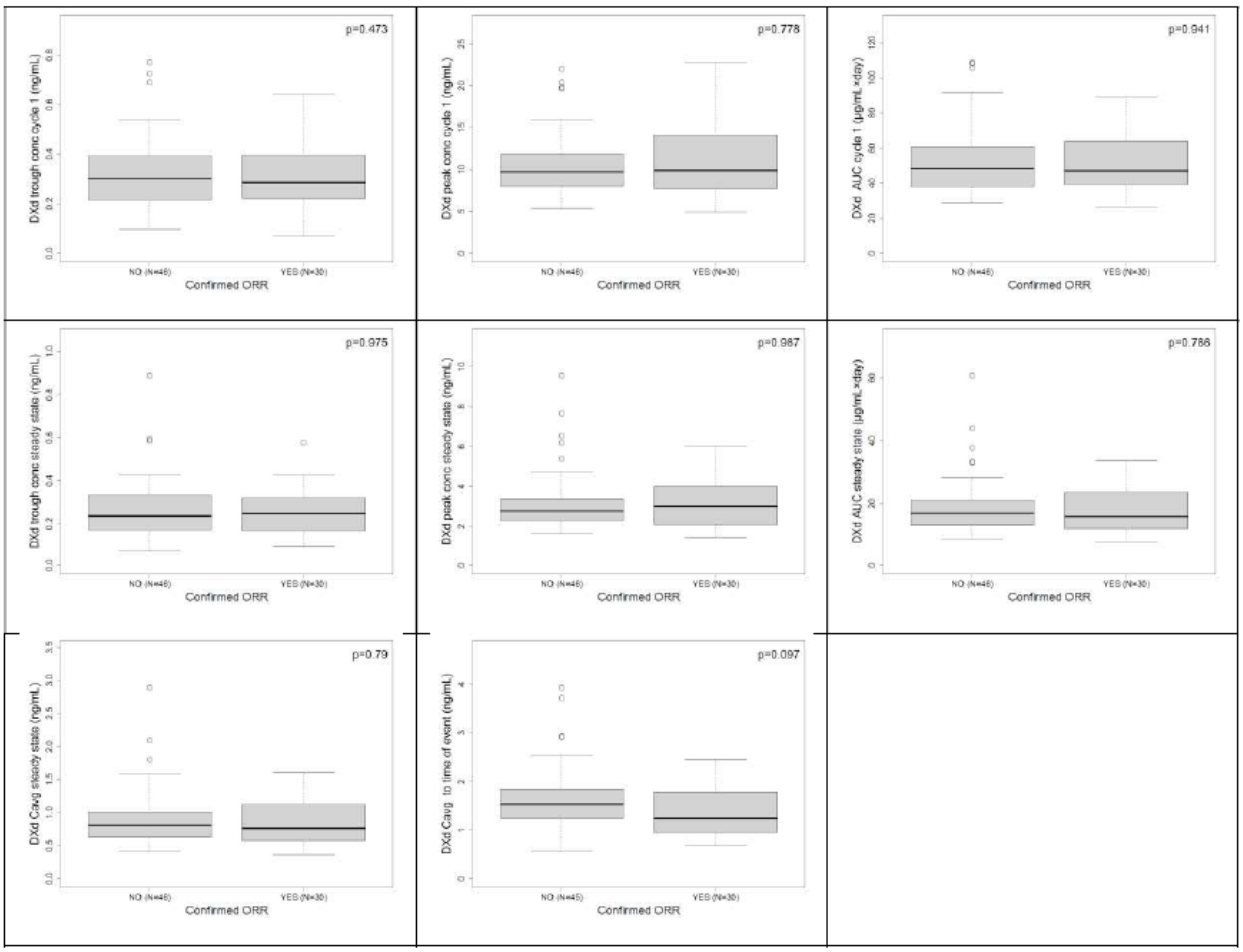
N at risk										
Q1	8	5	3	2	2	1	1	1	1	
Q2	7	4	3	1	1	1	1	1	1	
Q3	7	7	3	1	1	1	1	1	1	
Q4	8	6	3	2	1	1	1	1	1	

Cavg = average serum concentration; DoR = duration of response; N = number of subjects; Q = quartile.
Note: *P* value is significance level of log-rank test of the survival distributions by quartile.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-3.

DXd exposure metrics

In the exposure-response analysis report, the following figure is presented, showing the distribution of cORR (yes/no) in relation to different DXd exposure metrics (**Figure 10-2**).

Figure 10-2: Exploratory exposure boxplots stratified by ORR



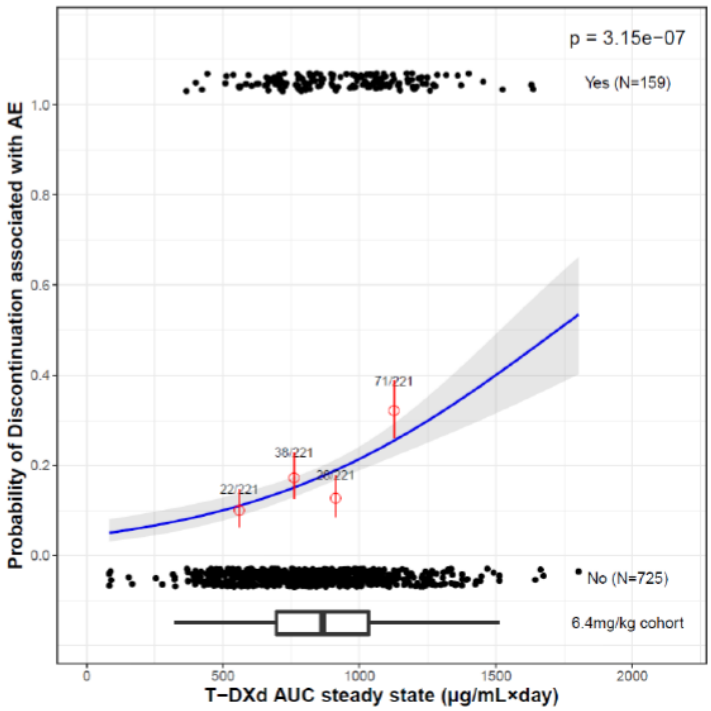
Abbreviations: AUC = area under the concentration-time curve; Cavg = average concentration; ORR = confirmed objective response by independent central review.
Note: Thick horizontal line represents the median, box ends show the upper and lower quartiles of the data, whiskers show the range of points within 1.5 times the interquartile range, and points are data that lie outside the whiskers (circles). The p-value is for a Kruskal-Wallis test of difference between distributions.
Source: ee.analysis.r

Exposure-safety analysis

An integrated dataset across five clinical studies (J101, J102, A103, A104, and U201) for the initial BC application was updated with inclusion of data from Study J202 and then further updated with inclusion of data from Study U205. The most recently updated report included 884 subjects with GC, BC, and other tumors for the E-R analysis for key safety endpoints. The safety endpoints and the exposure metrics evaluated in the current analysis are consistent with those evaluated in the analysis updated with data from Study J202 and the analysis included in the initial BC application. The analysis set was the same as in the PopPK analysis.

The exposure indicators investigated were Cavg in addition to the AUC, Cmax, and Cmin of T-DXd and DXd for Cycle 1 and at steady state.

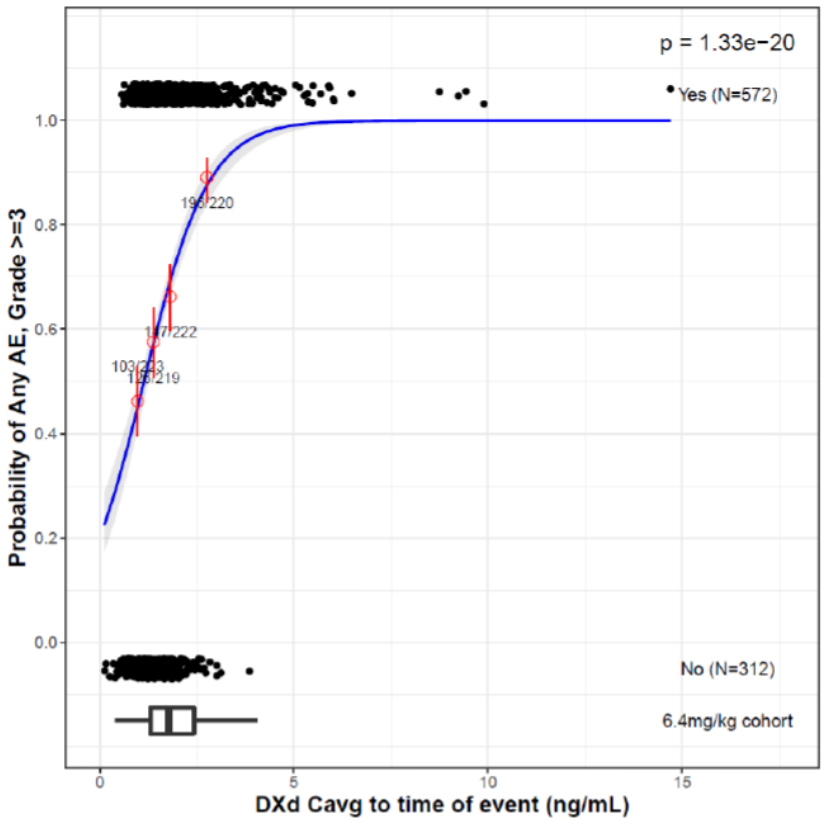
Figure 3.20: Relationship Between Exposure and Adverse Events Associated with Discontinuation of Study Drug



AE = adverse event; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience study drug discontinuation associated with AEs. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range. The p-value is for the slope of the logistic regression fit.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-6.

Grade ≥3 Adverse Events

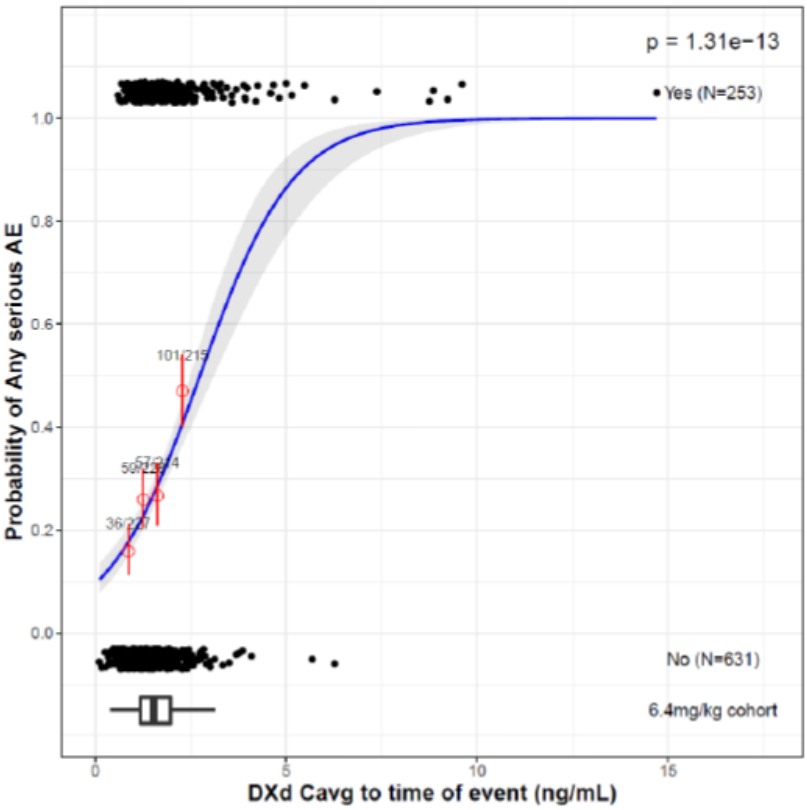
Figure 3.24: Relationship Between Exposure and Grade ≥3 Adverse Events



AE = adverse event; Cavg = average serum concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience Grade ≥3 AEs. Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the mean exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 6.4 mg/kg dose group the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-17.

Serious Adverse Events

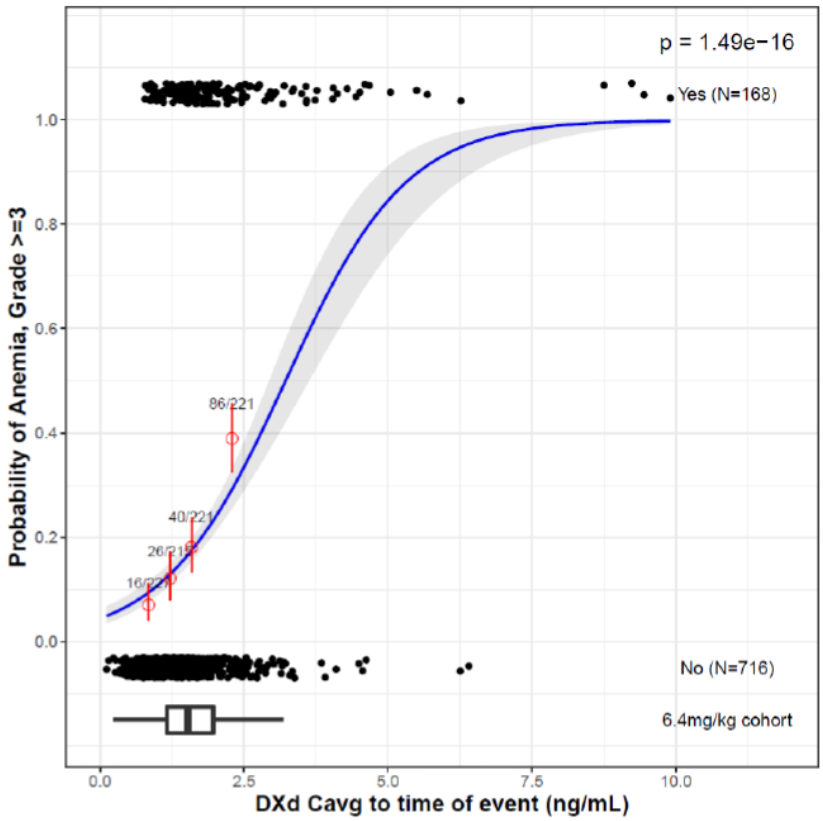
Figure 3.26: Relationship Between Exposure and Serious Adverse Events



AE = adverse event; Cavg = average serum concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience serious AEs. Subjects are stratified into exposure quartiles. Red points are mean AE rates per exposure quartile plotted at the mean exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The *P* value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-22.

Anemia

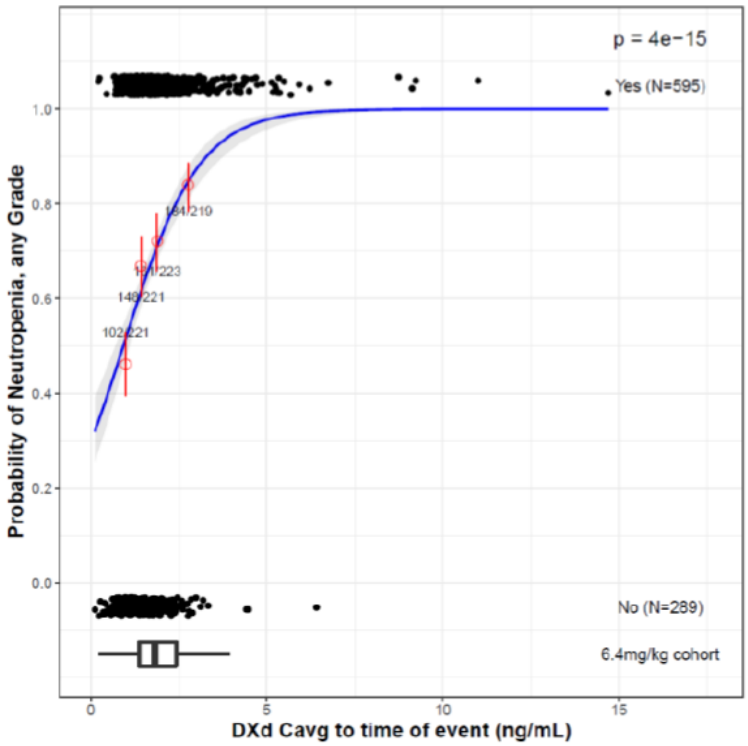
Figure 3.28: Relationship Between Exposure and Anemia (Grade ≥3)



AE = adverse event; Cavg = average serum concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience anemia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are mean AE rates per exposure quartile plotted at the mean exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-27.

Neutropenia

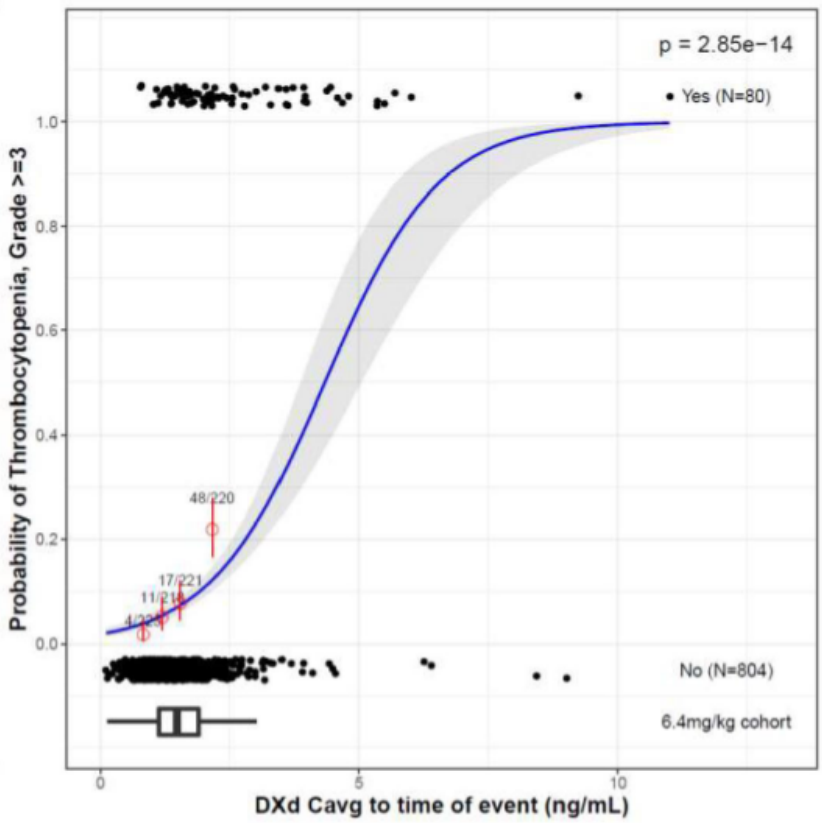
Figure 3.30: Relationship Between Exposure and Neutrophil Count Decreased (Any Grade)



AE = adverse event; Cavg = average serum concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience neutropenia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below the graph shows the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-32.

Thrombocytopenia

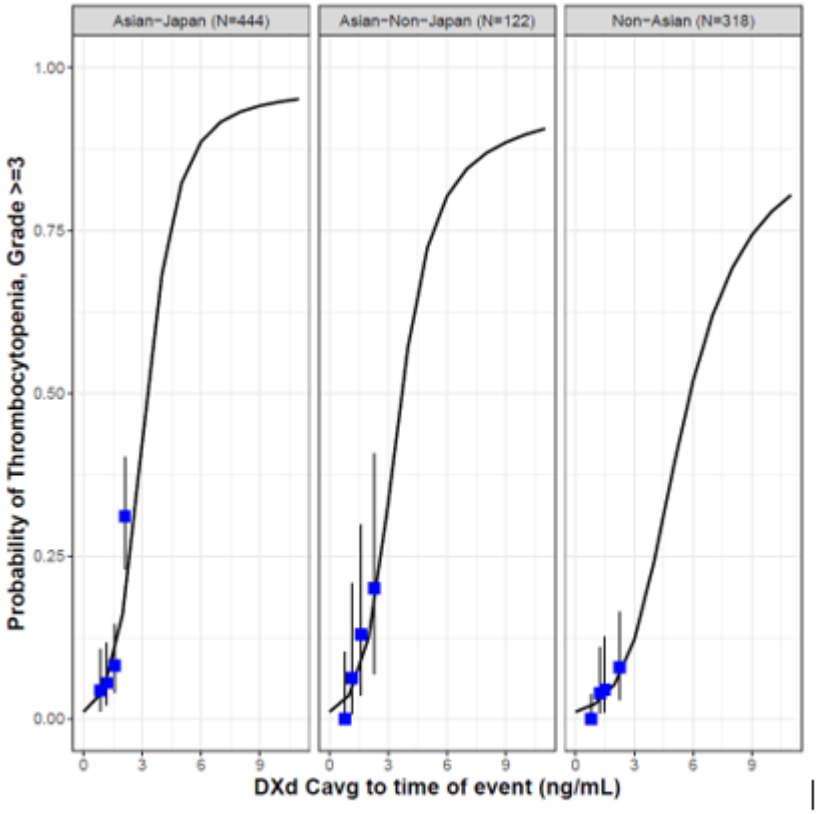
Figure 3.33: Relationship Between Exposure and Platelet Count Decreased (Grade ≥3)



AE = adverse event; Cavg = average serum concentration; CI = confidence interval; N = number of subjects.
Note: Plot shows probability of AE vs. exposure. Yes and No refer to if subjects experienced or did not experience thrombocytopenia (laboratory-based). Subjects are stratified into exposure quartiles. Red points are AE rates per exposure quartile plotted at the median exposure of the quartile. Vertical red bars are 90% CIs of the AE rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 6.4 mg/kg dose group; the box shows the interquartile range and whiskers show points within 1.5 times the interquartile range.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-37.

Figure 3.33 in the CTD is shown below (Figure 6). The risk for thrombocytopenia at 3 ng/mL in the Asian-Non-Japan group is approximately 25% (center panel). However, in the Japan-Asian group (left panel), the risk for Grade ≥3 thrombocytopenia at 3 ng/mL is approximately 50% (left panel), which is in line with the results as shown in the forest plot. Across all groups, the overall risk for Grade ≥3 thrombocytopenia is approximately 20%.

Figure 6: Probability of thrombocytopenia (Figure 3.33 in original report)

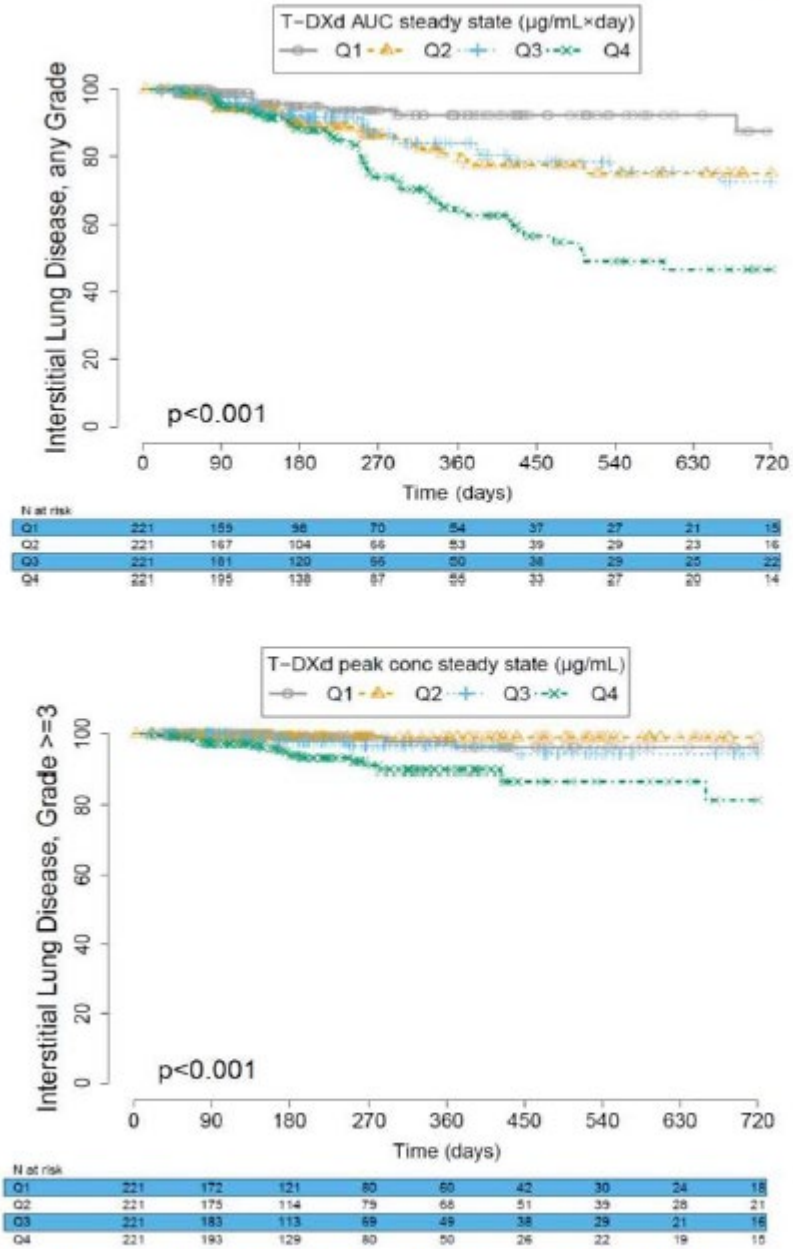


Abbreviations: Cavg = average concentration N = number of subjects.
Note: The solid line is the model-predicted curve per population.
Source: DS8201-PMx009 Figure 5-38[1]

Interstitial lung disease

Figure 3.37 shows Kaplan-Meier curves of the time to ILD (any grade and Grade >3) for each interquartile range based on an exposure metrics (AUC,ss and Cmax,ss of T-DXd). There was a statistically significant relationship between the exposure to T-DXd (AUCss) and the incidence rate of ILD (any grade and Grade >3) ($P < 0.001$); the incidence rate of ILD (any grade) tended to be higher in subjects with higher exposure.

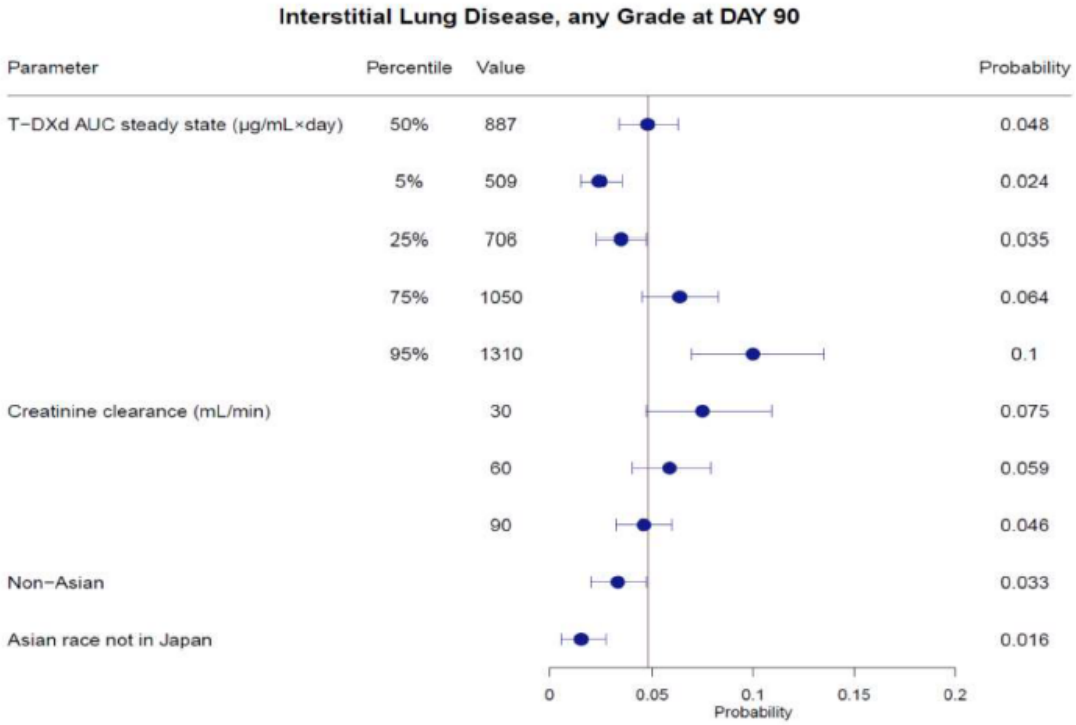
Figure 3.37: Kaplan-Meier Curves for Interstitial Lung Disease (Any Grade and Grade ≥3) Stratified by Interquartile Ranges of Exposure



AE = adverse event; ILD = interstitial lung disease; N = number of subjects; Q = exposure quartile.
Note: P-value in the top plot is for log-rank test.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figures 5-48 and 5-49.

On the basis of the result of Cox regression, race-country and baseline creatinine clearance were selected as statistically significant covariates for ILD (any grade). The effect of the exposure indicators and covariates based on the final model on the incidence rate was evaluated by forest plots at Day 90 (**Figure 3.38**).

Figure 3.38: Forest Plot of Interstitial Lung Disease (Any Grade) at Day 90



AUC = area under the concentration-time curve; ILD = interstitial lung disease.
Note: Dot and horizontal line corresponds to the probability estimate and 90% confidence interval, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical subject (Asian from Japan and median creatinine clearance of 85 mL/min) and the indicated median T-DXd exposure for 6.4 mg/kg T-DXd in the overall population including all tumor types. Creatinine clearance values correspond to boundaries for normal (90 mL/min), mild (60 mL/min), and moderate (30 mL/min) renal impairment.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Figure 5-54.

The **model-predicted E-R relationships for safety events** were used to estimate the probability of each safety variable for 5.4 mg/kg doses in subjects with BC and 6.4 mg/kg doses in subjects with GC (**Table 3.7**). The incidence of these safety endpoints at the 6.4 mg/kg dose in subjects with GC was estimated to be generally comparable to the 5.4 mg/kg dose in subjects with BC with the exception of Grade ≥3 TEAE, SAEs, anemia Grade ≥3, and neutropenia Grade ≥3, which were predicted to be >10% higher at the 6.4 mg/kg dose in subjects with GC.

Table 3.7: Model-Predicted Exposure-Response Relationships for Safety Parameters

Endpoint	Model-predicted Rate (%) Estimate (90% CI)	
	BC 5.4 mg/kg Q3W	GC 6.4 mg/kg Q3W
Study drug discontinuation associated with TEAE	18.7 [13.7, 25]	14 [9.7, 19.4]
Dose reduction associated with TEAE	23.2 [18.9, 28.4]	30.0 [22.8, 38.5]
Grade ≥3 TEAE	58.9 [54.3, 63.7]	69.4 [63.3, 74.7]
SAE	23.3 [18.5, 28.9]	35.2 [28.5, 41.9]
Anemia (laboratory-based), Grade ≥3	12.5 [8.9, 17.0]	27.5 [21.5, 34.4]
Neutropenia (laboratory-based), any grade	67.2 [60.8, 73.0]	64 [56.4, 70.9]
Neutropenia (laboratory-based), Grade ≥3	20.6 [16.2, 25.7]	31.7 [26.2, 38.2]
Thrombocytopenia (laboratory-based), any grade	60.4 [54.7, 65.3]	67.5 [62.1, 72.8]
Thrombocytopenia (laboratory-based), Grade ≥3	6.3 [4.3, 9.2]	10.5 [6.9, 14.8]
LVEF decreased (ECG-based), Grade ≥2	16.3 [12.7, 20.7]	9.7 [6.5, 14.3]

BC = breast cancer; CI = confidence interval; ECG = electrocardiogram; GC = gastric cancer; LVEF = left ventricular ejection fraction; Q3W = every 3 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Modeled safety rates include all subjects with BC and GC. Exposures are dose-normalized to 5.4 mg/kg in BC and to 6.4 mg/kg in GC. The number of subjects with BC is 512. The number of subjects with GC is 293.
Source: Module 5.3.3.5 Exposure-Response Analysis Report PMx009 Table 5-71.

Table 7 shows AEs for subjects in Study U205 who received 6.4 mg/kg, stratified by the 25th, 25th to 75th, and 75th percentile body weight (<65.5, 65.5 to <85.5, ≥85.5, respectively). For all safety endpoints, except thrombocytopenia, the event rates are comparable across the categories of body weight.

Table 7: Adverse events for subjects in Study U205 receiving 6.4 mg/kg, stratified by body weight

AE[a]	<65.5 kg (25th percentile)	65.5 kg to <85.5 kg (25th to 75th percentile)	≥85.5 kg (75th percentile)
Any AE, Grade ≥3	10/19 (52.6%)	17/38 (44.7%)	10/19 (52.6%)
Any serious AE	9/19 (47.4%)	11/38 (28.9%)	7/19 (36.8%)
Discontinuation associated with AE	2/19 (10.5%)	7/38 (18.4%)	3/19 (15.8%)
Dose reduction associated with AE	4/19 (21.1%)	9/38 (23.7%)	5/19 (26.3%)
Dose interruption associated with AE	3/19 (15.8%)	8/38 (21.1%)	5/19 (26.3%)
Lab-Based Anemia, any grade	17/19 (89.5%)	37/38 (97.4%)	17/19 (89.5%)
Lab-Based Anemia, Grade ≥3	3/19 (15.8%)	2/38 (5.3%)	2/19 (10.5%)
Lab-Based Neutropenia, any grade	8/19 (42.1%)	20/38 (52.6%)	11/19 (57.9%)
Lab-Based Neutropenia, Grade ≥3	2/19 (10.5%)	5/38 (13.2%)	1/19 (5.3%)

AE[a]	<65.5 kg (25th percentile)	65.5 kg to <85.5 kg (25th to 75th percentile)	≥85.5 kg (75th percentile)
Lab-Based Thrombocytopenia, any grade	8/19 (42.1%)	16/38 (42.1%)	15/19 (78.9%)
Lab-Based Thrombocytopenia, Grade ≥3	0/19 (0.0%)	0/38 (0.0%)	1/19 (5.3%)
LVEF decrease, any grade	0/19 (0.0%)	0/38 (0.0%)	0/19 (0.0%)
LVEF decrease (ECHO), Grade ≥2	2/19 (10.5%)	0/38 (0.0%)	1/19 (5.3%)
Interstitial Lung Disease, any grade	0/19 (0.0%)	6/38 (15.8%)	1/19 (5.3%)
Interstitial Lung Disease, Grade ≥3	0/19 (0.0%)	1/38 (2.6%)	0/19 (0.0%)

Abbreviations: AE = adverse event; ECHO = echocardiogram; LVEF = left ventricular ejection fraction.
Note: Anemia, neutropenia, and thrombocytopenia AEs are based on laboratory measurements.
[a] The dataset of AEs listed comes from the DSI ER Report (DS8201-PMx009) .
Source: responses-v3.r

2.3.4. Discussion on clinical pharmacology

The pharmacology package included in the current application includes data from two additional Phase 2 studies in subjects with HER2-positive advanced GC or gastroesophageal junction (GEJ) adenocarcinoma (Studies J202 and U205).

No new bioanalytical methods were applied for detection of the three moieties from T-DXd or ADA in Study J202 and U205. A new NAb assay was developed. No NAbs were detected in any samples.

The PK for T-DXd was described by a two-compartment model with IV infusion input and linear elimination which also served as the input to the released drug model DXd. The DXd formation was described by a one-compartment model with a two-component time-varying release rate (Krel) from T-DXd. Krel was modelled to decrease as a constant reduction after Cycle 1 (FPC1) and as gradual decline per cycle (FPC2). The PK data for Western GC patients is considered rather limited and the Pop PK model could not adequately describe this population.

A bridging analysis between Asian and Western population was conducted using a virtual second-line or later HER2-positive gastric cancer Western population by use of real-world data from gastric cancer patients in the US treated with trastuzumab deruxtecan. The PK/efficacy and safety predictions were largely comparable to the data achieved in Study U205 (US/European patients with HER2 gastric cancer, n=79). The virtual RWD analysis in Western subjects is not considered sufficiently reliable nor representative of an entire population to bridge to the Asian population.

The ADME characteristics were described in the original BC marketing application. Based on the efficacy and safety results observed when comparing the 5.4 and 6.4 mg/kg doses, the selected dose of 6.4 mg/kg Q3W in GC patients is considered acceptable. In section 5.2 of the SmPC, the value of DXd clearance has been changed from 19.2 L/h to 18.5 L/h due to new data included in the model (see SmPC for new issue). "The clearance of DXd based on population pharmacokinetic analysis was estimated to be 18.6 L/h and 16.7 L/h for patients with metastatic HER2-positive breast cancer and locally advanced or metastatic gastric or GEJ adenocarcinoma, respectively."
18.6 L/h x 24 = 446.4 L/day
16.7 L/h x 24 = 400.8 L/day
The exposure parameters in cycle 1 for DXd, the cytotoxic payload of T-DXd, is slightly higher in GC subjects receiving either 5.4 or 6.4 mg/kg compared with BC subjects receiving the same doses.

PopPK analyses show that the covariates of interest, except from an impact of extreme weight (5th and 95th percentile) and high AST, do not affect the PK of DXd compared with the reference subject. None of the estimated values are considered to have a clinically meaningful impact on DXd PK.

No new clinical DDI studies have been conducted since the BC application.

Across all studies, the rate of treatment-emergent ADAs was low (1.8% of the subjects (16/892)). No treatment-emergent Nab-positive samples were found.

Exposure-response analyses were performed using data from Study U205. The exposure-response models were linear logistic regression models, except for interstitial lung disease endpoints, DoR and PFS, which were linear Cox regression models. No relation to exposure was found for the efficacy endpoints. No covariates were tested on the intercept and slope terms for ORR or on the slope term for PFS and DoR. In general, race-country had impact on the slope term for most safety endpoints.

Exposure of trastuzumab deruxtecan and DXd in the first cycle were 16% and 9% higher in subjects with GC in study U205 compared to subjects in study J202. This is likely related to the higher bodyweight of subjects in study U205 vs J202, 75 kg vs 57 kg, respectively, and consequently higher doses. Based on the currently available data, capping the dose for subjects with higher body weight is not necessary. For subjects in study U205, there was no clear correlation between body-weight and AEs except for thrombocytopenia and to lesser extent for neutropenia any grade, but this did not result in more discontinuations due to AEs in subjects in the 75th percentile body-weight compared to subjects with a lower body-weight.

The flat exposure-efficacy relationship while exposure-safety relationships were generally steeper with higher exposures of trastuzumab deruxtecan and/or DXd were for the breast cancer indication reason to select the 5.4 mg/kg Q3W over the 6.4 mg/kg Q3W. It could be argued that the lower dose of 5.4 mg/kg Q3W might also be preferred for the treatment of GC because of the steep exposure-safety relationship and the lower AEs incidence observed for 5.4 mg/kg vs 6.4 mg/kg in breast cancer. However, there is insufficient data for trastuzumab deruxtecan treatment of GC other than with 6.4 mg/kg Q3W. Hence, the benefit-risk assessment for trastuzumab deruxtecan for treatment of HER2-positive advanced GC should be based on 6.4 mg/kg dose (see also B/R). It is, however, unknown if the optimal dose has been selected.

2.3.5. Conclusions on clinical pharmacology

The pharmacology package included in the current application includes data from two additional Phase 2 studies in the intended patient population and is considered adequate to support the extension of indication as 2L monotherapy (T-DXd dose 6.4 mg/kg) for treatment of patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma.

2.4. Clinical efficacy

The sought new therapeutic indication of Enhertu for advanced HER2+ GC/GEJC in the 2L+ setting (after a prior trastuzumab-based regimen) is based on efficacy data from the pivotal single-arm phase II trial **DS8201-A-U205 (DESTINY-Gastric02)**, which took place in Europe and the USA.

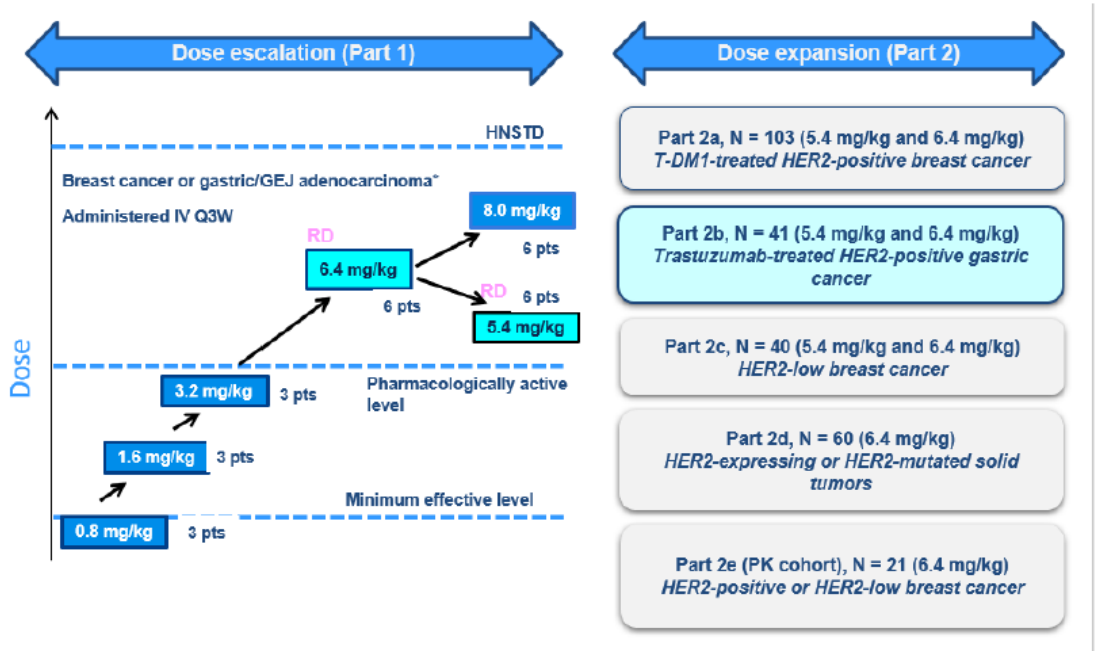
Results from phase II study **DS8201-A-J202 (DESTINY-Gastric01)**, a randomised controlled trial in the third line setting in patients from Japan and South Korea, are considered supportive.

2.4.1. Dose response studies

Study J101:

A completed phase 1, multicenter, 2-part (dose escalation followed by dose expansion), open-label, nonrandomized, multiple-dose first-in-human (FIH) study conducted in the US and Japan in several types of advanced solid malignant tumours that contributed 44 subjects with pre-treated metastatic HER2-positive gastric or GEJ adenocarcinoma who had received prior trastuzumab and were treated at 1 of 2 doses in the study: the 6.4 mg/kg target dose (N = 25) or a 5.4 mg/kg dose (N = 19).

Figure 4.3: Study J101 Design



Study D967LC00001 (DESTINY-Gastric03):

An on-going Phase 1b/2 open-label 2-part dose escalation (Part 1) and dose expansion (Part 2) study, to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and antitumor activity of T-DXd 6.4 mg/kg monotherapy and combinations in adult subjects with HER2-positive GC. As of 01 Aug 2021, 100 subjects have been enrolled and treated.

The MAH has provided a finished phase 1 dose escalation study followed by dose expansion in 44 subjects. This has been followed by a larger on-going Phase 1b/2 open-label 2-part dose escalation (Part 1) and dose expansion (Part 2) study, to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and antitumor activity of T-DXd 6.4 mg/kg monotherapy and combinations in adult subjects with HER2-positive GC. The Applicant did not submit dose response studies to justify the higher proposed posology in gastric cancer. The Applicant considers the ICH E4 requirements on dose-response evaluation were addressed by the analyses described above and the dose-response relationship in the BC population. However, it is not agreed with the Applicant that ICH E4 requirements are addressed.

Trastuzumab deruxtecan is considered to be a molecularly targeted agent (MTA). In particular in the case of dose-finding for MTAs, the dose-finding strategy should not only focus on safety endpoints, but also on determining an optimal biologically active dose (alternatively termed "optimal biological dose" or "optimum biologic dose") (EMA/CHMP/205/95 Rev.6). This refers to a dose at which optimal biological response according to a predefined effect marker is achieved (e.g. as determined in tumour tissue response) and giving a higher dose does not further improve outcomes (i.e. a dose somewhere at the beginning of the plateau of the dose–response curve). Identification of the beginning of the plateau on the dose response curve is not possible with two studied doses (6.4 mg/kg target dose (N = 25) or a

5.4 mg/kg dose (N = 19). At least three doses in a sufficient number of patients are required to identify the plateau on the dose response curve.

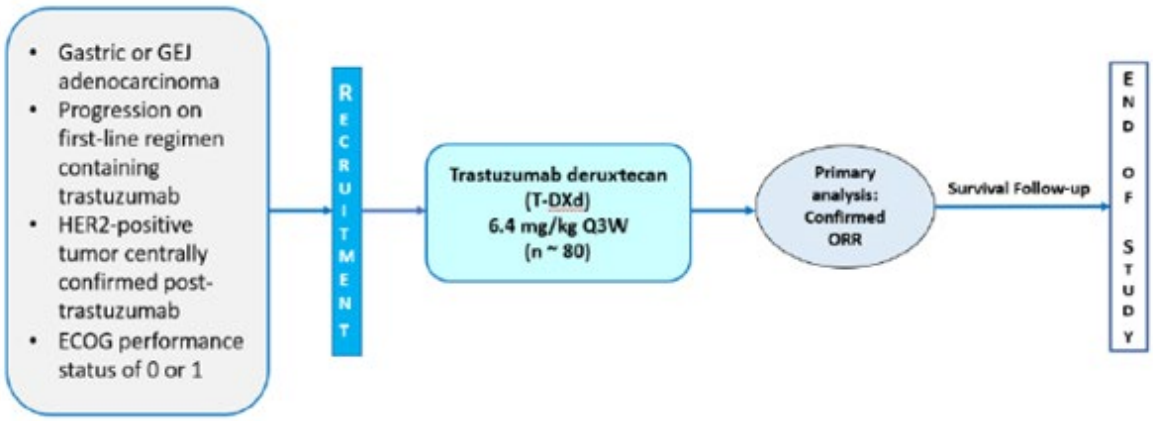
Approval decisions are based on a consideration of the totality of information on a drug. Although dose-response information should be available, depending on the kind and degree of effectiveness shown, imperfections in the database may be acceptable with the expectation that further studies will be carried out after approval (CPMP/ICH/378/95).

2.4.2. Main study

Study U205 (DESTINY-Gastric02)

Study U205 was a Phase 2, multicenter, single-arm, open-label study to evaluate the efficacy and safety of T-DXd (6.4 mg/kg as IV infusion Q3W) in subjects with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed during or after a trastuzumab-containing regimen (2L). The study was conducted in a Western population at 24 sites in the US and Europe. The primary efficacy analysis of confirmed ORR by ICR has been completed.

Figure 1.2: Study U205 Design



ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; ORR = objective response rate; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan, DS 8201a

Methods

Study participants

Inclusion Criteria

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

1. Must have been able to comprehend, sign, and date a main informed consent form (ICF) approved by the IRB or Ethics Committee (EC) before any study-specific procedures or tests were performed.

2. Men or women ≥18 years of age. (Followed local regulatory requirements if the legal age of consent for study participation was >18 years of age.)

3. Had pathologically documented gastric or GEJ cancer that was:

- Unresectable or metastatic, and

- Centrally confirmed HER2-positive disease (IHC 3+ or IHC 2+ and evidence of HER2 amplification by ISH) as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines based on a new tumor biopsy obtained after progression on or after a first-line trastuzumab-containing regimen. If a tumor biopsy was already collected after discontinuation of first-line treatment with a trastuzumab-containing regimen, it was acceptable to consider that biopsy to have been a new biopsy for the purpose of this study, provided that there was sufficient tissue for exploratory biomarker studies.

4. Experienced disease progression (based on RECIST v1.1 criteria) during or after first-line therapy with a trastuzumab-containing regimen. Note: Prior first-line treatment with trastuzumab brand name (Herceptin®) or approved biosimilar was acceptable.

- Note: Prior adjuvant therapy with a trastuzumab-containing regimen could have been counted as a line of therapy if the subject progressed on or within 6 months of completing adjuvant therapy.

5. Had at least 1 measurable lesion per RECIST v1.1 as confirmed by the investigator review.

6. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

7. Left ventricular ejection fraction (LVEF) ≥50% within 28 days before first dose per echocardiogram (ECHO)/multigated acquisition (MUGA) scan.

8. Had adequate organ function within 14 days before first dose.

9. Had adequate treatment washout period before first dose, defined as:

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

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

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

11. If the subject was a female of childbearing potential, she was to have a negative serum pregnancy test at screening and/or 72 hours before the first dose of study drug, during the treatment period, and for 7 months, following the last dose of study drug.

12. Male subjects were not allowed to freeze or donate sperm starting at screening and throughout the study period, and at least 4 months after the final study drug administration.

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

Exclusion Criteria

Subjects who met any of the following criteria were disqualified from entering the study:

1. Use of anticancer therapy after first-line treatment with a trastuzumab-containing regimen.

2. Uncontrolled or significant cardiovascular disease, including any of the following:
- History of myocardial infarction (MI) within 6 months of first dose
- History of symptomatic congestive heart failure (New York Heart Association Class II to IV)
- Troponin levels consistent with MI as defined according to the manufacturer within 28 days prior to first dose
- QT interval corrected for heart rate (QTc) prolongation to >470 milliseconds (ms) (female) or >450 ms (male) based on Screening triplicate 12-lead electrocardiogram (ECG).

3. History of non-infectious ILD/pneumonitis that required corticosteroid therapy, current ILD/pneumonitis, or suspected ILD/pneumonitis that could not be ruled out by imaging at screening.

4. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of the first dose, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, pleural effusion, etc.), and any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), or prior pneumonectomy.

5. Pleural effusion, ascites, or pericardial effusion that required drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART). (Drainage and CART were not allowed within 2 weeks prior to screening.)

6. Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Baseline brain CT/magnetic resonance imaging (MRI) scan was mandatory.
- Subjects with clinically inactive brain metastases could be included in the study.
- Subjects with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and signing of main ICF (1 week for stereotactic radiotherapy).

7. History of other malignancy(ies), except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥3 years.

8. History of severe hypersensitivity reactions to either the drug substance or inactive ingredients in the drug product.

9. History of severe hypersensitivity reactions to other monoclonal antibodies.

10. Current uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

11. Substance abuse or any other medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that could, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

12. Social, familial, or geographical factors that could interfere with study participation or follow-up.
13. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects were tested for HIV prior to enrollment if required by local regulations or IRB/EC. Subjects positive for hepatitis C virus (HCV) antibody were eligible only if polymerase chain reaction was negative for HCV ribonucleic acid (RNA).

14. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities could be eligible at the discretion of the investigator after consultation with the Sponsor Global Clinical Lead or designee (eg, Grade 2 chemotherapy-induced neuropathy).

15. Prior treatment with an antibody-drug conjugate consisting of an exatecan derivative that was a topoisomerase I inhibitor.

16. Therapeutic radiation therapy (including palliative stereotactic radiation to chest) or major surgery within 4 weeks before study drug treatment or palliative stereotactic radiation therapy within 2 weeks before study drug treatment (refer to exclusion criterion 6 for whole brain radiotherapy and stereotactic radiotherapy for central nervous system metastases).

17. Systemic treatment with anticancer chemotherapy therapy (immunotherapy [non-antibody-based therapy], retinoid therapy) within 3 weeks (≥2 weeks or 5 half-lives, whichever was longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥6 weeks for nitrosureas or mitomycin C).

18. Antibody-based anticancer therapy within 4 weeks of Cycle 1 Day 1.

19. Participation in a therapeutic clinical study within 3 weeks before study treatment (for small-molecule targeted agents, this non-participation period was 2 weeks or 5 half-lives, whichever was longer); or current participation in other investigational procedures.

20. Pregnant or breastfeeding subjects or subjects planning to become pregnant.

21. Subject was an immediate family member of study site personnel or of Sponsor personnel.

Treatments

Treatment cycles were 21 days (±2 days) in length. T-DXd at a body weight-based dose of 6.4 mg/kg was administered as an IV infusion on Day 1 (±2 days) of every 21-day cycle (Q3W).

The first infusion of T-DXd occurred over at least 90 minutes. If there was no infusion related reaction (IRR), the subsequent infusions of T-DXd were over at least 30 minutes. In case of IRR of any severity grade at any time during the first administration of T-DXd, all subsequent infusions occurred over approximately 90 minutes.

T-DXd was continued according to the dosing criteria until the occurrence of any of the events defined as reasons for discontinuation of study drug:

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

If the study drug was delayed more than 28 days from the planned date of administration, the subject was withdrawn from the study drug.

All subjects who were withdrawn from study drug completed protocol-specified withdrawal procedures and follow-up procedures.

Objectives

Primary Objectives

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

Secondary Objectives

The key secondary objective was to evaluate the efficacy of T-DXd on progression-free survival (PFS), based on ICR using RECIST v1.1.

Other secondary objectives were as follows:

- OS
- PFS, based on investigator assessment using RECIST v1.1
- ORR, based on investigator assessment using RECIST v1.1
- Duration of response (DoR), based on ICR and investigator assessment using RECIST v1.1

- To determine the pharmacokinetics (PK) of T-DXd in serum

- To further evaluate the safety of T-DXd based on treatment-emergent adverse events (TEAEs) and anti-drug antibodies (ADAs)

- To evaluate Health Economics and Outcomes Research (HEOR) endpoints based on patient-reported outcomes (PROs)

Exploratory Objectives

- Disease control rate (DCR), based on ICR and investigator assessment

- Time to response, based on both ICR and investigator assessment

- Best percentage change in the sum of diameters of measurable tumors

- Predictive, prognostic, and pharmacodynamic exploratory biomarkers in tissue samples and blood, and their association with disease status and/or response to treatment

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was confirmed ORR, defined as the proportion of subjects who achieved a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), as determined by ICR using RECIST v1.1.

Secondary Efficacy Endpoints

The key secondary efficacy endpoint was PFS, based on ICR, defined as the time from the date of the first dose of study drug to the date of radiographic disease progression per RECIST v1.1 or death due to any cause. Subjects who were alive with no objective documentation of (radiographic) disease progression by the data cut-off (DCO) date for PFS analysis were censored at the date of their last evaluable tumor assessment.

Other secondary efficacy endpoints included the following:

- OS, defined as the time from the date of first dose of study drug to the date of death due to any cause

- PFS, defined as the time from the date of first dose of study drug to the date of disease progression or death due to any cause based on investigator assessment

- ORR, based on investigator assessment

- DoR, defined as the time from the date of first documentation of objective response to the date of the first documentation of disease progression, based on ICR and investigator assessment, or to death due to any cause, using RECIST v1.1

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints included the following:

- DCR, based on both ICR and investigator assessment, defined as the proportion of subjects who achieved a BOR of CR or PR or stable disease (SD)

- Time to response, based on both ICR and investigator assessment

- Best percentage change in the sum of diameters of measurable tumors

Sample size

The target sample size of this study was 79 subjects.

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

Randomisation

U205 study was a single-arm study, randomisation did not take place.

Blinding (masking)

U205 study was an open-label study, and no blinding was performed.

Statistical methods

Analysis Sets

All Screened Analysis Set

The All Screened Analysis Set included all subjects who signed an ICF.

Full Analysis Set

The FAS included all subjects who received at least 1 dose of the study drug.

Response Evaluable Set

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

Table 7.1 Data Sets Analyzed

Analysis Sets	Number (%) of Subjects T-DXd
All Screened Analysis Set [a]	89
Full Analysis Set (FAS)	79 (100.0)
Response Evaluable Set (RES)	78 (98.7)
Safety Analysis Set	79 (100.0)
Pharmacokinetic (PK) Analysis Set	78 (98.7)

T-DXd = trastuzumab deruxtecan
Percentages are calculated based on the number of subjects in the Full Analysis Set as the denominator.
[a] All Screened Analysis Set presents the number of subjects with no percentage since it includes all subjects who signed a main informed consent form.
Data cut-off = 09 Apr 2021
Source: Table 14.1.1.1

Primary endpoint ORR

The estimate of ORR was calculated, along with the corresponding 95% exact CI using the Clopper-Pearson method. The primary efficacy analysis was performed based on the FAS and repeated on the RES.

Key secondary endpoint PFS

Subjects who were alive with no objective documentation of radiographic disease progression as assessed by ICR were censored at the date of their last adequate tumor assessment with additional censoring rules specified in the SAP (Appendix 16.1.4). Kaplan-Meier estimate and survival curve were presented. The median event time and the corresponding 95% CI were provided using the Brookmeyer and Crowley method. PFS rates at fixed time points along with the 95% CIs were estimated. The PFS analysis was performed on the FAS.

Other Secondary Efficacy Analyses

All analyses of secondary efficacy endpoints were performed based on the FAS, unless otherwise specified.

Additional secondary efficacy endpoints were analyzed as follows:

- PFS by investigator assessment was analyzed in the same way as that used for PFS based on ICR. PFS based on ICR and investigator assessment were compared to assess the concordance.

- OS: If a subject was alive at the time of data analysis, OS was censored at the last contact date at which the subject was known to be alive. The Kaplan-Meier estimate and survival curve were presented. The median event time and the corresponding 95% CI were provided using Brookmeyer and Crowley method. The proportion of subjects alive at fixed time points was also estimated.

- ORR based on investigator assessment, measured for responding subjects (PR or CR) only, was analyzed in a similar manner as used for the primary endpoint.

- DoR was measured for responding subjects (PR or CR) only. Subjects who were alive and progression-free at the time of the analyses were censored at the date of the last evaluable tumor assessment. DoR based on ICR and investigator assessment was summarized separately with median event times and its 95% CIs using the Brookmeyer and Crowley method. A swimmer's plot for response over time was provided.

Exploratory Efficacy Analyses

DCR was defined as the proportion of subjects with BOR of CR, PR or SD according to RECIST v1.1. DCR was calculated, along with the corresponding 95% exact CI using Clopper-Pearson method.

Time to response was defined as the time from the date of start of treatment to the date of the first documentation of objective response (CR or PR). Time to response was measured for subjects with confirmed response (confirmed BOR of CR or PR) only. Time to response based on ICR and investigator assessment was summarized separately with median event times and their 95% CIs for the median by using Brookmeyer and Crowley method.

Best percent change from baseline in the sum of diameters of measurable tumours was calculated based on RECIST v1.1 criteria. Best percent change was the percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters. The closest tumor measurement prior to the date of start of treatment was used as the baseline tumor measurement. Best percentage change in tumor size was graphed by using a waterfall plot and spider plot.

The following subgroups were examined for the primary endpoint of confirmed ORR based on ICR, PFS based on ICR, and DoR based on ICR to assess homogeneity of estimate of treatment effect: region, age, sex, ECOG PS, HER2 status, primary tumor location, histological subtype, number of metastatic sites, previous total gastrectomy, prior adjuvant/neoadjuvant therapy, prior nivolumab or pembrolizumab treatment, prior treatment with immuno-checkpoint inhibitor or other immuno-oncology therapy, presence of liver metastasis at baseline, renal impairment at baseline, and hepatic impairment at baseline. In each subgroup, the analysis was carried out using the same type of methodology as described for the corresponding endpoint. Results of the subgroup analyses were presented using descriptive summaries. Some subcategories may have been combined if the sample size within categories was too small (eg, <10 subjects). A forest plot was used to depict the estimated treatment effects for the corresponding endpoints.

Changes in the Planned Analyses

The SAP (Version 1.0, 18 Nov 2020) was amended (Version 2.0 08 April 2021) primarily driven by the updated safety information to be include in the selected adverse events and addition of analysis subgroups. Other minor changes are administrative and/or editorial.

Section Number	Description of Changes
1	Change the protocol version to the most current version (V3.0)
7.2.2.2	Add further analysis details for clarification
7.2.4 and 7.3.4	Subgroup Age (<75/>=75) is added for both efficacy and safety analyses per team request
7.3.2.2	List of selected AEs have been updated to include the most current program level list
7.3.3.1	Definition of major bleeding is updated by safety group
7.3.5	Remove the descriptive summary by visit for coagulation and troponin as the data are collected at limited visit. Listing will be sufficient to present.
7.5	Remove the analyses as the analysis plan and reported will be prepared by Translational Sciences Bioinformatics group
8.2.1	Visit window definition is revised per updated standard
8.2.3.3	Added imputation rule for calculating time since diagnosis in case of partial date of diagnosis.
8.2.3.4	Added imputation rule for partial date of death per updated program level standard
11.1 and 11.2	The grouped terms and list of PTs in AESI have been updated to include the most current program level list

Results

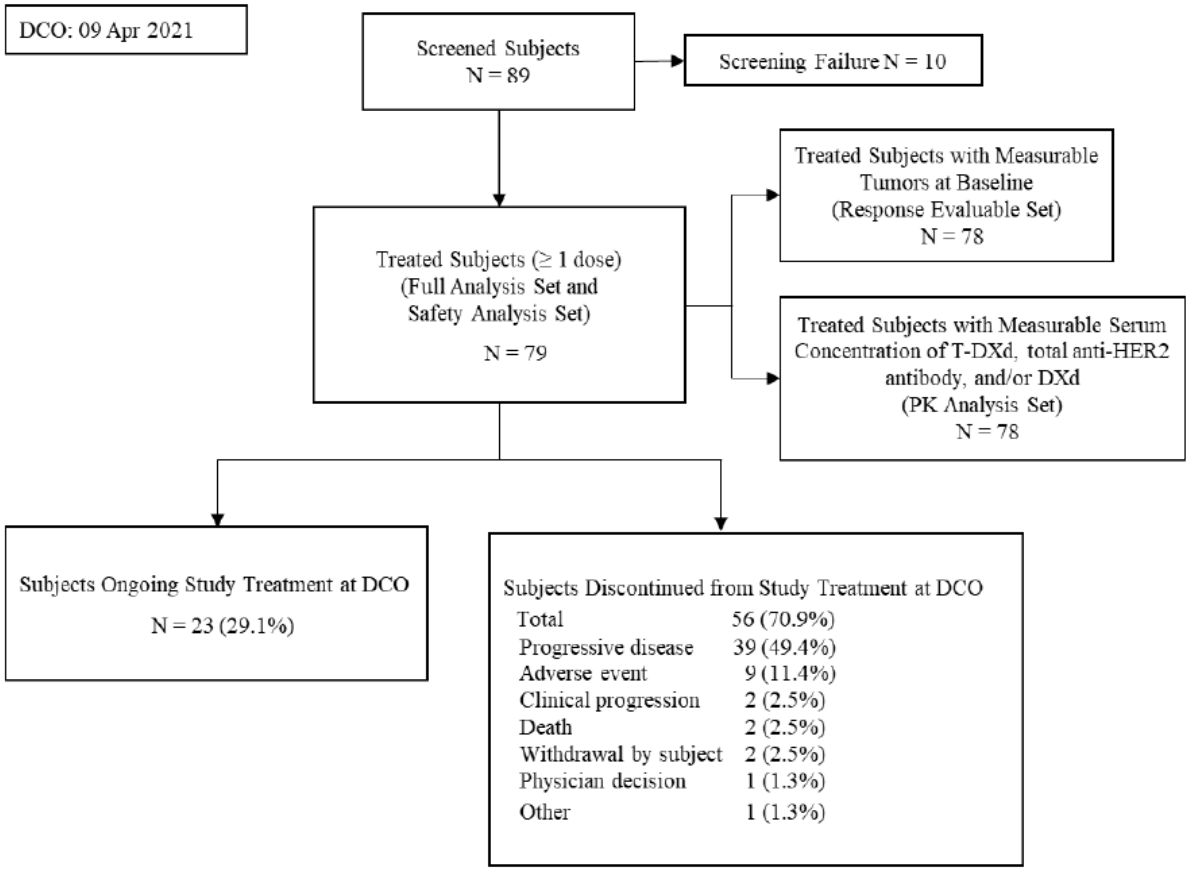
Patient flow

Table 7.2: Subject Disposition (All Screened Analysis Set)

Parameter	Number (%) of Subjects T-DXd (N = 89)
Screened (signed main informed consent form)[a]	89
Failed screening[b]	10 (11.2)
Treated subjects[c]	79 (88.8)
Discontinued from study drug	56 (70.9)
Primary reason for discontinuation from study treatment[c]	
Progressive disease[d]	39 (49.4)
Adverse event	9 (11.4)
Clinical progression[e]	2 (2.5)
Death	2 (2.5)
Withdrawal by subject	2 (2.5)
Physician decision	1 (1.3)
Other[f]	1 (1.3)
Duration of Follow-up (months)[g]	
Mean	6.8
Standard deviation	3.55
Median	5.7
Minimum, maximum	0.7, 15.2

T-DXd = trastuzumab deruxtecan
[a] The All Screened Analysis Set includes all subjects who signed a main informed consent form.
[b] Percentage is based on the number of subjects in the All Screened Analysis Set.
[c] Percentage is based on the number of subjects in the Full Analysis Set (N = 79).
[d] Discontinued based on objective evidence of disease progression.
[e] Discontinued based on clinical manifestations as judged by the investigator.
[f] A drug hold for a treatment-emergent adverse event (preferred term of COVID-19 pneumonia) that exceeded the protocol allowed time limit of 49 days from the last infusion date (Listing 16.2.7.3).
[g] Duration of follow-up (months) was defined as (last visit date – first dosing date +1)/365.25*12.
Data cut-off = 09 Apr 2021
Source: Table 14.1.1.1

Figure 7.1: Subject Disposition



DCO = data cut-off; DXd = released drug; HER2 = human epidermal growth factor receptor 2;
PK = pharmacokinetics; T-DXd = trastuzumab deruxtecan
Data cut-off = 09 Apr 2021
Source: Table 14.1.1.1

Recruitment

Date First Subject Enrolled: Date First Informed Consent Signed: 26 Nov 2019

Date First Subject Dosed: 24 Dec 2019

Data Cut-off Date: 09 Apr 2021/ Updated DCO 08 Nov 2021

A total of 79 subjects were enrolled and treated at 24 study sites in the following countries: US (11 study sites), Spain (4), Italy (3), the United Kingdom (4), and Belgium (2).

Conduct of the study

After the initial release (v1.0, 23 Apr 2019), the study protocol was amended 2 times.

Key changes in the amendments were as follows:

Amendment 1 (v2.0) - 28 Jul 2020, During the Course of the Study Version 2.0 was an interim version that was not sent to the study sites as it was found to contain typographical errors. All changes from v2.0 were included in v3.0.

Amendment 2 (v3.0) - 17 Sep 2020, During the Course of the Study The primary changes made by Amendment 2 were as follows:

- Because of the potential impact of COVID-19 on subject safety, the Sponsor added a dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with T-DXd.

- To evaluate the impact of the global pandemic caused by COVID-19, added an analysis to identify subjects affected by COVID-19, and updated the analysis plan to identify the impact of COVID-19 on safety, efficacy, and study conduct.

- Updated the inclusion criteria related to male and female subjects of reproductive/childbearing potential.

- Removed exclusion criteria related to significant corneal disease and to current treatment with strong cytochrome P450 3A4 and organic anion transporting polypeptide inhibitors.

- Added exclusion criteria related to clinically severe pulmonary compromise within 3 months of first dose and to antibody-based therapy within 4 weeks of Cycle 1 Day 1.

- The description of determining dose based on body weight was updated.

- Updated safety information to align with the latest safety information.

- Included cell-free RNA for biomarker analysis.

- "Health care resource utilization (hospitalization-related records)" was deleted from list of HEOR endpoints.

Updated the EOT Visit to provide the conditions under which EOT assessments were to be performed.

Protocol deviations

A major protocol deviation was defined as a deviation that had an impact on subject safety, could substantially alter risks to subjects, could have an effect on the integrity of study data, could influence the conduct of the study, or could affect the subject's willingness to participate in the study.

Table 7.6: Major Protocol Deviations (Full Analysis Set)

Parameter	Number (%) of Subjects T-DXd (N = 79)
Subjects with any major protocol deviation	39 (49.4)
Visit/procedure required	17 (21.5)
Dosing	12 (15.2)
Enrollment criteria	8 (10.1)
Informed consent	6 (7.6)
Laboratory	3 (3.8)
Safety reporting	3 (3.8)
Non-compliance	1 (1.3)
Visit schedule	1 (1.3)
Other	1 (1.3)

T-DXd = trastuzumab deruxtecan
Percentages are calculated using the number of subjects in the Full Analysis Set.
Subjects may have had protocol deviations in multiple categories.
There were no major protocol deviations reported as COVID-19 related.
Data cut-off = 09 Apr 2021
Source: Table 14.1.1.2 and Listing 16.2.2.3

Baseline data

Table 7.3: Key Demographic Characteristics (Full Analysis Set)

Parameter	T-DXd (N = 79)
Age (years)[a]	
Median	60.7
Minimum, maximum	20.3, 77.8
Age group (years) (n, %)	
<65	46 (58.2)
≥65	33 (41.8)
<75	75 (94.9)
≥75	4 (5.1)
Sex (n, %)	
Male	57 (72.2)
Female	22 (27.8)
Race (n, %)	
White	69 (87.3)
Asian	4 (5.1)
Black or African American	1 (1.3)
Native Hawaiian or Other Pacific Islander	1 (1.3)
Missing	1 (1.3)
Other	3 (3.8)
Weight (kg)	
Median	75.8
Minimum, maximum	41.9, 120.7
Body mass index (kg/m^2) [b]	
Median	25.2
Minimum, maximum	16.5, 35.4
Region/Country of Enrollment (n, %)	
North America	34 (43.0)
US	34 (43.0)
Europe	45 (57.0)
Italy	20 (25.3)
Great Britain	17 (21.5)
Belgium	4 (5.1)
Spain	4 (5.1)

T-DXd = trastuzumab deruxtecan; US = United States.
Percentages are calculated using the number of subjects in the column heading as the denominator.
[a] Age in years is calculated using the informed consent date and the birth date.
[b] Body mass index = weight (kg)/height (m^2).
Data cut-off = 09 Apr 2021
Source: Table 14.1.2.1

Table 7.4: Baseline Disease Characteristics (Full Analysis Set)

Parameter	T-DXd (N = 79)
Time from initial histological diagnosis (months)	
Median	14.2
Minimum, maximum	3.6, 88.5
Cancer type (n, %)	
Gastric	27 (34.2)
Gastro-esophageal junction	52 (65.8)
HER2 status (central laboratory) (n, %)	
IHC 3+	68 (86.1)
IHC 2+	10 (12.7)
ISH positive	10 (12.7)
Not evaluable [a]	1 (1.3)
Histological subtype (n, %)	
Adenocarcinoma	
Unknown	57 (72.2)
Intestinal	19 (24.1)
Diffuse	1 (1.3)
Mixed	1 (1.3)
Other	1 (1.3)
Number of metastatic sites (n, %)	
≥2	74 (93.7)
<2	5 (6.3)
Previous total gastrectomy (n, %)	
No	79 (100.0)
Prior adjuvant/neoadjuvant therapy (n, %)	
No	70 (88.6)
Yes	9 (11.4)
Presence of liver metastasis at baseline (n, %)	
No	29 (36.7)
Yes	50 (63.3)
Renal impairment at baseline (n, %)	
Normal	32 (40.5)
Mild	25 (31.6)
Moderate	8 (10.1)
Other[b]	14 (17.7)
Hepatic impairment at baseline (n, %)	
Normal	65 (82.3)
Mild	13 (16.5)
Missing	1 (1.3)
Baseline ECOG performance status (n, %)	
0	29 (36.7)
1	50 (63.3)
Lines of prior systemic therapy intended for locally advanced or metastatic (n, %)	
0[c]	6 (7.6)
1	73 (92.4)

Table 35: Summary of Histological Subtypes at Baseline of Study U205

Variable	Study U205 HER2-positive GC (DCO = 09 Apr 2021) T-DXd 6.4 mg/kg N = 79
Histology, n (%)	
Adenocarcinoma	78 (98.7)
Diffuse	1 (1.3)
Intestinal	19 (24.1)
Mixed	1 (1.3)
Unknown	57 (72.2)
Other	1 (1.3)

DCO = data cut-off; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; T-DXd = trastuzumab deruxtecan
Source: Module 5.3.5.2 DS8201-A-U205 Table 14.1.3.1

Table 36: Confirmed Overall Response Rate by Histological Subtype in Study U205

Variable	Study U205 HER2-positive GC (DCO = 08 Nov 2021) T-DXd 6.4 mg/kg	
Histological subgroup	Confirmed ORR	95% CI
Diffuse (N = 1)	100	2.5, 100.0
Intestinal (N = 19)	31.6	12.6, 56.6
Others (N = 59)	39.0	26.5, 52.6

Numbers analysed

Table 3.2: Analysis Sets in Study U205

Analysis Sets	Study U205 HER2-positive GC (DCO = 09 Apr 2021) T-DXd 6.4 mg/kg
All Screened Analysis Set	89
FAS	79 (100.0)
RES	78 (98.7)
Excluded from RES	1 (1.3)
No baseline measurable tumor per ICR	1 (1.3)

CSR = clinical study report; DCO = data cut-off; FAS = Full Analysis Set; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; RES = response evaluable set; T-DXd = trastuzumab deruxtecan
All Screened Analysis Set includes a count with no percentage since it includes all subjects who signed an informed consent form.
Percentages are calculated based on the number of subjects in the FAS as the denominator.
The FAS included all subjects who received at least 1 dose of study drug.
Source: Module 5.3.5.2 DS8201-A-U205 CSR Table 14.1.1.1

Outcomes and estimation

Note: Since this is a single arm trial with overall response rate as primary endpoint, results from the most recent data cut-off (08-NOV-2021) have been prioritised in this section.

Primary endpoint – Confirmed ORR by Independent Central Review (ICR), FAS, DCO 08-NOV-2021

Table 43: Updated Confirmed Overall Response Rate in Study U205 (DCO 08 Nov 2021) (Full Analysis Set)

Parameter	Study U205 HER2-positive GC (DCO = 08 Nov 2021) T-DXd 6.4 mg/kg
Full Analysis Set, N	79
Best overall response by ICR (with confirmation of CR or PR), n (%)	
Complete response	4 (5.1)
Partial response	29 (36.7)
Stable disease	31 (39.2)
Progressive disease	13 (16.5)
Not evaluable	2 (2.5)
Confirmed ORR by ICR	
ORR n (%)	33 (41.8)
95% CI	30.8, 53.4

CI = confidence interval; CR = complete response; DCO = data cut-off; GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; ORR = overall response rate; PR = partial response; T-DXd = trastuzumab deruxtecan

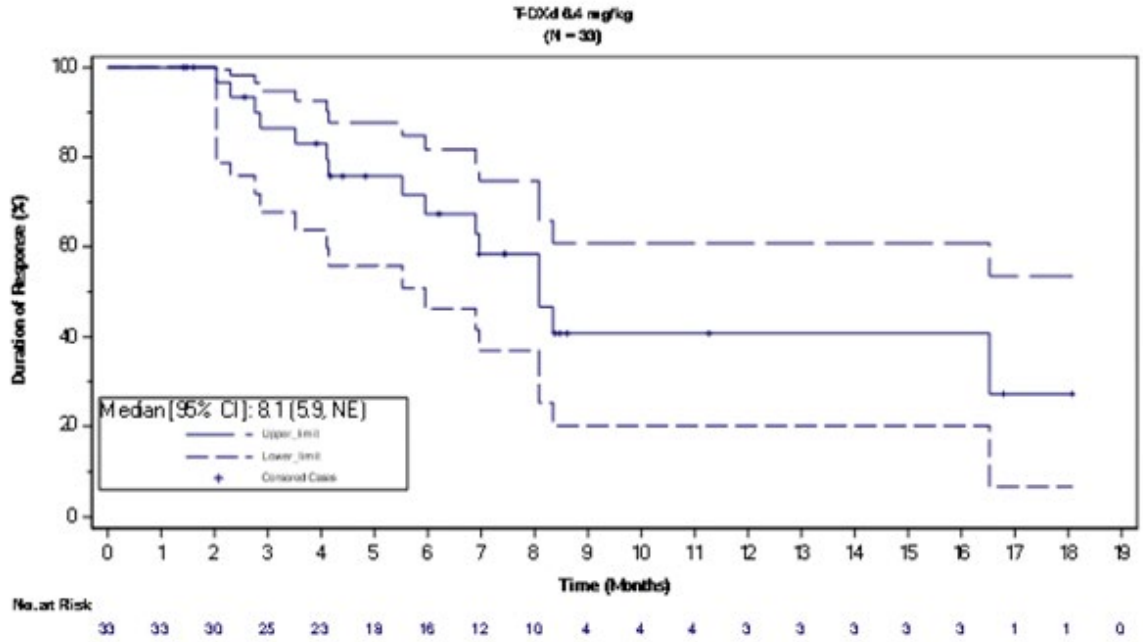
Notes: The 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution.
Percentages were based on the number of subjects in the Full Analysis Set.
Source: Module 5.3.5.2 U205 Ad Hoc Table 2 DCO 08 Nov 2021

Secondary endpoint – Duration of Response (DOR) by ICR in responders, DCO 08-NOV-2021

Table 44: Updated Duration of Confirmed Response in Study U205 (DCO 08 Nov 2021) (Full Analysis Set)

Parameter	Study U205 HER2-positive GC (DCO = 08 Nov 2021) T-DXd 6.4 mg/kg
Full Analysis Set, N	79
Subjects with confirmed CR or PR	33
Subjects with PD (%)	13 (39.4)
Subjects with death (%)	2 (6.1)
Subjects censored (%)	18 (54.5)
Median DoR (months)	8.1
95% CI	5.9, NE

Figure 7: Kaplan-Meier Plot of Duration of Confirmed Response Based on Independent Central Review in Study U205 (DCO 08 Nov 2021)

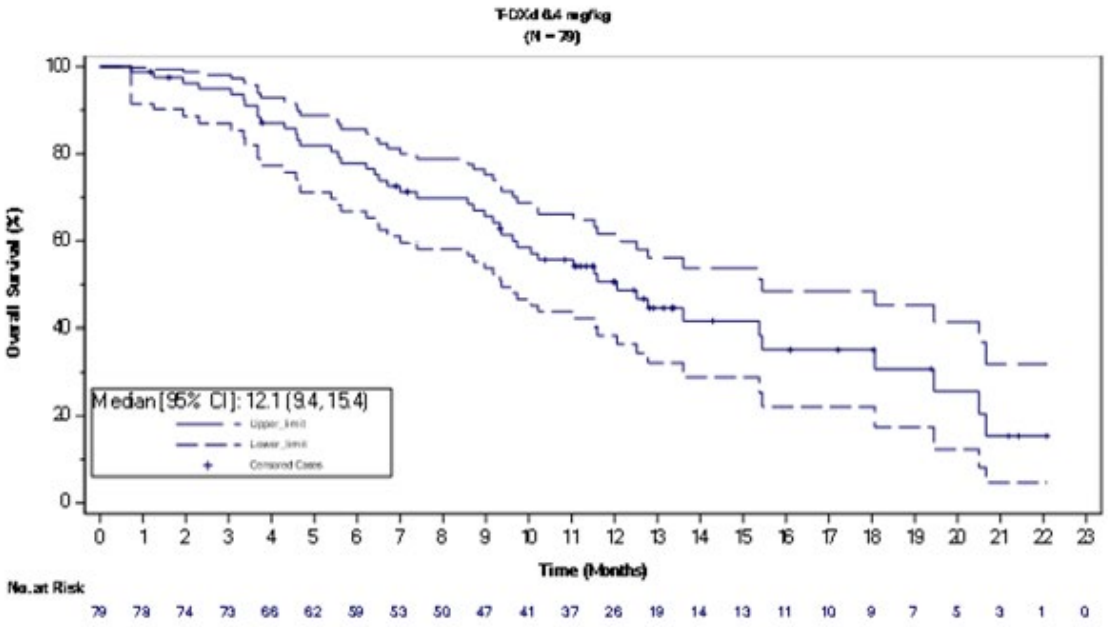


Secondary endpoint – overall survival (OS), FAS, DCO 08-NOV-2021

Table 41: Updated Overall Survival in Study U205 (DCO 08 Nov 2021) (Full Analysis Set)

Parameter	Study U205 HER2-positive GC (DCO = 08 Nov 2021) T-DXd 6.4 mg/kg
Duration of follow-up (months)	
N	79
Median	10.2
Min, max	0.7, 22.1
Overall survival	
OS events, n (%)	46 (58.2)
Censored, n (%)	33 (41.8)
25th percentile (months)	6.5
95% CI	4.6, 9.2
Median OS (months)	12.1
95% CI	9.4, 15.4
OS rate at 6 months (%)	77.8
95% CI	66.8, 85.6
OS rate at 12 months (%)	50.6
95% CI	38.4, 61.5
OS rate at 18 months (%)	35.1
95% CI	22.1, 48.4

Figure 6: Kaplan-Meier Plot of Overall Survival in Study U205 (Update DCO 08 Nov 2021)



Secondary endpoint – PFS by IRC, FAS, DCO 08-NOV-2021

Table 42: Updated Progression-free Survival in Study U205 (DCO 08 Nov 2021) (Full Analysis Set)

Parameter	Study U205 HER2-positive GC (DCO = 08 Nov 2021) T-DXd 6.4 mg/kg
Duration of follow-up (months)	
N	79
Median	10.2
Min, max	0.7, 22.1
PFS	
PFS events, n (%)	51 (64.6)
Censored, n (%)	28 (35.4)
New anticancer therapy	15 (19.0)
Missed 2 consecutive tumor assessments	2 (2.5)
Ongoing without progression[a]	7 (8.9)
Adequate assessment no longer available[a]	4 (5.1)
25th percentile (months)	2.8
95% CI	1.4, 4.1
Median PFS (months)	5.6
95% CI	4.2, 8.3
PFS rate at 6 months (%)	48.9
95% CI	36.6, 60.2
PFS rate at 12 months (%)	20.0
95% CI	9.4, 33.3

Ancillary analyses

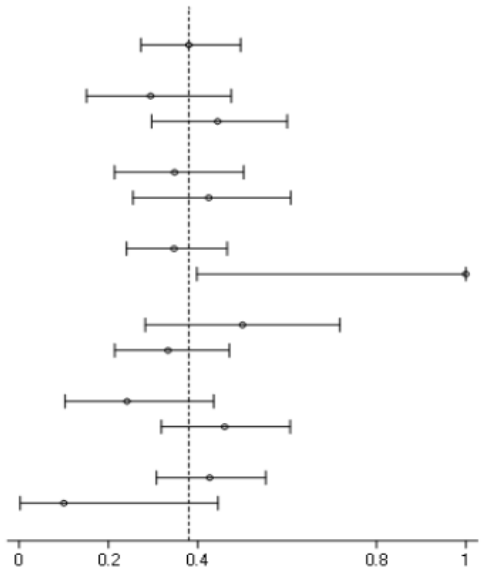
Subgroup analyses

Note: These analyses correspond to the initial DCO on 09-APR-2021.

Figure 8.1: Forest Plot of Confirmed Objective Response Rate by Independent Central Review by Subgroup (Full Analysis Set)

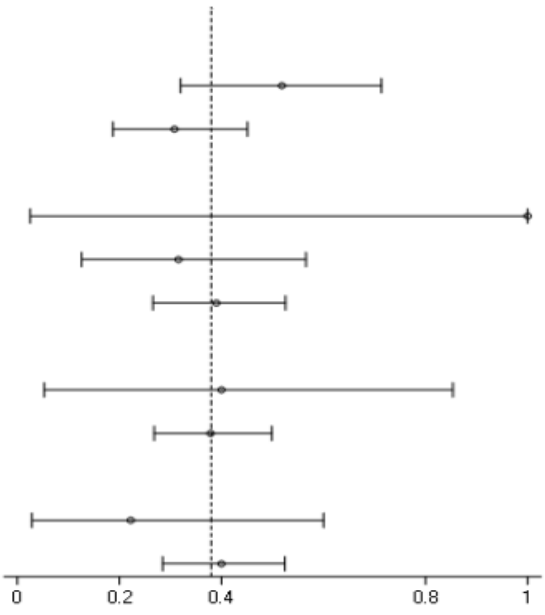
T-DXd 6.4 mg/kg (N=79)

Subgroup	# Subjects	# CR/PR	ORR (95% CI)
Overall	79	30	38.0 (27.3, 49.6)
Region			
North America	34	10	29.4 (15.1, 47.5)
Europe	45	20	44.4 (29.6, 60.0)
Age			
<65 Years	46	16	34.8 (21.4, 50.2)
>=65 Years	33	14	42.4 (25.5, 60.8)
<75 Years	75	26	34.7 (24.0, 46.5)
>=75 Years	4	4	100.0 (39.8, 100.0)
Sex			
Female	22	11	50.0 (28.2, 71.8)
Male	57	19	33.3 (21.4, 47.1)
ECOG PS			
0	29	7	24.1 (10.3, 43.5)
1	50	23	46.0 (31.8, 60.7)
HER2 status			
IHC 3+	68	29	42.6 (30.7, 55.2)
IHC 2+/ISH +	10	1	10.0 (0.3, 44.5)



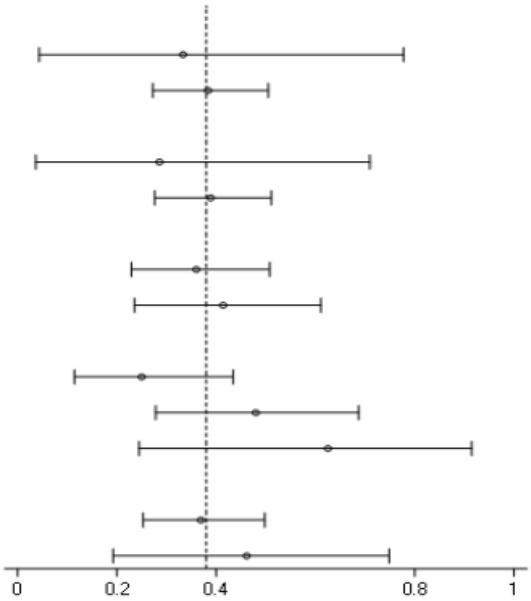
T-DXd 6.4 mg/kg (N=79)

Subgroup	# Subjects	# CR/PR	ORR (95% CI)
Primary tumor location			
Gastric	27	14	51.9 (31.9, 71.3)
GEJ	52	16	30.8 (18.7, 45.1)
Histological subtype			
Diffuse	1	1	100.0 (2.5, 100.0)
Intestinal	19	6	31.6 (12.6, 56.6)
Others	59	23	39.0 (26.5, 52.6)
Number of metastatic sites			
<2	5	2	40.0 (5.3, 85.3)
>=2	74	28	37.8 (26.8, 49.9)
Prior adjuvant/neoadjuvant therapy			
Yes	9	2	22.2 (2.8, 60.0)
No	70	28	40.0 (28.5, 52.4)



T-DXd 6.4 mg/kg (N=79)

Subgroup	# Subjects	# CR/PR	ORR (95% CI)
Prior nivolumab or pembrolizumab treatment			
Yes	6	2	33.3 (4.3, 77.7)
No	73	28	38.4 (27.2, 50.5)
Pr. immune-chkpnt inhibitor/bth immuno-onco			
Yes	7	2	28.6 (3.7, 71.0)
No	72	28	38.9 (27.6, 51.1)
Presence of liver metastasis at baseline			
Yes	50	18	36.0 (22.9, 50.8)
No	29	12	41.4 (23.5, 61.1)
Renal impairment at baseline			
Normal	32	8	25.0 (11.5, 43.4)
Mild	25	12	48.0 (27.8, 68.7)
Moderate	8	5	62.5 (24.5, 91.5)
Hepatic impairment at baseline			
Normal	65	24	36.9 (25.3, 49.8)
Mild	13	6	46.2 (19.2, 74.9)



Immunogenicity

None of the subjects had NAb-positive samples (Table 14.4.7.4).

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Protocol: DS8201-A-U205 Program Name: s812is03.sas
CSR Final Run (Data Cut Date: 09APR2021) Run Date: 09JUN21:20:02

Table 14.4.7.4 Summary of Anti-Drug Antibody (ADA) and Neutralizing antibody (NAb) Incidence
Safety Analysis Set

	T-DXd 6.4 mg/kg (N=79) n (%)
Number of subjects with baseline or post-baseline immunogenicity data (ADA)	78
Number of subjects with baseline immunogenicity data (ADA)	76
Number of subjects with post-baseline immunogenicity data (ADA)	73
ADA Positive prevalence at Baseline [a]	5 (6.6)
NAb Positive prevalence at Baseline [a]	0
ADA Positive prevalence at Post-Baseline [b]	2 (2.7)
NAb Positive prevalence at Post-Baseline [b]	0
ADA Positive prevalence at both Baseline and Post-Baseline [b]	0
NAb Positive prevalence at both Baseline and Post-Baseline [b]	0
ADA Positive prevalence at Baseline or Post-Baseline [c]	7 (9.0)
NAb Positive prevalence at Baseline or Post-Baseline [c]	0
Treatment-Emergent incidence of ADA Positive [b]	2 (2.7)
Treatment-boosted ADA incidence [b]	0
Treatment-induced ADA incidence [b]	2 (2.7)
Treatment-Emergent incidence of NAb Positive [b]	0

as the benefit-risk assessment (see later sections).

Table 1. Summary of Efficacy for trial DS8201-A-U205 (DESTINY-Gastric02)

Title: A Phase 2, Open-label, Single-arm Trial of Trastuzumab Deruxtecan in HER2-positive, Unresectable or Metastatic Gastric or Gastro-esophageal Junction (GEJ) Adenocarcinoma Subjects Who Have Progressed On or After a Trastuzumab-containing Regimen	
Study identifier	DS-8201-A-U205
Design	Pivotal phase 2, single-arm trial of T-DXd in a Western population (EU/US) with advanced HER-2+ GC/GEJ adenocarcinoma who have progressed on or after 1L trastuzumab containing treatment, i.e. in the 2L setting.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18-24 months not applicable not applicable
Hypothesis	Exploratory: to evaluate the efficacy and safety of T-DXd (6.4 mg/kg as IV infusion Q3W) in subjects with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed during on or after a trastuzumab-containing regimen (2L).		
Treatment groups	Primary Cohort		T-DXd 6.4 mg/kg IV Q3W until a discontinuation criterion was met, 79 objects randomized and treated.
Endpoints and definitions	Primary endpoint	IRC-assessed ORR	Objective response rate (ORR) based on a centrally reviewed evaluation in the primary cohort. ORR was defined as the proportion of patients with best overall response of complete or partial response by group (confirmed).
	Secondary endpoint	DOR	Duration Of Response in responders
	Secondary endpoint	PFS	Progression Free Survival
	Secondary endpoint	OS	Overall Survival
Database lock	Updated DCO 08 Nov 2021		

Results and Analysis

Analysis description	**Primary Analysis (pre-planned).**			
Analysis population and time point description	The ITT set included all subjects randomized in the Primary Cohort of Study U205 (subjects with HER2-positive gastric cancer with a rebiopsy post-trastzumab). Data are presented for the CSR DCO (09 Apr 2021)/Updated DCO 08 Nov 2021.			
Descriptive statistics and estimate variability	Treatment group	T-DXd		
	Number of subjects (ITT)	79		
	ORR (confirmed), number of subjects (rate)	33 (41.8%)		
	95% CI	30.8, 53.4		
	Median DOR in responders, months	8.1		
	95% CI	5.9, NE		
	Median PFS, months 95% CI	5.6 4.2, 8.3		
	Median OS, months 95% CI	12.1 8.6, NE		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No studies in special populations were provided.

Table 34: Age Groups of Subjects with Gastric Cancer Treated with T-DXd 6.4 mg/kg in Studies J202, U205, and J101

	Age 65-74 (older subject number/total number)	Age 75-84 (older subject number/total number)	Age 85+ (older subject number/total number)
Controlled trials (J202)	54/126	17/126	0/126
Noncontrolled trials (U205 and J101[a])	43/104	7/104	0/104

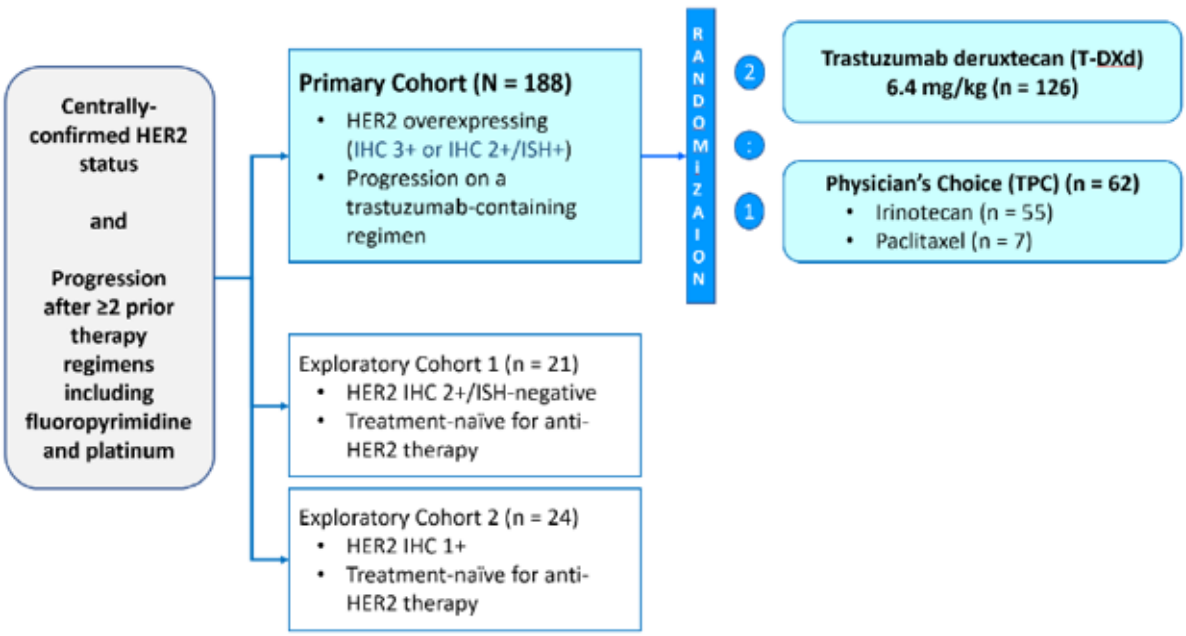
[a] An additional 19 subjects with gastric cancer were treated at the 5.4-mg/kg dose level in Study J101, including 10 subjects aged 65 to 74 years and 3 subjects aged 75 to 84 years.
Source: Module 5.3.5.1 DS8201-A-J202 CSR Table 14.1.2.1_1; Module 5.3.5.2 DS8201-A-U205 CSR Table 14.1.2.1; Module 5.3.5.3 SCE J101 Table 14.1.3.4.2.3

Supportive studies

Study DS8201-A-J202 (DESTINY-Gastric01)

This was a Phase 2, multicentre, open-label, randomized study in subjects with advanced HER2-positive gastric or GEJ adenocarcinoma who had progressed on 2 or more prior regimens that had to include a fluoropyrimidine agent (fluorouracil, capecitabine, or S-1) and a platinum agent (oxaliplatin or cisplatin) (3L). The study was conducted at sites in Japan and South Korea. Subjects were divided into 3 cohorts based on HER2 status and prior therapy with trastuzumab. The target population that is the focus of this application is the cohort of subjects with HER2-positive (i.e., IHC 3+ or IHC 2+/in situ hybridization [ISH]-positive) tumours (HER2 status could be determined either pre- or post-trastuzumab) in the Primary Cohort (N=188), in which subjects were randomized to receive either T-DXd monotherapy at the proposed dose (6.4 mg/kg Q3W) or treatment of physician's choice (TPC), (N=45), (limited to 1 of 2 choices of standard regimens: irinotecan or paclitaxel in a 2:1 ratio. Subjects in the Primary Cohort had to have progressed on prior trastuzumab or a trastuzumab biosimilar in addition to a fluoropyrimidine agent and a platinum agent (i.e., 2 or more prior therapies). Subjects with a HER2 status of IHC 2+/ISH-negative or IHC 1+ and treatment-naïve for trastuzumab were enrolled in the nonrandomized Exploratory Cohort 1 and Exploratory Cohort 2, respectively, and are not the focus of this application.

Figure 4.1: Study J202 Design



Study participants

In Study J202, demographic and baseline disease characteristics of the ITT population were generally balanced between treatment arms (see Module 2.7.3 Table 3.7 and Module 5.3.5.3 J202 SCE Table 14.1.2.1_1):

- All subjects were Asian and were mostly from Japan (T-DXd: 79.4%; TPC: 80.6%).
- A majority of subjects were male (T-DXd: 76.2%; TPC: 75.8%) and the median age at informed consent was 65.5 years for the T-DXd arm and 66.0 years for the TPC arm.
- There was a similar proportion of subjects with an ECOG PS of 0 (T-DXd: 49.2% ; TPC 48.4%) or 1 (T-DXd: 50.0% ; TPC 51.6%) in both treatment arms.
- A majority of subjects had GC (T-DXd: 86.5%; TPC: 88.7%) as opposed to GEJ (T-DXd: 13.5%; TPC: 11.3%), with most having Stage IV cancer at study entry (T-DXd: 96.0%; TPC: 100.0%).
- The cancer was classified as "inoperable advanced" in 61.1% of subjects on T-DXd and 74.2% of those on TPC, and as "postoperative advanced" in 38.9% and 25.8% of subjects, respectively.
- A majority of subjects had the intestinal histologic subtype (T-DXd: 70.6%; TPC: 61.3%).
- All subjects had tumors with an HER2 status of IHC 3+ or IHC 2+/ISH-positive based on central laboratory testing of most recent archived tumor tissue sample. If archived sample was not available, a new sample was required as per protocol.
- Prior treatment included cancer surgery for 44.1% of subjects (T-DXd: 47.6%; TPC: 37.1%): 16.5% of subjects had prior total gastrectomy (T-DXd: 17.5%; TPC: 14.5%); 21.8% had prior partial gastrectomy (T-DXd: 23.8%; TPC: 17.7%); and 11.7% had "other" cancer surgery (T-DXd: 11.1%; TPC: 12.9%).
- 12.8% of subjects had prior radiation therapy (T-DXd: 11.1%; TPC: 16.1%).
- 21.3% of subjects had received prior adjuvant/neoadjuvant therapy (T-DXd: 23.8%; TPC: 16.1%).
- The median number of prior anticancer regimens in the locally advanced or metastatic setting excluding radiation and surgery was 2.0 (range: 2 to 9) in the T-DXd arm and 2.0 (range: 2 to 5) in the TPC arm (Note: this included therapies intended for locally advanced or metastatic disease or for neoadjuvant or adjuvant therapy if there was progressive disease within 6 months since the end of therapy). A higher proportion of subjects had received 4 or more prior regimens in the T-DXd arm than in the TPC arm (20.6% vs. 9.7%, respectively).
- The most common prior anticancer agents were trastuzumab or a biosimilar (100.0% of subjects in both arms as per protocol), capecitabine (T-DXd: 74.6%; TPC: 66.1%), cisplatin (T-DXd: 63.5%; TPC: 59.7%), PTX (T-DXd: 68.3%; TPC: 74.2%), Ram (T-DXd: 74.6%; TPC: 66.1%), oxaliplatin (T-DXd: 49.2%; TPC: 43.5%), and S-1 (T-DXd: 49.2%; TPC: 46.8%). In addition, 27.0% of subjects in the T-DXd arm and 24.2% of subjects in the TPC arm had received prior nivolumab. Both S-1 and nivolumab are approved for use in Japan in this setting.

Treatments

Subjects were randomized to receive either T-DXd monotherapy at the proposed dose (6.4 mg/kg Q3W) or treatment of physician's choice (TPC).

Therapeutic options in the TPC arm were limited to 1 of 2 choices: irinotecan (N = 55) or paclitaxel (N = 7) and the investigator had to preselect TPC therapy before the subject was randomized. Randomization was stratified by region (Japan or South Korea), ECOG PS (0 or 1), and HER2 status (IHC 3+ or IHC 2+/ISH-positive) (HER2 status was confirmed from the most recent archival tumour sample or determined on a new tissue sample, i.e., either pre- or post-trastuzumab).

Tumour assessments were performed at screening and every 6 weeks (± 7 days) thereafter from Cycle 1 Day 1 until progressive disease, start of a new anticancer treatment, death, or withdrawal of consent by the subject. Assessments were conducted using computed tomography (CT) or magnetic resonance imaging (MRI). Copies of CT or MRI images were provided to a blinded ICR.

Prior therapies required for randomization in the Primary Cohort (i.e., a fluoropyrimidine agent, a platinum agent, and trastuzumab) and the choice of irinotecan or PTX as active controls for the comparator arm in the third-line setting or later reflected the Japanese Gastric Cancer Treatment Guidelines 2018 (5th edition) at the time of study planning and were aligned with the 2018 Korean12 Practice Guideline.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was ORR (the sum of CR rate and PR rate), without confirmation of CR/PR, assessed by the ICR based on RECIST Version 1.1 (for the Primary Cohort only).

Secondary Efficacy Endpoints

The secondary efficacy endpoints included the following, which were assessed by the ICR unless otherwise indicated.

• OS, defined as the time from the date of randomization (the date of the registration for the Exploratory Cohorts) to the date of death due to any cause.

• PFS, defined as the time from the date of randomization (the date of the registration for the Exploratory Cohorts) to the earliest date of the first objective documentation of PD or death due to any cause. The PD was determined based on RECIST Version 1.1 criteria.

• Duration of response (DoR), defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first objective documentation of PD or death due to any cause. DoR was measured for responding subjects (PR or CR) only.

• Disease control rate (DCR), defined as the sum of CR rate, PR rate, and stable disease (SD) rate.

• Time to treatment failure (TTF), defined as the time from the date of randomization (the date of the registration for Exploratory Cohorts) to the earliest date of the first objective documentation of PD, death due to any cause, or treatment discontinuation.

• ORR assessed by the investigator based on RECIST Version 1.1, defined as the sum of CR rate and PR rate, assessed by the investigator.

Sample size

The target sample size of this study was approximately 220 subjects (Primary Cohort, N=approximately 180; Exploratory Cohort 1, N=approximately 20; and Exploratory Cohort 2, N=approximately 20).

Primary Cohort

A combined analysis of ORR data taken from published Phase 2 and 3 studies (a total of 13 studies) of second- or subsequent-line chemotherapy in patients with gastric cancer was conducted. As a result, the

combined ORR was 9.4% (95% CI: 1.1% to 17.7%). The ORR for the physician's choice group was conservatively assumed to be 15%, which exceeded the above-mentioned combined mean estimate of ORR. The ORR for the DS-8201a group was also assumed to be 40%. The sample size of 180 subjects (120 subjects in the DS-8201a group and 60 subjects in the physician's choice group) could provide a 92.9% power to detect this magnitude of difference according to Fisher's exact test with 2-sided significance alpha=0.05.

Approximately 133 OS events would be needed to detect an HR of 0.61 for OS (a 64% improvement in median OS from 5.5 months in the physician's choice group to 9.0 months in the DS-8201a group) with 2-sided significance alpha=0.05 and 80% power. The sample size of 180 subjects could provide an 80.8% power to detect this magnitude of OS difference, assuming a 10-month enrolment period and a 12-month follow-up period after the last subject randomization.

The sample size was calculated assuming that the ORR for the control arm would be approximately 15% and that the ORR for DS-8201a would be 40%. The MAH estimated that 120 and 60 subjects would be required to observe the mentioned difference with 93% power using a Fisher's exact test. Of note, the CMH test was implemented in the primary analysis, and therefore the expected power for the primary analysis was not reported.

The MAH expected to observe a HR of 0.61 or lower for OS with approximately 80% power if 133 OS are included in the analysis.

Exploratory Cohorts

The exploratory cohorts are not the scope of this assessment.

Randomisation

Subjects in Primary Cohort were randomized by IXRS into the two treatment groups in a 2:1 ratio (120 DS-8201a group and 60 physician's choice group) and the randomization will be stratified by region, ECOG PS, and HER2 status:

- Region (Japan or Korea)
- ECOG PS (0 or 1)
- HER2 status (IHC 3+ or IHC 2+/ISH +)

Blinding (masking)

This was an open-label study, and no blinding was performed. It was not feasible to blind treatment allocations for individual subjects because of different treatment schedules and different AE profiles between DS-8201a and the physician's choice treatment.

To reduce potential bias, ICR reviewers were blinded to the treatment assignment when assessing the primary endpoint of ORR. Additionally, the sponsor was not allowed to have access to aggregate efficacy data except when data from both the DS-8201a and the physician's choice groups were combined in the Primary Cohort.

Statistical methods

Analysis Sets

The efficacy analyses were conducted on the following analysis sets:

- The Enrolled Analysis Set included all subjects who signed the ICF and were enrolled in the study.
- The Intent-to-Treat (ITT) Analysis Set, which included all randomized subjects.
- The FAS, which included all randomized subjects who received at least 1 dose of study drug.
- The Response Evaluable Set (RES), defined as randomized subjects who received at least 1 dose of study drug and had measurable disease per ICR at baseline.

Analyses of ORR and DCR will be performed on the Response Evaluable Set. The other efficacy analyses will be performed on the full analysis set (FAS).

Several analysis sets were used for the primary analysis. The intent-to-treat analysis set (ITT) includes as randomized subjects while the Full analysis set (FAS) includes all randomized subjects who received at least one dose of study drug. The Response evaluable set (RES) includes all randomized subjects who received at least one dose of study drug and had measurable disease at baseline according to the ICR.

For the primary endpoint ORR, the response evaluable set was the RES and for OS was the FAS. The use of RES and FAS as primary analysis set is not endorsed. From a regulatory point of view, the results obtained with the ITT set are the most relevant ones since they follow the intention to treat principle. According to Table 7.1 in the CSR (page 80 /202), there was one participant randomized to study arm DS-8201a who was excluded from the FAS and several participants were excluded from the RES (7 and 4 for the DS-8201a and control arm, respectively).

Primary endpoint ORR

Objective response rate was compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test, with region (Japan or South Korea) as a stratification factor, for statistical significance at 2-sided alpha=0.05.

If there is no on-treatment tumour assessment, the best overall response will be assigned as "Inevaluable". In the case of a best overall response of SD, tumour measurements and assessments must have met the SD criteria at least once after study entry at a minimum time interval from the date of first dose of study drug, 6 weeks (± 7 days). If this minimum requirement is not met, the best overall response will be determined starting with the next tumour assessment. If there is no next tumour assessment, the best overall response will be assigned as "Inevaluable". If a subject has no on-treatment tumour assessment, the best overall response of the subject will be assigned as "Inevaluable".

Subjects without on-treatment tumour assessment will be included in the denominators of best overall response and ORR (as best overall response of "Inevaluable").

<u>Secondary endpoint OS</u>

OS will be compared between the treatment groups using stratified log-rank tests with region as a stratification factor in Primary Cohort.

The HRs and their 95% CI will be estimated using stratified Cox proportional hazards regression models with region as a stratification factor. Kaplan-Meier estimates and survival curves will be presented for each cohort/treatment group. The HRs over time will be also plotted. The unstratified results will also be provided as a sensitivity analysis.

<u>Censoring rules for OS</u>

If there is no death reported for a subject before the data cut-off for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

Secondary endpoint PFS

PFS will be analysed as described for OS.

Censoring rules for PFS

Subjects who are alive and progression-free at the data cut-off date will be censored at the date of the last evaluable tumour assessment.

Subjects who discontinue from the study prior to the first post-baseline evaluable tumour assessment for a reason other than disease progression or death will be censored at the date of randomization (the date of the registration for Exploratory Cohorts).

Subjects who discontinue from the study without disease progression and death will be censored at the date of the last evaluable tumour evaluation.

Subjects who start other anti-cancer therapy prior to disease progression or death will be censored at the date of the last tumour evaluable assessment prior to starting new anti-cancer therapy.

Subjects who progress or die after missing $\geq$2 consecutive scheduled tumour assessments will be censored at the date of the last evaluable tumour evaluation prior to progression or death.

Subjects without baseline evaluable tumour assessment will be censored at the date of randomization or registration (the date of the registration for Exploratory Cohorts), except death within the first 2 scheduled tumour assessments (i.e., 14 weeks) will be considered as a PFS event.Interim analysis

One formal interim OS analysis will be conducted when all subjects have completed tumour assessment approximately at 24 weeks (or discontinued the study) in Primary Cohort if the OS events observed thus far do not reach the target number of OS events (i.e., 133 OS events in Primary Cohort). The interim OS will be tested only if ORR show the statistical significance at 2-sided alpha = 0.05. The overall one-sided alpha is to be controlled at 0.025 for the interim OS analysis and final OS analysis using the Lan-De Mets alpha-spending function with an O'Brien-Fleming boundary. The boundary used at the interim and final OS analysis depends on the actual number of observed deaths at the interim analysis.

Multiple Comparisons/Multiplicity

The primary and specified secondary endpoints will be analysed using a hierarchically ordered gatekeeping testing procedure to control overall type I error at a significance level of a 2-sided alpha of 0.05 and allow the secondary analysis results to be claimed in the label, the sequence of test for secondary efficacy endpoint OS will be employed. They will proceed only after the result of the primary efficacy analysis of ORR (based on ICR) is statistically significant. The tests will be performed in the following order: ORR (based on ICR) and OS. The sequence of tests will continue until the test does not meet the significance level of 2-sided alpha 0.05.

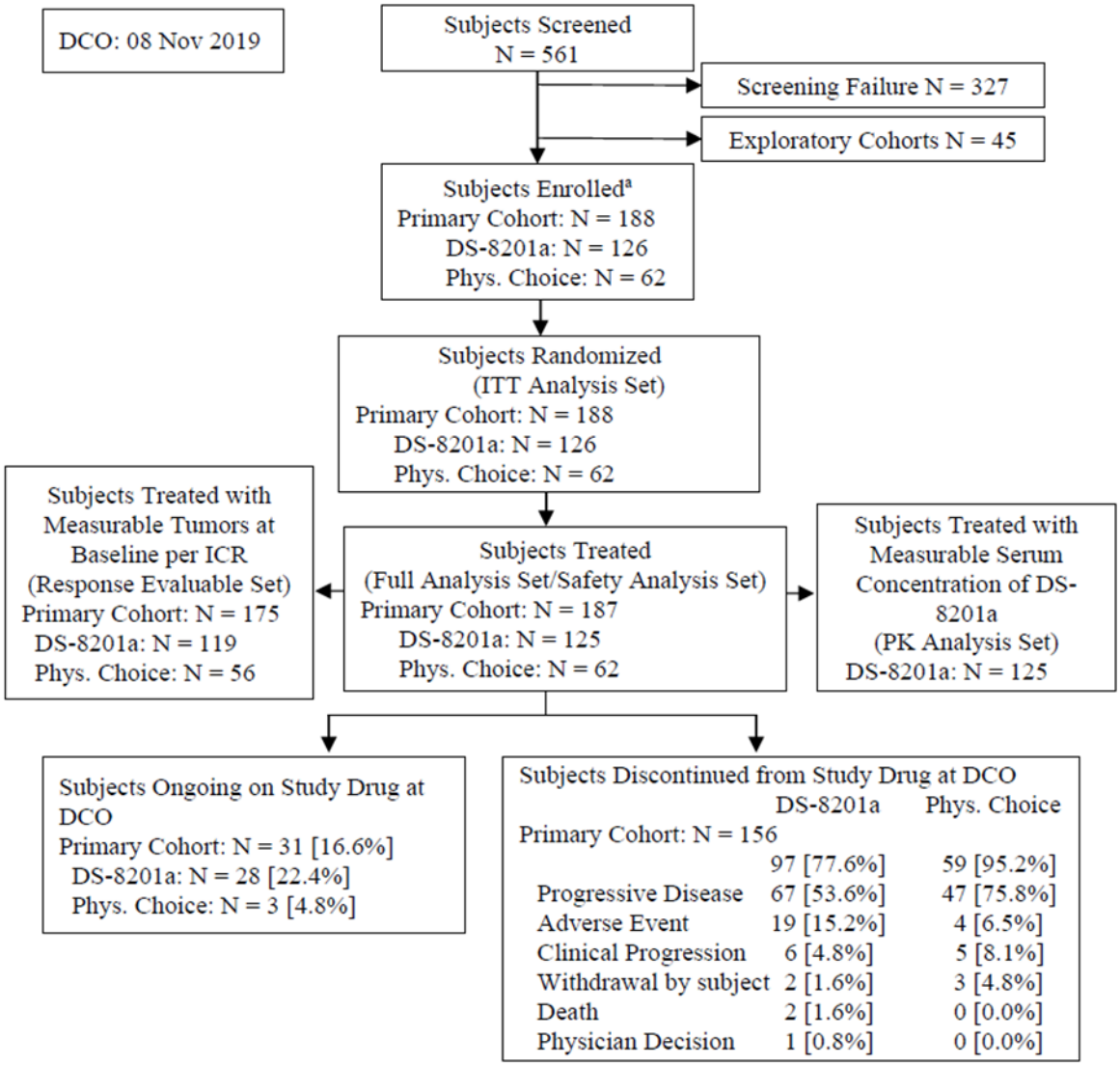
Changes in the Planned Analyses

The SAP (Version 1.0, 11 Sep 2019) was finalized prior to database lock (25 Dec 2019). There were no changes to the planned analyses. Since some duplicates and one missing protocol deviation record were found, the database was unlocked and relocked on 15 Jan 2020 to update only the protocol deviation dataset, with no impact on other than the protocol deviation dataset. Since the ADA result of the sample collected on 26 Apr 2019 was not reported correctly due to the process error for data selection by the vendor, the database was unlocked and relocked on 27 Feb 2020 to update only the ADA dataset, with no impact on other than the ADA dataset.

Results

Participant flow

Primary Cohort



Recruitment

Date First Subject Enrolled: 02 Nov 2017 (First Informed Consent Signed)

14 Nov 2017 (First Subject Dosed)

Data Cut-off Date: 08 Nov 2019/ Updated DCO as of 03 Jun 2020

Subjects in the pivotal study were enrolled and treated at study centres in Japan (48) and Korea (18).

Baseline data

Table 3.7: Demographic and Baseline Disease Characteristics in Study J202 (Intent-to-Treat Analysis Set)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg (N = 126)	Physician's Choice		
		Irinotecan (N = 55)	Paclitaxel (N = 7)	Total (N = 62)
Age at informed consent (years)				
Median	65.5	66.0	65.0	66.0
Min-Max	34-82	28-82	51-74	28-82
Age group (years), n (%)				
<65	55 (43.7)	24 (43.6)	3 (42.9)	27 (43.5)
≥65	71 (56.3)	31 (56.4)	4 (57.1)	35 (56.5)
<75	109 (86.5)	46 (83.6)	7 (100.0)	53 (85.5)
≥75	17 (13.5)	9 (16.4)	0 (0.0)	9 (14.5)
Sex, n (%)				
Male	96 (76.2)	42 (76.4)	5 (71.4)	47 (75.8)
Female	30 (23.8)	13 (23.6)	2 (28.6)	15 (24.2)
Race, n (%)				
Asian	126 (100.0)	55 (100.0)	7 (100.0)	62 (100.0)
Country of enrollment, n (%)				
Japan	100 (79.4)	44 (80.0)	6 (85.7)	50 (80.6)
South Korea	26 (20.6)	11 (20.0)	1 (14.3)	12 (19.4)
ECOG performance status, n (%)				
0	62 (49.2)	28 (50.9)	2 (28.6)	30 (48.4)
1	63 (50.0)	27 (49.1)	5 (71.4)	32 (51.6)
Type of cancer, n (%)				
Gastric	109 (86.5)	50 (90.9)	5 (71.4)	55 (88.7)
GEJ	17 (13.5)	5 (9.1)	2 (28.6)	7 (11.3)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg (N = 126)	Physician's Choice		
		Irinotecan (N = 55)	Paclitaxel (N = 7)	Total (N = 62)
Inoperable advanced (yes)	77 (61.1)	40 (72.7)	6 (85.7)	46 (74.2)
Postoperative advanced (yes)	49 (38.9)	15 (27.3)	1 (14.3)	16 (25.8)
Histological subtype, n (%)				
Intestinal	89 (70.6)	34 (61.8)	4 (57.1)	38 (61.3)
Diffuse	29 (23.0)	15 (27.3)	3 (42.9)	18 (29.0)
Other	8 (6.3)	6 (10.9)	0 (0.0)	6 (9.7)
Time from initial diagnosis (months)				
Median	22.9	20.7	13.9	20.3
Min-Max	4.6-156.3	4.5-233.4	10.3-52.4	4.5-233.4
Prior treatment type, n (%)				
Prior cancer therapy excluding radiation and surgery (yes)	126 (100.0)	55 (100.0)	7 (100.0)	62 (100.0)
Prior adjuvant/neoadjuvant therapy	30 (23.8)	9 (16.4)	1 (14.3)	10 (16.1)
Prior radiation therapy (yes)	14 (11.1)	9 (16.4)	1 (14.3)	10 (16.1)
Prior cancer surgery (yes)	60 (47.6)	22 (40.0)	1 (14.3)	23 (37.1)
Total gastrectomy (yes)	22 (17.5)	9 (16.4)	0 (0.0)	9 (14.5)
Partial gastrectomy (yes)	30 (23.8)	10 (18.2)	1 (14.3)	11 (17.7)
Other	14 (11.1)	7 (12.7)	1 (14.3)	8 (12.9)
HER2 expression (IHC) per central laboratory (archived and fresh samples)[a], n (%)				
2+	29 (23.0)	13 (23.6)	2 (28.6)	15 (24.2)
ISH-positive	29 (23.0)	13 (23.6)	2 (28.6)	15 (24.2)
3+	96 (76.2)	42 (76.4)	5 (71.4)	47 (75.8)
IHC missing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor stage at study entry, n (%)				
Stage 0 to III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage IV	121 (96.0)	55 (100.0)	7 (100.0)	62 (100.0)
Other	5 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung metastases at baseline, n (%)				
Yes	39 (31.0)	12 (21.8)	3 (42.9)	15 (24.2)
No	87 (69.0)	43 (78.2)	4 (57.1)	47 (75.8)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg (N = 126)	Physician's Choice		
		Irinotecan (N = 55)	Paclitaxel (N = 7)	Total (N = 62)
Liver metastases at baseline, n (%)				
Yes	68 (54.0)	29 (52.7)	5 (71.4)	34 (54.8)
No	58 (46.0)	26 (47.3)	2 (28.6)	28 (45.2)
Sum of diameters of target lesions based on ICR at baseline, n (%)				
n	120	51	5	56
Median (cm)	4.8	5.0	7.9	5.3
<5 cm	63 (50.0)	25 (45.5)	1 (14.3)	26 (41.9)
≥5 , <10 cm	34 (27.0	19 (34.5)	3 (42.9)	22 (35.5)
≥10 cm	23 (18.3)	7 (12.7)	1 (14.3)	8 (12.9)
Missing	6 (4.8)	4 (7.3)	2 (28.6)	6 (9.7)
Prior cancer regimens in the locally advanced or metastatic setting (excluding radiation and surgery)[b]				
Median	2.0	2.0	2.0	2.0
Min-Max	2-9	2-5	2-5	2-5
Number of prior cancer regimens in the locally advanced or metastatic setting,[a] n (%)				
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	66 (52.4)	33 (60.0)	5 (71.4)	38 (61.3)
3	34 (27.0)	18 (32.7)	0 (0.0)	18 (29.0)
4	18 (14.3)	3 (5.5)	1 (14.3)	4 (6.5)
5	5 (4.0)	1 (1.8)	1 (14.3)	2 (3.2)
>5	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Prior anticancer agents,[c] n (%)				
Tegafur/gimeracil/oteracil (S-1)	62 (49.2)	25 (45.5)	4 (57.1)	29 (46.8)
Fluorouracil	8 (6.3)	6 (10.9)	0 (0.0)	6 (9.7)
Capecitabine	94 (74.6)	36 (65.5)	5 (71.4)	41 (66.1)
Cisplatin	80 (63.5)	33 (60.0)	4 (57.1)	37 (59.7)
Oxaliplatin	62 (49.2)	24 (43.6)	3 (42.9)	27 (43.5)
Paclitaxel	86 (68.3)	44 (80.0)	2 (28.6)	46 (74.2)
Docetaxel	9 (7.1)	1 (1.8)	0 (0.0)	1 (1.6)
Irinotecan or irinotecan monohydrochloride trihydrate	9 (7.1)	0 (0.0)	5 (71.4)	5 (8.1)
Trastuzumab	125 (99.2)	54 (98.2)	7 (100.0)	61 (98.4)
Trastuzumab biosimilar	1 (0.8)	2 (3.6)	0 (0.0)	2 (3.2)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg (N = 126)	Physician's Choice		
		Irinotecan (N = 55)	Paclitaxel (N = 7)	Total (N = 62)
Ramucirumab	94 (74.6)	39 (70.9)	2 (28.6)	41 (66.1)
Nivolumab	34 (27.0)	13 (23.6)	2 (28.6)	15 (24.2)
Pembrolizumab	10 (7.9)	1 (1.8)	1 (14.3)	2 (3.2)
Margetuximab	7 (5.6)	0 (0.0)	1 (14.3)	1 (1.6)
Other	35 (27.8)	13 (23.6)	1 (14.3)	14 (22.6)
Renal function at baseline, n (%)				
Normal	33 (26.2)	11 (20.0)	2 (28.6)	13 (21.0)
Mild impairment	53 (42.1)	24 (43.6)	4 (57.1)	28 (45.2)
Moderate impairment	39 (31.0)	19 (34.5)	1 (14.3)	20 (32.3)
Severe impairment	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.6)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic function at baseline, n (%)				
Normal	88 (69.8)	42 (76.4)	5 (71.4)	47 (75.8)
Mild impairment	36 (28.6)	13 (23.6)	2 (28.6)	15 (24.2)
Moderate impairment	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

DCO = data cut-off; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; ISH = in situ hybridization; Max = maximum; Min = minimum; QTcF = QT interval corrected for heart rate by Fridericia's formula; SAP = Statistical Analysis Plan; SCE = Summary of Clinical Efficacy; T-DXd = trastuzumab deruxtecan

[a] Subject [redacted] who was randomized to the T-DXd arm of J202 became ineligible before first dose as his ECG results at Cycle 1 Day 1 predose met exclusion criterion 2 (ie, QTcF prolongation to >470 ms [females] or >450 ms [males] based on average of the screening triplicate 12-lead ECG). Since the HER2 status by central laboratory was derived as the last value before the date of first dose (as per baseline definition in the SAP) and the subject did not have a first dose date, his central laboratory HER2 status was entered as "IHC missing" in demographic tables. However, the subject had a central HER2 status of IHC 2+/ISH-positive before randomization date.

[b] Therapies intended for locally advanced/metastatic or intended for neoadjuvant or adjuvant if progressive disease was within 6 months since the end of therapy

[c] Coded with World Health Organization Drug Dictionary March 1, 2015 version.

Source: Module 5.3.5.3 SCE J202 Tables 14.1.2.1_1, 14.1.3.1_1, and 14.1.3.3

Numbers analysed

Table 3.1: Analysis Sets in Study J202

Analysis Sets	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg	Physician's Choice		
		Irinotecan	Paclitaxel	Total
ITT Analysis Set[a]	126	55	7	62
FAS[b]	125	55	7	62
Excluded from FAS	1[c]	0	0	0
No study drug administration	1[c]	0	0	0
RES[d]	119	51	5	56
Excluded from RES	7	4	2	6
No study drug administration	1	0	0	0
No baseline measurable tumor burden per ICR	6	4	2	6

CSR = clinical study report; DCO = data cut-off; ECG = electrocardiogram; FAS = Full Analysis Set; ICR = independent central review; ITT = Intent-to-Treat; QTcF = QT interval corrected for heart rate by Fridericia's formula; RES = Response Evaluable Set; SAP = Statistical Analysis Plan; T-DXd = trastuzumab deruxtecan

[a] The ITT Analysis Set included all subjects who signed an informed consent form and were randomized in the Primary Cohort of Study J202.

[b] The FAS included all subjects who received at least 1 dose of study drug.

[c] One subject randomized to the T-DXd arm (Subject [redacted]) became ineligible prior to dosing (predose ECG at Cycle 1 Day 1 met exclusion criterion 2 [QTcF prolongation >470 ms for females or >450 ms for males based on average of the screening triplicate 12-lead ECG]) and was not dosed. The subject was excluded from the FAS.

[d] The RES included all subjects randomized in the Primary Cohort of Study J202 who received at least 1 dose of study drug and had measurable tumors assessed by ICR at Baseline.

Source: Module 5.3.5.1 DS8201-A-J202 CSR Appendix 16.1.9 SAP and Table 14.1.1.2

The ITT Analysis Set, which is the relevant set to focus on, included all subjects who signed an informed consent form and were randomized in the Primary Cohort of Study J202. The MAH has confirmed the results of Study J202 giving in the SmPC to stem from the ITT population.

Outcomes and estimation

Primary endpoint – ORR- by Independent Central Review per RECIST v1.1 (Unconfirmed)- DCO 03 Jun 2020

Table 8.2: Objective Response Rate and Best Overall Response for the Primary Cohort (Based on ICR) as of 03 Jun 2020 Data Cut-off (Intent-to-Treat Analysis Set and Response Evaluable Set)

	Primary Cohort (DCO = 03 Jun 2020)			
	T-DXd 6.4 mg/kg	Physician's choice		
		Irinotecan	Paclitaxel	Total
Intent-to-Treat Analysis Set[a]				
N	126	55	7	62
Best Overall Response (Unconfirmed) by ICR, n (%)				
Complete Response	11 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response	50 (39.7)	7 (12.7)	1 (14.3)	8 (12.9)
Stable Disease	47 (37.3)	27 (49.1)	3 (42.9)	30 (48.4)
Progressive Disease	15 (11.9)	18 (32.7)	0 (0.0)	18 (29.0)
Not Evaluable	3 (2.4)	3 (5.5)	3 (42.9)	6 (9.7)
Unconfirmed ORR by ICR[b]				
n (%)	61 (48.4)	7 (12.7)	1 (14.3)	8 (12.9)
95% CI[c]	39.4, 57.5	5.3, 24.5	0.4, 57.9	5.7, 23.9
Best Overall Response (Confirmed) by ICR, n (%)				
Complete Response	10 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response	40 (31.7)	6 (10.9)	1 (14.3)	7 (11.3)
Stable Disease	57 (45.2)	28 (50.9)	3 (42.9)	31 (50.0)
Progressive Disease	15 (11.9)	18 (32.7)	0 (0.0)	18 (29.0)
Not Evaluable	4 (3.2)	3 (5.5)	3 (42.9)	6 (9.7)
Confirmed ORR by ICR[b]				
n (%)	50 (39.7)	6 (10.9)	1 (14.3)	7 (11.3)
95% CI[c]	31.1, 48.8	4.1, 22.2	0.4, 57.9	4.7, 21.9

Table 14.2.1.8 Subgroup Analyses for Objective Response Rate (ORR)
(Response Evaluable Set)
(Based on ICR)

	Primary Cohort HER2-Positive					Exp Cohort 1 HER2 IHC 2+/ISH-	Exp Cohort 2 HER2 IHC 1+
	DS-8201a (N=119)	Phys. Choice Irinotecan (N=51)	Phys. Choice Paclitaxel (N=5)	Phys. Choice Overall (N=56)	Overall (N=175)	DS-8201a (N=19)	DS-8201a (N=21)
Subgroup: Sex = male	n=89	n=40	n=4	n=44	n=133	n=15	n=14
Objective Response Rate (CR + PR) (n, %)	47 (52.8)	5 (12.5)	1 (25.0)	6 (13.6)	53 (39.8)	5 (33.3)	4 (28.6)
95% CI[1]	(41.9, 63.5)	(4.2, 26.8)	(0.6, 80.6)	(5.2, 27.4)	(31.5, 48.7)	(11.8, 61.6)	(8.4, 58.1)
Fisher's exact test between the treatments groups	p <0.0001	-	-		-	-	-
Subgroup: ECOG PS = 0	n=59	n=27	n=2	n=29	n=88	n=10	n=10
Objective Response Rate (CR + PR) (n, %)	31 (52.5)	2 (7.4)	1 (50.0)	3 (10.3)	34 (38.6)	3 (30.0)	3 (30.0)
95% CI[1]	(39.1, 65.7)	(0.9, 24.3)	(1.3, 98.7)	(2.2, 27.4)	(28.4, 49.6)	(6.7, 65.2)	(6.7, 65.2)
Fisher's exact test between the treatments groups	p = 0.0001	-	-		-	-	-
Subgroup: ECOG PS = 1	n=60	n=24	n=3	n=27	n=87	n=9	n=11
Objective Response Rate (CR + PR) (n, %)	30 (50.0)	5 (20.8)	0 (0.0)	5 (18.5)	35 (40.2)	4 (44.4)	1 (9.1)
95% CI[1]	(36.8, 63.2)	(7.1, 42.2)	(0.0, 70.8)	(6.3, 38.1)	(29.9, 51.3)	(13.7, 78.8)	(0.2, 41.3)
Fisher's exact test between the treatments groups	p = 0.0087	-	-		-	-	-
Subgroup: HER2 status in central laboratory = Primary Cohort: IHC 3+	n=91	n=40	n=4	n=44	n=135	n=0	n=0
Objective Response Rate (CR + PR) (n, %)	53 (58.2)	4 (10.0)	1 (25.0)	5 (11.4)	58 (43.0)	-(-)	-(-)
95% CI[1]	(47.4, 68.5)	(2.8, 23.7)	(0.6, 80.6)	(3.8, 24.6)	(34.5, 51.8)	(-, -)	(-, -)
Fisher's exact test between the treatments groups	p <0.0001	-	-		-	-	-
Subgroup: HER2 status in central laboratory = Primary Cohort: IHC 2+/ISH +	n=28	n=11	n=1	n=12	n=40	n=0	n=0
Objective Response Rate (CR + PR) (n, %)	8 (28.6)	3 (27.3)	0 (0.0)	3 (25.0)	11 (27.5)	-(-)	-(-)
95% CI[1]	(13.2, 48.7)	(6.0, 61.0)	(0.0, 97.5)	(5.5, 57.2)	(14.6, 43.9)	(-, -)	(-, -)
Fisher's exact test between the treatments groups	p = 1.0000	-	-		-	-	-
Subgroup: Primary tumor location = Gastric	n=104	n=46	n=3	n=49	n=153	n=15	n=19
Objective Response Rate (CR + PR) (n, %)	52 (50.0)	6 (13.0)	1 (33.3)	7 (14.3)	59 (38.6)	7 (46.7)	3 (15.8)
95% CI[1]	(40.0, 60.0)	(4.9, 26.3)	(0.8, 90.6)	(5.9, 27.2)	(30.8, 46.8)	(21.3, 73.4)	(3.4, 39.6)
Fisher's exact test between the treatments groups	p <0.0001	-	-		-	-	-
Subgroup: Primary tumor location = GEJ	n=15	n=5	n=2	n=7	n=22	n=4	n=2
Objective Response Rate (CR + PR) (n, %)	9 (60.0)	1 (20.0)	0 (0.0)	1 (14.3)	10 (45.5)	0 (0.0)	1 (50.0)
95% CI[1]	(32.3, 83.7)	(0.5, 71.6)	(0.0, 84.2)	(0.4, 57.9)	(24.4, 67.8)	(0.0, 60.2)	(1.3, 98.7)
Fisher's exact test between the treatments groups	p = 0.0743	-	-		-	-	-
Subgroup: Histological subtype = Intestinal	n=86	n=34	n=3	n=37	n=123	n=12	n=6
Objective Response Rate (CR + PR) (n, %)	41 (47.7)	7 (20.6)	1 (33.3)	8 (21.6)	49 (39.8)	3 (25.0)	3 (50.0)
95% CI[1]	(36.8, 58.7)	(8.7, 37.9)	(0.8, 90.6)	(9.8, 38.2)	(31.1, 49.1)	(5.5, 57.2)	(11.8, 88.2)
Fisher's exact test between the treatments groups	p = 0.0087	-	-		-	-	-

Percentage is calculated using the number of subjects in the column heading as the denominator.
[1] 95% exact binomial confidence interval.Fisher's exact test was performed to compare ORR between DS-8201a and Phys. Choice Overall in Primary Cohorts.
Two subjects ([redacted]) are excluded from Exploratory Cohort 2 due to no HER2 status in central laboratory.

Secondary efficacy endpoint – OS

The primary efficacy analysis was conducted at a DCO date of 08 Nov 2019 (DCO for the primary CSR). A formal IA of OS was conducted at the time of the primary analysis and this IA is considered to be the final OS analysis. A supportive efficacy analysis was conducted as of a DCO of 03 Jun 2020 and is presented for descriptive purposes only.

Table 3.13: Overall Survival in Study J202 (Full Analysis Set and Intent-to-Treat Analysis Set)

	Study J202 Primary Cohort			
	T-DXd 6.4 mg/kg	Physician's Choice		
		Irinotecan	Paclitaxel	Total
Full Analysis Set[a]	CSR DCO 08 Nov 2019			
Duration of survival follow-up (months)[b]				
N	125	55	7	62
Median	8.1	7.1	5.5	7.0
Min-Max	1.0-23.1	0.3-20.3	2.0-14.3	0.3-20.3
OS (months)				
OS events, n (%)	62 (49.6)	35 (63.6)	4 (57.1)	39 (62.9)
Censored, n (%)	63 (50.4)	20 (36.4)	3 (42.9)	23 (37.1)
Median OS[c]	12.5	8.4	14.3	8.4
95% CI[c]	9.6, 14.3	6.9, 10.4	2.0, 14.3	6.9, 10.7
Stratified log-rank test[d,e]	*P*-value = 0.0097			
Stratified HR[e] (95% CI)	0.59 (0.39, 0.88)			
Intent-to-Treat Analysis Set[f]	CSR DCO 08 Nov 2019			
Duration of survival follow-up (months)				
N	126	55	7	62
Median (months)[a]	8.0	7.1	5.5	7.0
Min-Max	0.4-23.1	0.3-20.3	2.0-14.3	0.3-20.3
OS events, n (%)	62 (49.2)	35 (63.6)	4 (57.1)	39 (62.9)
Censored, n (%)	64 (50.8)	20 (36.4)	3 (42.9)	23 (37.1)
OS (months)				
Median OS[c]	12.5	8.4	14.3	8.4
95% CI[c]	9.6, 14.3	6.9, 10.4	2.0, 14.3	6.9, 10.7
Stratified log-rank test[d,e]	*P*-value = 0.0097			
Stratified HR[e] (95% CI)	0.59 (0.39, 0.88)			
Full Analysis Set[a]	Update DCO 03 Jun 2020			
Duration of survival follow-up (months)				
N	125	55	7	62
Median	12.0	8.4	12.2	8.5
Min-Max	1.0-29.7	0.3-26.5	2.0-16.2	0.3-26.5
OS (months)				
OS events, n (%)	84 (67.2)	45 (81.8)	4 (57.1)	49 (79.0)
Censored, n (%)	41 (32.8)	10 (18.2)	3 (42.9)	13 (21.0)
Median OS[c]	12.5	8.6	14.3	8.9
95% CI[c]	10.3, 15.2	6.4, 10.4	2.0, NE	6.4, 10.4
Stratified log-rank test[e]	*P*-value = 0.0051			
Stratified HR[e] (95% CI)	0.60 (0.42, 0.86)			
Intent-to-Treat Analysis Set[f]	Update DCO 03 Jun 2020			
Duration of survival follow-up (months)				
N	126	55	7	62
Median (months)	11.9	8.4	12.2	8.5
Min-Max	0.4-29.7	0.3-26.5	2.0-16.2	0.3-26.5
OS events, n (%)	84 (66.7)	45 (81.8)	4 (57.1)	49 (79.0)
Censored, n (%)	42 (33.3)	10 (18.2)	3 (42.9)	13 (21.0)
Median OS[c]	12.5	8.6	14.3	8.9
95% CI[c]	10.3, 15.2	6.4, 10.4	2.0, NE	6.4, 10.4
Stratified log-rank test[e]	*P*-value = 0.0051			
Stratified HR[e] (95% CI)	0.60 (0.42, 0.86)			

CI = confidence interval; CSR = clinical study report; DCO = data cut-off; FAS = Full Analysis Set; HR = hazard ratio; ITT = Intent-to-Treat; Max = maximum; Min = minimum; ORR = objective response rate; OS = overall survival; NE = not estimable; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

Percentage was calculated using the number of subjects in the column heading as denominator.

[a] The FAS in Study J202 included all randomized subjects who received at least 1 dose of study drug.

[b] Duration of survival follow-up (months) = (last contact date – date of randomization/registration + 1).

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

[d] The hypothesis testing was conducted only if the primary endpoint of ORR was proven to be statistically significant.

[e] The comparison was between the T-DXd arm and the TPC arm, with region (Japan or South Korea) as a stratification factor.

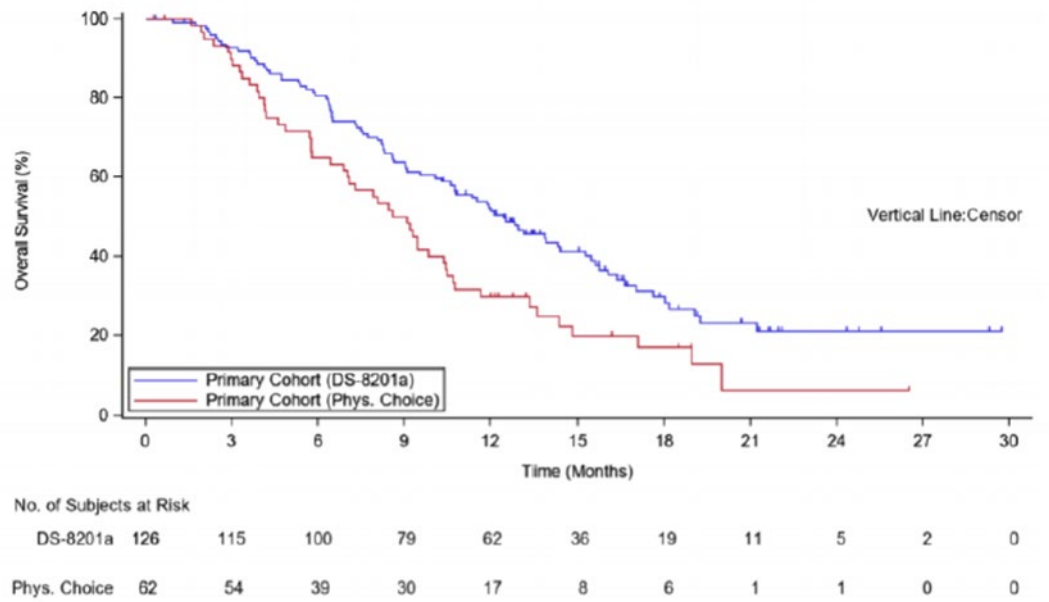
[f] The ITT analysis set included all subjects who signed an informed consent form and were randomized in the Primary Cohort of Study J202.

Table 14.2.3.2 Overall Survival (OS)
(Intent-to-treat Analysis Set)

	DS-8201a (N=126)	Phys. Choice Irinotecan (N=55)	Primary Cohort HER2-Positive Phys. Choice Paclitaxel (N=7)	Phys. Choice Overall (N=62)	Overall (N=188)	Exp Cohort 1 HER2 IHC 2+/ISH- DS-8201a (N=21)	Exp Cohort 2 HER2 IHC 1+ DS-8201a (N=22)
Duration of Survival Follow-Up (months)							
n	126	55	7	62	188	21	22
Mean	11.6	8.9	9.3	8.9	10.7	10.5	9.2
Standard Deviation	6.26	5.58	5.88	5.57	6.15	7.29	5.38
Median	11.9	8.4	12.2	8.5	10.4	7.3	8.5
Q1, Q3	6.5, 15.7	4.2, 11.7	3.4, 14.3	4.1, 12.2	5.8, 14.3	4.7, 16.5	4.3, 13.9
Min, Max	0.4, 29.7	0.3, 26.5	2.0, 16.2	0.3, 26.5	0.3, 29.7	0.2, 25.6	1.8, 19.6
Subjects with Events (n, %)	84 (66.7)	45 (81.8)	4 (57.1)	49 (79.0)	133 (70.7)	14 (66.7)	18 (81.8)
Subjects Censored (n, %)	42 (33.3)	10 (18.2)	3 (42.9)	13 (21.0)	55 (29.3)	7 (33.3)	4 (18.2)
Overall Survival (Months)[1]							
Median	12.5	8.6	14.3	8.9	10.7	7.8	8.5
95% CI for Median	(10.3, 15.2)	(6.4, 10.4)	(2.0, -)	(6.4, 10.4)	(9.1, 12.6)	(4.7, 16.5)	(4.3, 12.6)
Min, Max	0.4+, 29.7+	0.3+, 26.5+	2.0, 16.2+	0.3+, 26.5+	0.3+, 29.7+	0.2+, 25.6+	1.8, 19.6+
Stratified Log-rank Test [2] [3]	p = 0.0051[4]	p = 0.0031[5] [7]	p = 0.7677[6] [7]	-	-	-	-

Percentage is calculated using the number of subjects in the column heading as the denominator.
[1] Median is from Kaplan-Meier Estimate. CI for median is computed using the Brookmeyer-Crowley method. Minimum and maximum include the censored observations where using "+" after value indicates censoring.
[2] P-value is outputted as a reference since OS was proven to be statistically significant at the interim analysis.
[3] Region as a stratification factor.
[4] Comparison was between DS-8201a and Phys. Choice Overall in Primary Cohorts.
[5] Comparison was between DS-8201a and Phys. Choice Irinotecan in Primary Cohorts.
[6] Comparison was between DS-8201a and Phys. Choice Paclitaxel in Primary Cohorts.
[7] P-value is outputted as a reference and the comparison is not intended for the demonstration of superiority.
Duration of survival follow-up (months) = (last contact date - date of randomization/ registration + 1).
Two subjects ([redacted]) are excluded from Exploratory Cohort 2 due to no HER2 status in central laboratory.

Figure 3.5: Kaplan-Meier Plot of Overall Survival in Subjects with Metastatic HER2-positive Gastric or Gastroesophageal Junction Cancer in Primary Cohort of Study J202 at Update Data Cut-off 03 Jun 2020 (Intent-to-Treat Analysis Set)



CSR = clinical study report; DS-8201a = T-DXd (trastuzumab deruxtecan); HER2 = human epidermal growth factor receptor 2; No. = number; phys. = physician
Source: Module 5.3.5.1 DS8201-A-J202 Abbreviated CSR Figure 14.2.3.1_5.

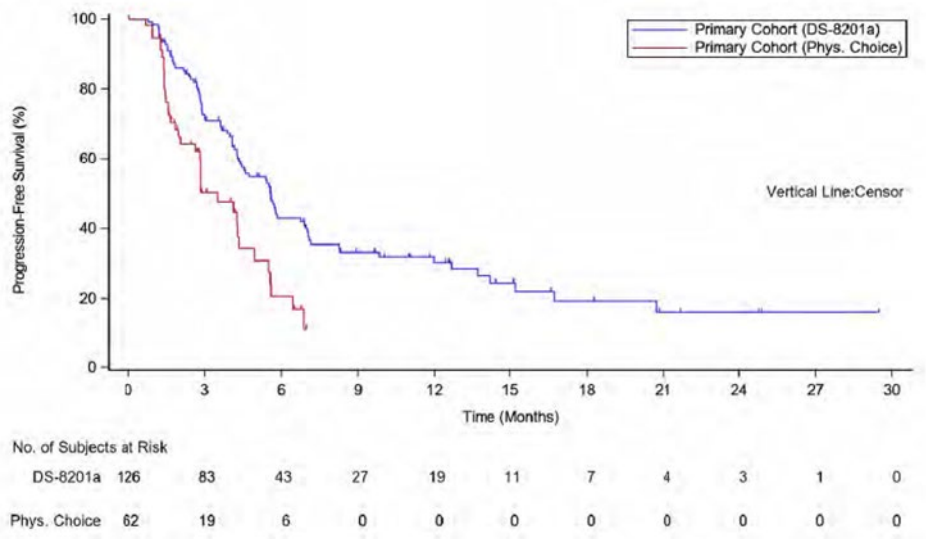
Secondary endpoint – PFS

Table 14.2.4.2 Progression-Free Survival (PFS)
(Intent-to-treat Analysis Set)
(Based on ICR)

	DS-8201a (N=126)	Phys. Choice Irinotecan (N=55)	Primary Cohort HER2-Positive Phys. Choice Paclitaxel (N=7)	Phys. Choice Overall (N=62)	Overall (N=188)	Exp Cohort 1 HER2 IHC 2+/ISH- DS-8201a (N=21)	Exp Cohort 2 HER2 IHC 1+ DS-8201a (N=22)
Subjects with Events (n, %)	82 (65.1)	33 (60.0)	3 (42.9)	36 (58.1)	118 (62.8)	14 (66.7)	16 (72.7)
Earliest Contributing Event:							
Progressive Disease	71 (56.3)	32 (58.2)	2 (28.6)	34 (54.8)	105 (55.9)	13 (61.9)	16 (72.7)
Death	11 (8.7)	1 (1.8)	1 (14.3)	2 (3.2)	13 (6.9)	1 (4.8)	0 (0.0)
Subjects Censored (n, %)	44 (34.9)	22 (40.0)	4 (57.1)	26 (41.9)	70 (37.2)	7 (33.3)	6 (27.3)
No baseline tumor assessments	0 (0.0)	1 (1.8)	1 (14.3)	2 (3.2)	2 (1.1)	0 (0.0)	0 (0.0)
No post-baseline tumor assessments	2 (1.6)	2 (3.6)	1 (14.3)	3 (4.8)	5 (2.7)	1 (4.8)	0 (0.0)
New anti-cancer therapy	14 (11.1)	13 (23.6)	1 (14.3)	14 (22.6)	28 (14.9)	4 (19.0)	6 (27.3)
Missed 2 consecutive tumor assessments	5 (4.0)	1 (1.8)	0 (0.0)	1 (1.6)	6 (3.2)	0 (0.0)	0 (0.0)
No PD or death	23 (18.3)	5 (9.1)	1 (14.3)	6 (9.7)	29 (15.4)	2 (9.5)	0 (0.0)
Progression-Free Survival (Months)[1]							
Median	5.6	2.8	4.9	3.5	4.6	4.4	2.8
95% CI for Median	(4.3, 6.9)	(2.0, 4.3)	(2.0, -)	(2.0, 4.3)	(4.1, 5.6)	(2.7, 7.1)	(1.5, 4.3)
Min, Max	0.0+, 29.5+	0.0+, 7.0+	0.0+, 6.8+	0.0+, 7.0+	0.0+, 29.5+	0.0+, 13.8+	0.5+, 13.9
Stratified Log-rank Test[2]	p = 0.0003[3]	p = 0.0002[4] [6]	p = 0.6273[5] [6]	-	-	-	-
Log-rank Test	p = 0.0003[3] [6]	p = 0.0002[4] [6]	p = 0.6162[5] [6]	-	-	-	-
Adjusted Hazard Ratio[2]	0.47[3]	0.45[4]	0.75[5]	-	-	-	-
95% CI	(0.31, 0.71)	(0.29, 0.69)	(0.24, 2.40)	-	-	-	-
Hazard Ratio	0.47[3]	0.45[4]	0.75[5]	-	-	-	-
95% CI	(0.31, 0.71)	(0.29, 0.69)	(0.23, 2.38)	-	-	-	-
Kaplan-Meier estimates and 95% CI on each time point							
3 Months	71.9 (63.0, 79.1)	47.9 (32.6, 61.8)	75.0 (12.8, 96.1)	50.3 (35.5, 63.5)	65.6 (57.9, 72.2)	71.5 (44.3, 87.1)	41.6 (18.1, 63.7)
6 Months	43.0 (33.6, 52.0)	20.7 (8.2, 36.9)	25.0 (0.9, 66.5)	20.6 (8.9, 35.6)	37.3 (29.5, 45.0)	33.5 (12.7, 56.1)	13.9 (2.3, 35.4)
9 Months	33.3 (24.4, 42.4)	- (-, -)	- (-, -)	- (-, -)	27.8 (20.5, 35.5)	25.1 (7.1, 48.6)	13.9 (2.3, 35.4)
12 Months	30.4 (21.5, 39.7)	- (-, -)	- (-, -)	- (-, -)	25.3 (18.0, 33.2)	8.4 (0.6, 30.6)	6.9 (0.4, 26.7)

Percentage is calculated using the number of subjects in the column heading as the denominator.
[1] Median is from Kaplan-Meier Estimate. CI for median is computed using the Brookmeyer-Crowley method. Minimum and maximum include the censored observations where using "+" after value indicates censoring.
[2] Region as a stratification factor.
[3] Comparison was between DS-8201a and Phys. Choice Overall in Primary Cohorts.
[4] Comparison was between DS-8201a and Phys. Choice Irinotecan in Primary Cohorts.
[5] Comparison was between DS-8201a and Phys. Choice Paclitaxel in Primary Cohorts.
[6] P-value is outputted as a reference and the comparison is not intended for the demonstration of superiority.
Two subjects ([redacted]) are excluded from Exploratory Cohort 2 due to no HER2 status in central laboratory.

Figure 8.6: Kaplan-Meier Plot of Progression-free Survival Based on Independent Central Review as of 03 June 2020 (Intent-to-Treat Analysis Set)



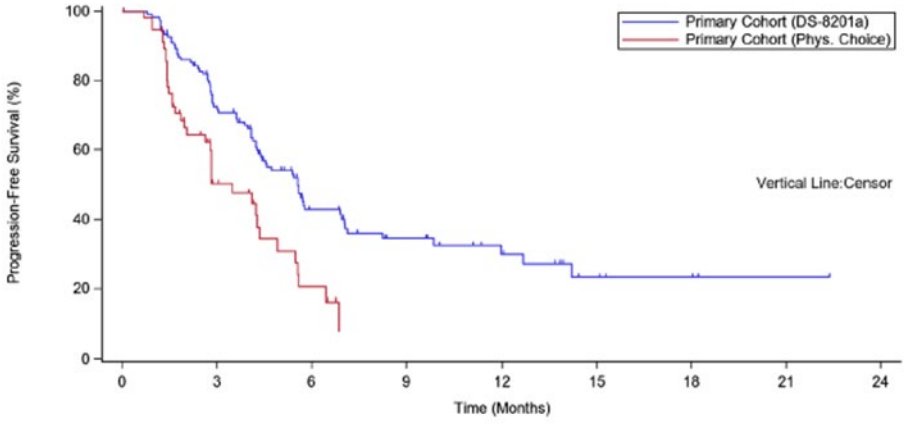
Source: DS8201-A-J202 updated CSR Figure 14.2.3.3_5

Table 3.16: Progression-free Survival in Study J202 (Full Analysis Set and Intent-to-Treat Analysis Set)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)			
	T-DXd 6.4 mg/kg	Physician's choice		
		Irinotecan	Paclitaxel	Total
FAS[a]				
N	125	55	7	62
PFS by ICR (months)				
PFS events, n (%)	73 (58.4)	33 (60.0)	3 (42.9)	36 (58.1)
Censored, n (%)	52 (41.6)	22 (40.0)	4 (57.1)	26 (41.9)
Median PFS[b]	5.6	2.8	4.9	3.5
95% CI[b]	4.3, 6.9	2.0, 4.3	2.0, NE	2.0, 4.3
Stratified HR[c]	0.47			
95% CI	0.31, 0.71			
ITT Analysis Set[d]				
N	126	55	7	62
PFS by ICR (months)				
PFS events, n (%)	73 (57.9)	33 (60.0)	3 (42.9)	36 (58.1)
Censored, n (%)	53 (42.1)	22 (40.0)	4 (57.1)	26 (41.9)
Median PFS[b]	5.6	2.8	4.9	3.5
95% CI[b]	4.3, 6.9	2.0, 4.3	2.0, NE	2.0, 4.3
Stratified HR[c]	0.47			
95% CI	0.31, 0.71			

CI = confidence interval; CSR = clinical study report; DCO = data cut-off; FAS = Full Analysis Set; HR = hazard ratio
ICR = independent central review; ITT = Intent-to-Treat; NE = not estimable; PFS = progression-free survival;
T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Percentage was calculated using the number of subjects in the column heading as denominator.
[a] The FAS in Study J202 included all randomized subjects who received at least 1 dose of study drug.
[b] Median was from Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method.
[c] The comparison was between the T-DXd arm and the TPC arm, with region (Japan or South Korea) as a stratification factor.
[d] The ITT analysis set included all subjects who signed an informed consent form and were randomized in the Primary Cohort of Study J202.
Source: Module 5.3.5.1 DS8201-A-J202 CSR Tables 14.2.4.1 and 14.2.4.2; Module 5.3.5.1 DS8201-A-J202 Abbreviated CSR Tables 14.2.4.1 and 14.2.4.2

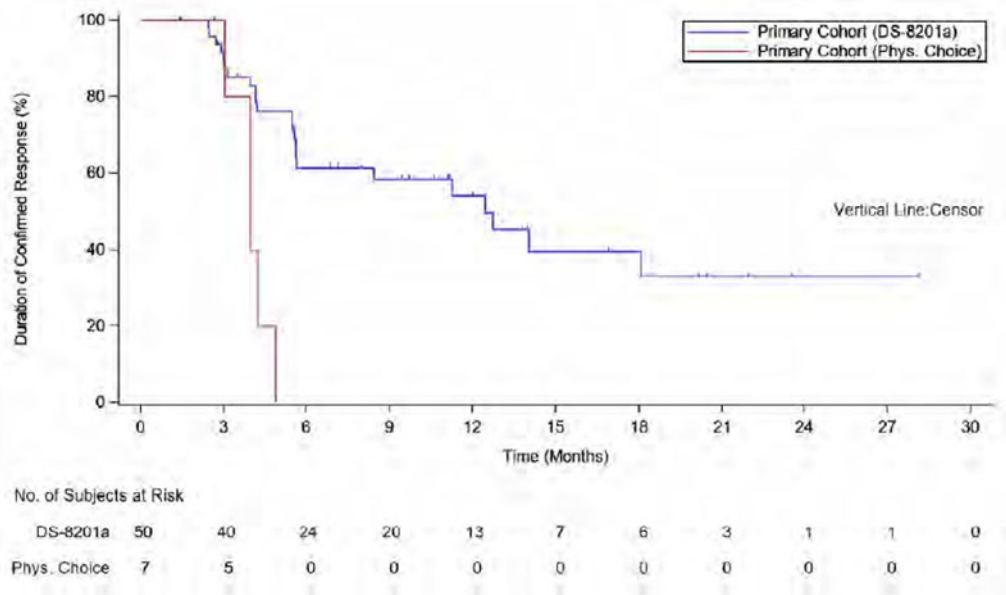
Figure 3.6: Kaplan-Meier Plot of Progression-free Survival Based on Independent Central Review in Subjects with Metastatic HER2-positive Gastric or Gastroesophageal Junction Cancer in Primary Cohort of Study J202 (Intent-to-Treat Analysis Set)



DS-8201a = trastuzumab deruxtecan, T-DXd; HER2 = human epidermal growth factor receptor 2; No. = number; Phys. = physician; T-DXd = trastuzumab deruxtecan
Source: Module 5.3.5.3 SCE J202 Figure 14.2.3.3_5

Secondary endpoint – DoR

Figure 8.5: Kaplan-Meier Plot of Duration of Confirmed Response Based on Independent Central Review as of 03 June 2020 Data Cut-off (Intent-to-Treat Analysis Set*)



Source: DS8201-A-J202 updated CSR Figure 14.2.3.6
*: Results of DoR were identical between the ITT Analysis Set and the FAS because the FAS included 187 subjects, excluding only 1 subject from ITT Analysis Set who did not receive the study drug.

Table 26: Confirmed Best Overall Response by Independent Central Review in Study J202 at Update DCO (ie, 03 Jun 2020) (Intent-to-Treat Analysis Set)

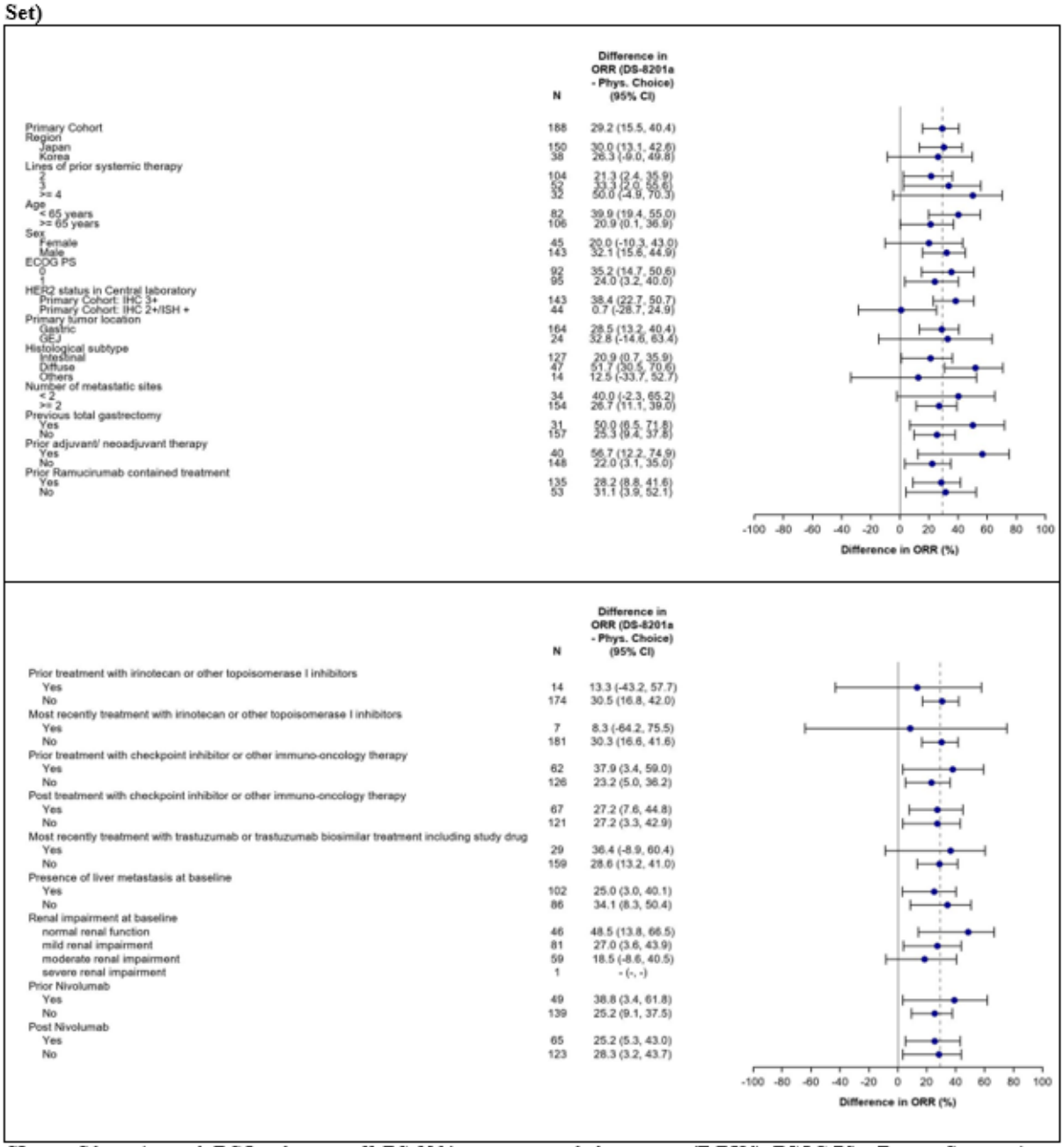
	Study J202 Primary Cohort (DCO = 03 Jun 2020)			
	T-DXd 6.4 mg/kg	TPC		
		Irinotecan	Paclitaxel	Total
ITT Analysis Set[a]				
N	126	55	7	62
Best overall response by ICR (with confirmation of CR or PR), n (%)				
Complete response	10 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	40 (31.7)	6 (10.9)	1 (14.3)	7 (11.3)
Stable disease	57 (45.2)	28 (50.9)	3 (42.9)	31 (50.0)
Progressive disease	15 (11.9)	18 (32.7)	0 (0.0)	18 (29.0)
Not evaluable	4 (3.2)	3 (5.5)	3 (42.9)	6 (9.7)
Confirmed ORR by ICR				
ORR[b] n (%)	50 (39.7)	6 (10.9)	1 (14.3)	7 (11.3)
95% CI[c]	31.1, 48.8	4.1, 22.2	0.4, 57.9	4.7, 21.9
CMH test[d]	*P*-value <0.0001			

Table 28: Confirmed Median Duration of Response by Independent Central Review in Study J202 at Update DCO (ie, 03 Jun 2020) (Intent-to-Treat Analysis Set)

	Study J202 Primary Cohort (DCO = 03 Jun 2020)			
	T-DXd 6.4 mg/kg	TPC		
		Irinotecan	Paclitaxel	Total
ITT Analysis Set[a]				
N	126	55	7	62
Confirmed median DoR by ICR				
Number with confirmed CR or PR	50	6	1	7
Median DoR[b], months	12.5	4.1	3.9	3.9
95% CI[b]	5.6, NE	3.0, 4.9	NE, NE	3.0, 4.9

Ancillary analyses

Figure 2: Forest Plot Comparing Confirmed Objective Response Rate Based on Independent Central Review Between Treatment Arms in Subgroups in Primary Cohort of Study J202 (Intent-to-Treat Analysis Set)



CI = confidence interval; DCO = data cut-off; DS-8201a = trastuzumab deruxtecan, (T-DXd); ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; ORR = objective response rate; Phys. = physician; SCE = Summary of Clinical Efficacy

DCO = 08 Nov 2019

Source: Module 5.3.5.3 SCE J202 Figure 14.2.6.18 1.

2.4.3. Discussion on clinical efficacy

The sought new therapeutic indication of Enhertu for advanced HER2+ GC/GEJC in the 2L+ setting (after a prior trastuzumab-based regimen) is based on efficacy data from pivotal study DESTINY-Gastric02 (U205) and supportive data from study DESTINY-Gastric01 (J202).

The pivotal study DESTINY-Gastric02 (U205) was a Phase 2, multicentre, single-arm, open-label study to evaluate the efficacy and safety of T-DXd (6.4 mg/kg as IV infusion Q3W) in subjects with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed during or after a trastuzumab-containing regimen (2L setting). The study was conducted at 24 sites in the US and Europe.

Supportive data come from study DESTINY-Gastric01 (J202), a Phase 2, multicentre, open-label, 2:1 randomized study to evaluate efficacy and safety of T-DXd (6.4 mg/kg as IV infusion Q3W) in subjects with advanced HER2-positive gastric or GEJ adenocarcinoma, who had progressed on 2 or more prior regimens (3L setting) that had to include a fluoropyrimidine agent (fluorouracil, capecitabine, or S-1) and a platinum agent (oxaliplatin or cisplatin) in addition to prior trastuzumab or a trastuzumab biosimilar. This primary cohort was compared with a TPC chemotherapy arm (irinotecan or paclitaxel). The study was conducted in Asian patients at multiple sites in Japan and South Korea.

It is acknowledged that there is an unmet medical need for patients with advanced HER2+ GC, who have progressed on 1L chemotherapy combined with trastuzumab or a trastuzumab biosimilar. The applied indication concerns a HER-2 driven disease and the focus of assessment of the pivotal trial is ORR and DOR as indicators of disease activity.

Design and conduct of clinical studies

The pivotal U205 study enrolled 79 subjects in EU/USA. The subjects were treated with T-DXd at the dose of 6.4 mg/kg after progressing on or after a trastuzumab-containing regimen (2L setting), which is the target population for the sought extension of indication. The primary efficacy endpoint was confirmed ORR by ICR and secondary endpoints were OS, PFS and DoR. All patients provided fresh tumour samples for central assessment of HER2 status (IHC 3+ or IHC 2+ and evidence of HER2 amplification by ISH) as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines based on this new tumor biopsy obtained after progression on or after a first-line trastuzumab-containing regimen. Since HER-2 status can change post-trastuzumab, this approach was endorsed. The inclusion/exclusion criteria for the U205 study clearly define a second line patient population with disease progression on or after treatment including trastuzumab and are still in a good condition, i.e. ECOG PS 0-1. The main limitations are related to the single-arm and open-label design of the study, which hampers the assessment, particularly of the time-to-event endpoints.

In the supportive J202 (DESTINY-Gastric01) study, 188 subjects with progressive disease after two or more lines (3L+ setting) were randomized: 126 to the experimental T-DXd arm and 62 to the chemotherapy arm. The study was conducted in Japan and North Korea. The primary endpoint was unconfirmed ORR by ICR. OS, PFS and DoR were secondary endpoints. The baseline characteristics and demographics across both arms of treatment were overall well-balanced. The choice of irinotecan and paclitaxel as comparators in the control arm (TPC) are considered appropriate and in line with clinical practice in the EU.

Efficacy data and additional analyses

In the pivotal study U205, the primary endpoint of confirmed ORR is 41.8% (DCO 08 Nov 2021). With a median duration of follow-up of 5.9 months (range: 0.7 to 15.4) median DOR was 8.1 months (range 5.9, not estimable). Median OS was 12.1 months (95% CI: 8.6, NE). Median PFS was 5.6 months (95% CI: 4.2, 8.3). These results shows that T-DXd offers promising activity in a patient population with a high unmet medical need harbouring a highly symptomatic disease. Response rates in the range seen in pivotal U205 trial might relate to reduction of symptoms and duration of response. Overall, T-

DXd would offer a targeted option for these patients. All patients enrolled in the study were high expressors of HER-2, as per rebiopsy before enrolment.

At DCO as of 03 Jun 2020, the supportive study J202 showed a confirmed ORR of 39.7% for the primary cohort compared to 11.3% for the TPC group. In the ITT, median DoR was 12.5 months (95% CI: 5.6, NE) in the 50 subjects who obtained a response. For the TPC group, median DoR was 3.9 months (95% CI: 3.0, 4.9). The secondary endpoint of median OS is 12.5 and 8.9 months for the T-DXd and TPC arms respectively, with a HR=0.59 (95%CI: 0.39, 0.88), which implies a clinically relevant median improvement of survival of nearly 4 months.

It is well known that prognosis of Asian patients with gastric cancer is better than prognosis of non-Asian patients. This is thought to be related to different factors, including differences in disease biology, differences in treatment patterns, and differences in methods for screening/diagnosis. For example, in Europe approximately 50% of the patients have advanced disease at the time of diagnosis, while this is true for ~20% in Asian patients (likely due to national screening programmes for gastric cancer in Asia). Furthermore, there are differences in the initial tumour localisation between regions, as GEJ cancer is much more common in non-Asian patients compared with Asian patients.

As a consequence Asian patients receive more lines of therapy for advanced disease than patients in the EU. For example, in Japan almost all patients with metastatic gastric cancer receive second-line therapy, and more than half of patients receive three lines of therapy. In Europe, on the other hand, only half of the patient population is offered second-line treatment on progression after first-line therapy, and only a small proportion of the patients receive third-line therapy.

Additional expert consultation

A SAG-O was held on 03-NOV-2022. Minutes from this meeting are presented.

1) The representativeness of the 3L Japanese/Korean GC/GEJC population for the 2L European population, given regional differences in prognosis, diagnostic approach and treatment strategy;

The SAG discussed the many differences between populations, especially between the J202 Asian population and the target 2nd line European population in U205, such as early diagnostic approaches (screening), surgical procedures and systemic therapies. However, opinions were split in terms of the impact of such differences on expected treatment effects:

- According to a majority view, it is unclear to what extent the differences are predictive of a different treatment effect. As such, the observed differences do not have an obvious effect on the possibility to generalise or extrapolate results. Extrapolation between 3rd and 2nd line of chemotherapy treatment, for a HER2-targeted agent did not seem problematic in the target indication. Additionally, the prognostic parameters and outcome in respect to ORR, DOR, PFS and OS of the patients in the J202 3L trial are similar to those of the U205 2L trial. Thus, extrapolation between regions in terms of treatment effects seem acceptable.
- According to a minority view, the impact of observed differences is uncertain and generalisation and extrapolation across lines of treatment are difficult, regardless of the type of agent. According to this view, extrapolation of treatment effects cannot be justified.

The SAG agreed that the analyses presented based on external controls are difficult to interpret due to possible selection bias, as evidenced by the long event-free period in the treatment group. The SAG also

recommended that it is important to assess prior treatments by treatment group to ensure relevance of the trial populations.

2) Whether the effect size as observed in the Japanese/Korean 3L patients (J202) and the anti-disease activity as shown in the European patients included in the U205 study are sufficiently large to overcome the uncertainty (if any) related to representativeness as considered above. Please elaborate.

The SAG-O is aware that the patient numbers in both trials are low and that the U205 trial is a single arm trial with limitations in respect especially to the magnitude of OS in comparison with other therapies.

However, according to the majority of experts, looking at the totality of evidence especially the results observed in trial J202, including a clear effect on overall survival, the high overall response rate (ORR) observed in the single arm trial U205, the likelihood of an improvement in tumour related symptoms, an acceptable toxicity profile, and considering the limited therapeutic options with no well established treatment in this targeted population, justify that overall the activity and efficacy observed are sufficiently convincing to justify conditional approval even if the confirmatory data from the phase III trial in second-line are still outstanding. According to this view, it is important that the confirmatory trial should provide clinically and statistically convincing results in terms of true clinical endpoints in the target population. Feasibility of such confirmatory trial following early approval should be clearly demonstrated and required.

According to a minority view, the differences among populations are too large to overcome uncertainties, particularly taking into account the likely problem with phase III trial feasibility in the target population following early approval. Even if the available exploratory results are promising, overall they do not justify early approval in the target population.

Additional efficacy data needed in the context of a conditional MA

Overall, data on the T-DXd in the intended 2L+ setting for patients with HER2-positive GC/GECJ are not deemed comprehensive, but it is likely that the MAH will be able to provide comprehensive data through results from the ongoing study DS8201-A-U306 (phase III RCT of trastuzumab deruxtecan versus ramucirumab + paclitaxel in the 2L population including EU and USA patients). The Study U306 will provide interpretable results of time to event endpoints in the 2L setting in a patient population representative of the EU population.

As of 08 Nov 2022, 148 subjects have been enrolled and treated. Planned sample size is ~490 subjects. Study U306 enrollment is projected to be completed in Dec 2024 and the CSR ready in Q4 of 2025. The study is conducted in 22 countries from Europe, Latin America and Asia. This requirement constitutes a specific obligation (SOB) and is reflected in Annex II of the Opinion

Assessment of paediatric data on clinical efficacy

Not applicable

2.4.4. Conclusions on the clinical efficacy

The single-arm pivotal study U205 in an European population with advanced GC/GEJC showed compelling results of T-DXd in terms of ORR and DoR in the 2L setting which is the sought indication.

The main limitations of these data are related to the single-arm design of the study, which hampers the assessment, particularly of the time-to-event endpoints. The supportive randomised Phase II study J202 in an Asian population showed similar results but was conducted in a different line of treatment.

The following measures are considered necessary to address issues related to efficacy:

SOB: In order to confirm the efficacy and safety of Enhertu in the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen, the MAH should submit the final results of study DS-8201-A-U306, a phase 3, multicentre, 2-arm, randomised, open-label study of Enhertu in subjects with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen.

2.5. Clinical safety

2.5.1.1. Introduction

The safety information to support the extension of indication comes from 3 studies. The proposed **recommended dose** is 6.4 mg/kg administered intravenously (IV) once **every 3 weeks** (Q3W).

- **Study J202** (asian (Japan+South Korea) population, 3L+, n=125, DCO 3.6.2020), phase II randomised
- **Study U205** (western (US+EU) population, 2L, n=79, DCO 9.4.2021), phase II SAT
- **Study J101** (from this study only asian GC patients treated with 6.4mg/kg, n=25, DCO 1.8.2019), phase I

were pooled to form **the HER2-positive GC Pool** (N = 229) (Table 1.2).

The pooled safety population has been evaluated for patients who received at least one dose of Enhertu 6.4 mg/kg (n = 619), across multiple tumour types in clinical studies.

This dossier only presented safety data for the patients with GC receiving 6.4 mg/kg. Other patients with other cancer diseases in other trials have also received 6.4mg/kg, but their safety data was not presented in this dossier, and therefore not assessed in this procedure.

Table 1.2: Summary of Groups Included in Data Presentations

Group	Description (Safety Population) [a]	Number of Subjects Treated
Study J202 (HER2-positive GC)	T-DXd 6.4 mg/kg (primary cohort) or TPC (irinotecan or paclitaxel)	125 62
Study U205 (HER2-positive GC)	T-DXd 6.4 mg/kg	79
HER2-positive GC T-DXd 6.4 mg/kg Pool	Total Study J202 T-DXd 6.4 mg/kg (primary cohort) Study U205 T-DXd 6.4 mg/kg Study J101 T-DXd 6.4 mg/kg (Part 1 Cohort 5 and Part 2b)	229 125 79 25
All Tumor Types T-DXd ≥5.4 mg/kg Pool	Total Study J202 T-DXd 6.4 mg/kg Q3W (primary and exploratory cohort) Study U205 T-DXd 6.4 mg/kg Study J101 T-DXd 5.4, 6.4, and 8.0 mg/kg Study U201 T-DXd 5.4, 6.4, and 7.4 mg/kg Study U204 T-DXd 5.4 and 6.4 mg/kg	962 169 79 280 253 181

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; Q3W = once every 3 weeks; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
[a] The indicated dose was to be administered intravenously Q3W.
Source: Module 5.3.5.3 SCS SAP Version 3.0

Table 1.2 Summary of Groups Included in Safety Data Presentations

Evaluation	Drug / Dose	Number of Subjects Treated
Data for Primary Analysis Subjects with HER2-low BC from Study U303	T-DXd 5.4 mg/kg TPC	T-DXd: 371 TPC: 172
All BC T-DXd 5.4 mg/kg Pool Multi-study pool of subjects with HER2-positive or HER2-low BC who received T-DXd 5.4 mg/kg (N = 883)	T-DXd 5.4 mg/kg	883 Study U303: 371 Study U302: 257 Study U201: 184 Study J101: 71
All Tumor Types T-DXd ≥5.4 mg/kg Pool Multi-study pool of subjects with any tumor type who received T-DXd ≥5.4 mg/kg (N = 1590)	T-DXd 5.4 mg/kg	944 Study U303: 371 Study U302: 257 Study U201: 184 Study J101: 91 Study U204: 41
	T-DXd 6.4 mg/kg	619 Study J101: 183 Study J202: 169 Study U201: 48 Study U204: 140 Study U205: 79
	T-DXd 7.4 mg/kg	Study U201: 21
	T-DXd 8.0 mg/kg	Study J101: 6

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice
Source:, Module 5.3.5.3 SCS SAP v1.0

Patients in study U205 had slightly worse characteristics compared to patients in the T-DXd arm of J202 regarding: tumor burden, proportion of subjects with ECOG PS 1, liver metastases, and ≥2 metastatic sites. Conversely, other baseline characteristics were worse for subjects in the T-DXd arm of J202 than for subjects in U205: age ≥65 years, normal renal function, normal hepatic function, prior systemic anticancer therapy (median 3 vs. 1).

Table 2: Gastric Cancer History in Studies J202 and U205 (Intent-to-Treat Analysis Set)

	Study J202 Primary Cohort (DCO = 08 Nov 2019)		**Study U205 (DCO = 09 Apr 2021)**
	T-DXd (N = 126)	**TPC (N = 62)**	**T-DXd (N = 79)**
Type of cancer, n (%)			
Gastric	109 (86.5)	55 (88.7)	27 (34.2)
GEJ	17 (13.5)	7 (11.3)	52 (65.8)
HER2 expression (IHC) per central laboratory (archived and fresh samples)[a], n (%)			
2+/ISH-positive	29 (23.0)	15 (24.2)	10 (12.7)
3+	96 (76.2)	47 (75.8)	68 (86.1)
IHC missing	1 (0.8)	0	-
Not evaluable	0	0	1 (1.3)
Histological subtype, n (%)			
Adenocarcinoma	-	-	78 (98.7)
Intestinal	89 (70.6)	38 (61.3)	19 (24.1)
Diffuse	29 (23.0)	18 (29.0)	1 (1.3)
Mixed	-	-	1 (1.3)
Unknown	-	-	57 (72.2)
Other	8 (6.3)	6 (9.7)	1 (1.3)
Time from initial diagnosis (months)			
Median	22.9	20.3	14.19
Min-Max	4.6-156.3	4.5-233.4	3.6-88.5
Tumor stage at study entry, n (%)			
Stage IIB[b]	0	0	1 (1.3)
Stage IV	121 (96.0)	62 (100.0)	78 (98.7)
Other (ie, recurrence)	5 (4.0)	0	0
Number of metastatic sites at baseline, n (%)			
<2	24 (19.0)	10 (16.1)	5 (6.3)
≥2	102 (81.0)	52 (83.9)	74 (93.7)
Lung metastases at baseline, n (%)	39 (31.0)	15 (24.2)	21 (26.6)
Liver metastases at baseline, n (%)	68 (54.0)	34 (54.8)	50 (63.3)
Brain metastases at baseline, n (%)	4 (3.7)	4 (6.5)	4 (5.1)
Peritoneal metastases at baseline, n (%)	21 (16.7)	11 (17.7)	8 (10.1)
Tumor burden (sum of diameters of target lesions based on ICR at baseline)			
n	120	56	78
Median (cm)	4.8	5.3	6.3

	Study J202 Primary Cohort (DCO = 08 Nov 2019)		Study U205 (DCO = 09 Apr 2021)
	T-DXd (N = 126)	TPC (N = 62)	T-DXd (N = 79)
Min-Max	1.2-20.4	1.0-22.8	1.0-30.6
Missing	6 (4.8)	6 (9.7)	1 (1.3)
<5 cm, n (%)	63 (50.0)	26 (41.9)	32 (40.5)
≥5 to <10 cm	34 (27.0)	22 (35.5)	26 (32.9)
≥10 cm	23 (18.3)	8 (12.9)	20 (25.3)
ECOG performance status, n (%)			
0	62 (49.2)	30 (48.4)	29 (36.7)
1	63 (50.0)	32 (51.6)	50 (63.3)
Prior treatment type, n (%)			
Prior cancer surgery	60 (47.6)	23 (37.1)	21 (26.6)
Total gastrectomy (yes)	22 (17.5)	9 (14.5)	0

DCO = data cut-off; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; ISH = in situ hybridization; Max = maximum; Min = minimum; QTcF = QT interval corrected for heart rate by Fridericia's formula; SAP = Statistical Analysis Plan; SCE = Summary of Clinical Efficacy; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice

[a] Subject No. [redacted], who was randomized to the T-DXd arm of J202, became ineligible before first dose, as the subject's ECG results at Cycle 1 Day 1 predose met exclusion criterion 2 (ie, QTcF prolongation to >470 ms [females] or >450 ms [males] based on average of the screening triplicate 12-lead ECG). Because the HER2 status by central laboratory was derived as the last value before the date of first dose (as per baseline definition in the SAP) and the subject did not have a first dose date, his central laboratory HER2 status was entered as "IHC missing" in demographic tables. However, the subject had a central HER2 status of IHC 2+/ISH-positive before randomization date.

[b] Subject No. [redacted] was described as Stage IV at initial diagnosis and stage IIB at study entry with metastasis (liver, lymph node).

Source: Module 5.3.5.3 SCE J202 Tables 14.1.2.1_1, 14.1.3.1_1, and 14.1.3.3, Module 5.3.5.2 DS8201-A-U205 CSR.

Amendment Tables 14.1.2.1, 14.1.3.1, 14.2.6.1, Listing 16.2.4.2, Module 5.3.5.2 U205 Ad Hoc Table 14 DCO 08 Nov 2021

Table 3 summarizes the number (%) of subjects with the most common (reported in ≥10% of subjects) ongoing PMHs, with both ongoing PMHs and TEAEs, and with TEAEs in the HER2-positive GC Pool.

Table 3: Most Common (Reported in ⩾10% of Subjects) Ongoing Past Medical Histories and Treatment-emergent Adverse Events (Safety Analysis Set)

MedDRA PT (PMH)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)		
	Subjects with Ongoing PMH at Baseline[a] n (%)	Subjects with Both TEAE and Ongoing PMH[a] n (%)	Subjects with TEAEs[a] n (%)
Hypertension	88 (38.4)	2 (2.3)	4 (1.7)
Anaemia	77 (33.6)	50 (64.9)	112 (48.9)
Peripheral sensory neuropathy	63 (27.5)	0	5 (2.2)
Constipation	53 (23.1)	7 (13.2)	59 (25.8)
Insomnia	34 (14.8)	1 (2.9)	18 (7.9)
Cataract	33 (14.4)	3 (9.1)	4 (1.7)
Decreased appetite	29 (12.7)	17 (58.6)	124 (54.1)
Gastrooesophageal reflux disease	27 (11.8)	2 (7.4)	10 (4.4)

MedDRA PT (PMH)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)		
	Subjects with Ongoing PMH at Baseline[a] n (%)	Subjects with Both TEAE and Ongoing PMH[a] n (%)	Subjects with TEAEs[a] n (%)
Abdominal pain	26 (11.4)	8 (30.8)	27 (11.8)
Fatigue	24 (10.5)	11 (45.8)	62 (27.1)
Back pain	24 (10.5)	1 (4.2)	19 (8.3)
Nausea	23 (10.0)	13 (56.5)	150 (65.5)
Neuropathy peripheral	23 (10.0)	0	2 (0.9)

CRF = case report form; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subject with event; N = total subjects; PMH = past medical history; PT = preferred term; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event
The HER2-positive GC 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Medical history information was taken from the Medical History CRF page, and "Ongoing" was based on the CRF checkbox.
[a] Percentage of subjects with ongoing PMH at Baseline was calculated with subjects in the safety analysis set as denominator.
[b] Baseline PMH symptoms were reported as TEAEs if they worsened after the first T-DXd dose. Percentage of subjects with both (drug-related) TEAE and ongoing PMH was calculated with subjects having that particular PMH PT as denominator.
[c] Percentage of subjects with TEAEs was calculated with subjects in the safety analysis set as denominator.
Source: Module 5.3.5.3 SCS Table 1.2.1.3; Appendix 1 Table 1

Table 1.7: Summary of Prior Systemic Anticancer Therapy (Safety Analysis Set)

Parameter	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Number of Regimens				
Mean (Std Dev)	2.9 (1.15)	2.6 (0.78)	1.0 (0.19)	2.4 (1.40)
Median	3.0	2.0	1.0	2.0
Range	2, 9	2, 5	1, 2	1, 9
Number of Regimens, n (%)				
1	0	0	76 (96.2)	77 (33.6)

2	58 (46.4)	34 (54.8)	3 (3.8) [b]	67 (29.3)
3	37 (29.6)	21 (33.9)	0	40 (17.5)
4	21 (16.8)	5 (8.1)	0	27 (11.8)
≥5	9 (7.2)	2 (3.2)	0	18 (7.9)
Regimen Intent, n (%) [a]				
Neo-Adjuvant	5 (4.0)	1 (1.6)	8 (10.1)	17 (7.4)
Adjuvant	26 (20.8)	10 (16.1)	3 (3.8)	38 (16.6)
Locally Advanced	0	0	7 (8.9)	7 (3.1)
Metastatic	0	0	68 (86.1)	68 (29.7)
Locally Advanced/Metastatic	125 (100)	62 (100)	0	149 (65.1)
Maintenance	0	0	10 (12.7)	10 (4.4)
Preventive	0	0	0	0
Other	2 (1.6)	0	3 (3.8)	6 (2.6)
Any Prior Anticancer Therapy Reported in At Least 20% of subjects in HER2-positive GC 6.4 mg/kg Pool, n (%) [c,d]				
Trastuzumab	125 (100)	62 (100)	79 (100)	229 (100)
Capecitabine	93 (74.4)	41 (66.1)	34 (43.0)	147 (64.2)
Cisplatin	79 (63.2)	37 (59.7)	36 (45.6)	135 (59.0)
Ramucirumab	94 (75.2)	41 (66.1)	0	111 (48.5)
Oxaliplatin	61 (48.8)	27 (43.5)	38 (48.1)	109 (47.6)
Paclitaxel	86 (68.8)	46 (74.2)	2 (2.5)	108 (47.2)
Gimeracil W/Oteracil Potassium/Tegafur	61 (48.8)	29 (46.8)	0	61 (26.6)
Fluorouracil	8 (6.4)	6 (9.7)	44 (55.7)	52 (22.7)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

If a subject received more than 1 regimen, that subject was counted in each relevant category.

[a] Study J101/J202 collected locally advanced and metastatic regimen intent as a combined parameter, whereas Study U205 collected locally advanced and metastatic regimen separately.

[b] Among the 3 subjects receiving 2 regimens, [redacted] received trastuzumab intended for neoadjuvant and a second regimen intended for metastatic. [redacted] and [redacted] both received only 1 trastuzumab-containing regimen.

[c] If a subject received more than 1 therapy within the same regimen, that subject was counted for each relevant therapy.

[d] Agents are sorted in descending frequency based on the HER2-positive GC T-DXd 6.4 mg/kg Pool.

Source: Module 5.3.5.3 SCS Table 1.1.4

2.5.2. Patient exposure

Table 1.3: Summary of Exposure (Safety Analysis Set)

Parameter	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	Irinotecan (N = 55)	Paclitaxel (N = 7)	TPC (N = 62)		
Treatment Duration (months) [a]						
Mean (Std Dev)	6.71 (5.717)	2.97 (1.985)	4.83 (4.289)	3.18 (2.377)	5.06 (3.536)	6.03 (4.953)
Median	4.60	2.76	4.60	2.76	4.34	4.60
Range	0.7, 29.7	0.5, 11.3	0.9, 13.1	0.5, 13.1	0.7, 15.9	0.7, 29.7
Treatment Duration (months Categories) [a], n (%)						
0 to ≤3	40 (32.0)	37 (67.3)	3 (42.9)	40 (64.5)	30 (38.0)	81 (35.4)
>3 to ≤6	35 (28.0)	14 (25.5)	2 (28.6)	16 (25.8)	25 (31.6)	64 (27.9)
>6 to ≤9	20 (16.0)	3 (5.5)	1 (14.3)	4 (6.5)	14 (17.7)	39 (17.0)
>9 to ≤12	9 (7.2)	1 (1.8)	0	1 (1.6)	5 (6.3)	16 (7.0)
>12 to ≤18	15 (12.0)	0	1 (14.3)	1 (1.6)	5 (6.3)	23 (10.0)
>18 to ≤24	3 (2.4)	0	0	0	0	3 (1.3)
>24	3 (2.4)	0	0	0	0	3 (1.3)
Patient-years of exposure [b]	69.9	13.6	2.8	16.5	33.3	115.1
Cumulative Dose Level [c]						
Mean (Std Dev)	53.45 (43.927)	807.64 (591.483)	1120.00 (1110.015)		43.08 (29.779)	48.88 (38.606)
Median	39.98	630.00	1060.00		38.20	38.65
Range	6.4, 236.6	150, 3600	80, 3280		6.4, 138.8	6.4, 236.6
Number of Cycles [d]						
Mean (Std Dev)	9.0 (7.71)				6.9 (4.79)	8.1 (6.65)
Median	6.0				6.0	6.0
Range	1, 41				1, 22	1, 41
Dose Intensity [e]						
Mean (Std Dev)	5.74 (0.742)	126.86 (20.358)	188.44 (52.912)		5.99 (0.583)	5.81 (0.724)
Median	5.91	126.00	196.49		6.19	6.00
Range	3.7, 6.8	79.8, 161.5	80, 230.6		3.9, 6.7	3.2, 6.8
Relative Dose Intensity [f] (%)						
Mean (Std Dev)	89.67 (11.596)	84.58 (13.572)	78.52 (22.047)	83.89 (14.650)	93.52 (9.109)	90.75 (11.311)
Median	92.39	84.00	81.87	83.67	96.78	93.78
Range	58.2, 106.5	53.2, 107.7	33.3, 96.1	33.3, 107.7	60.3, 104.1	50.4, 106.5
Relative Dose Intensity Categories [f], n (%)						
≥90%	67 (53.6)	22 (40.0)	3 (42.9)	25 (40.3)	56 (70.9)	136 (59.4)
<90% to ≥80%	36 (28.8)	12 (21.8)	1 (14.3)	13 (21.0)	15 (19.0)	56 (24.5)
<80% to ≥60%	21 (16.8)	19 (34.5)	2 (28.6)	21 (33.9)	8 (10.1)	35 (15.3)
<60%	1 (0.8)	2 (3.6)	1 (14.3)	3 (4.8)	0	2 (0.9)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
1 month = 365.25/12 = 30.44 days.
[a] Treatment duration (months):
T-DXd = (date of the last dose - date of the first dose + 21) / 30.44
Irinotecan = (date of the last dose - date of the first dose + 14) / 30.44
Paclitaxel = (date of last dose - date of first dose + 28 [if the last dose is the first dose in a cycle], or + 21 [if the last dose is the second dose in a cycle], or + 14 [if the last dose is the third dose in a cycle]) / 30.44.
[b] Total patient-years of exposure = sum of duration of treatment (months) / 12.
[c] Cumulative dose level = sum (the actual dose level received) (mg/kg for T-DXd and mg/m^2 for irinotecan and paclitaxel).
[d] Irinotecan monotherapy was administered as an intravenous infusion biweekly. The subjects were given this treatment followed by a rest period of at least 3 weeks as necessary. Paclitaxel monotherapy was administered as an intravenous infusion weekly. The subjects were given this treatment for 3 consecutive weeks, followed by a rest period of at least 2 weeks as necessary. Therefore, there are no data on number of cycles for irinotecan, paclitaxel, and TPC.
[e] Dose Intensity:
T-DXd (mg/kg/3 weeks) = total amount of doses taken / (days of treatment / 21)
Irinotecan (mg/m^2/2 weeks) = total amount of doses taken / (days of treatment / 14)
Paclitaxel (mg/m^2/4 weeks) = total amount of doses taken / (days of treatment / 28).
[f] Relative Dose Intensity (%):
T-DXd = dose intensity / assigned dose level (mg/kg / 3 weeks)
Irinotecan = dose intensity / 150 (mg/m^2 / 2 weeks)
Paclitaxel = dose intensity / 240 (mg/m^2 / 4 weeks).
Source: Module 5.3.5.3 SCS Table 1.1.3

The numbers missing in table 1.3 above are presented in table 2 below.

Table 2: Number of Drug Doses - Study J202 HER2-positive GC, Primary Cohort (Safety Analysis Set)

	Irinotecan (N = 55)	**PTX (N = 7)**	**TPC (N = 62)**
n	55	7	62
Mean (Std Dev)	6.0 (4.22)	14.6 (13.88)	7.0 (6.50)
Median	5.0	14.0	5.0
Range	1, 24	1, 41	1, 41

CSR = clinical study report; DCO = data cut-off; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; PTX = paclitaxel; Std Dev = standard deviation; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])
Source: Module 5.3.5.1 DS8201-A-J202 Abbreviated CSR Table 14.1.5.1 for 03 Jun 2020 DCO

The **median treatment duration** across all subgroups for the HER2-postive GC Pool ranged between **3.89** and **5.63** months, with elderly, male subjects, subjects with moderate renal impairment, and European population having a relatively longer median duration.

Table 1.4: Summary of Subject Disposition (Safety Analysis Set)

Parameter	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-Positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects who were Ongoing Study Drug at DCO, n (%)	10 (8.0)	0	23 (29.1)	33 (14.4)
Subjects who Discontinued Study Drug for Any Reason, n (%)	115 (92.0)	62 (100)	56 (70.9)	196 (85.6)
Progressive Disease [a]	82 (65.6)	50 (80.6)	39 (49.4)	140 (61.1)
Adverse Event	22 (17.6)	4 (6.5)	9 (11.4)	37 (16.2)
Clinical Progression [b]	6 (4.8)	5 (8.1)	2 (2.5)	8 (3.5)
Death	2 (1.6)	0	2 (2.5)	4 (1.7)
Withdrawal by Subject	2 (1.6)	3 (4.8)	2 (2.5)	4 (1.7)
Physician Decision	1 (0.8)	0	1 (1.3)	2 (0.9)
Other [c]	0	0	1 (1.3)	1 (0.4)

DCO = Date of data cutoff; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; n = number of subjects; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] Based on RECIST v1.1

[b] Per investigator assessment

[c] Other reason was reported for a subject in Study U205 and was "drug hold too long." (see Module 5.3.5.2 DS8201-A-205 CSR U205 Listing 16.2.7.3)

Source: Module 5.3.5.3 SCS Table 1.1.1

2.5.3. Adverse events

In the HER2-positive GC Pool, all subjects (100%) had **at least 1 TEAE**, 167/229 (72.9%) subjects had a **worst TEAE of ≥Grade 3**, 92/229 (40.2%) subjects had an **SAE**, and 19/229 (8.3%) subjects had a TEAE associated with an outcome of **death**. For 2/229 (0.9%) subjects this TEAE was considered drug-related; see Section 2.1.6.2 (Table 2.2).

Table 2.2: Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

Parameter	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any TEAE	125 (100)	61 (98.4)	79 (100)	229 (100)
TEAEs with worst CTCAE ≥Grade 3 [a]	107 (85.6)	35 (56.5)	40 (50.6)	167 (72.9)
Serious TEAEs	56 (44.8)	16 (25.8)	29 (36.7)	92 (40.2)
TEAEs associated with study drug discontinuation	22 (17.6)	4 (6.5)	12 (15.2)	38 (16.6)
TEAEs associated with dose reduction	40 (32.0)	21 (33.9)	19 (24.1)	68 (29.7)
TEAEs associated with study drug interruption	79 (63.2)	23 (37.1)	17 (21.5)	109 (47.6)
TEAEs associated with an outcome of death [b]	8 (6.4)	2 (3.2)	10 (12.7)	19 (8.3)
Subjects with any drug-related TEAE [c]	122 (97.6)	56 (90.3)	74 (93.7)	221 (96.5)
Drug-related TEAEs with worst CTCAE ≥Grade 3 [a]	94 (75.2)	27 (43.5)	21 (26.6)	131 (57.2)
Drug-related serious TEAEs	30 (24.0)	5 (8.1)	8 (10.1)	41 (17.9)
Drug-related TEAEs associated with study drug discontinuation	14 (11.2)	3 (4.8)	7 (8.9)	24 (10.5)
Drug-related TEAEs associated with dose reduction	38 (30.4)	21 (33.9)	15 (19.0)	62 (27.1)
Drug-related TEAEs associated with study drug interruption	65 (52.0)	19 (30.6)	7 (8.9)	83 (36.2)
Drug-related TEAEs associated with an outcome of death [b]	1 (0.8)	0	1 (1.3)	2 (0.9)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.

[c] If relationship was missing, the TEAE was considered to be related to the drug.

Source: Module 5.3.5.3 SCS Table 1.2.1.1.1

Table 2.3: Treatment-Emergent Adverse Events Reported in at Least 10% of Subjects in the HER2-positive GC T-DXd 6.4 mg/kg Pool, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any TEAE	125 (100)	61 (98.4)	79 (100)	229 (100)
Nausea	79 (63.2)	29 (46.8)	52 (65.8)	150 (65.5)
Decreased appetite	76 (60.8)	28 (45.2)	26 (32.9)	124 (54.1)
Fatigue [a]	69 (55.2)	27 (43.5)	44 (55.7)	121 (52.8)
Anaemia [a]	72 (57.6)	19 (30.6)	27 (34.2)	113 (49.3)
Neutropenia [a]	81 (64.8)	22 (35.5)	20 (25.3)	113 (49.3)
Thrombocytopenia [a]	50 (40.0)	4 (6.5)	16 (20.3)	78 (34.1)
Vomiting	33 (26.4)	5 (8.1)	33 (41.8)	74 (32.3)
Diarrhoea	41 (32.8)	20 (32.3)	27 (34.2)	73 (31.9)
Leukopenia [a]	48 (38.4)	22 (35.5)	7 (8.9)	66 (28.8)
Constipation	31 (24.8)	15 (24.2)	21 (26.6)	59 (25.8)
Alopecia	28 (22.4)	9 (14.5)	19 (24.1)	51 (22.3)
Pyrexia	31 (24.8)	10 (16.1)	8 (10.1)	47 (20.5)
Weight decreased	19 (15.2)	5 (8.1)	27 (34.2)	46 (20.1)
Lymphopenia [a]	29 (23.2)	2 (3.2)	4 (5.1)	37 (16.2)
Abdominal pain [a]	19 (15.2)	9 (14.5)	16 (20.3)	35 (15.3)
Hypoalbuminaemia	18 (14.4)	8 (12.9)	6 (7.6)	28 (12.2)
Hypokalaemia	10 (8.0)	4 (6.5)	12 (15.2)	25 (10.9)
Interstitial lung disease [b]	16 (12.8)	0	6 (7.6)	25 (10.9)
Aspartate aminotransferase increased	12 (9.6)	3 (4.8)	9 (11.4)	24 (10.5)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SMQ = Standardised MedDRA Query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

PT/grouped terms are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool.

If a subject had multiple occurrences of the same PT/grouped term, the subject was counted once for that PT/grouped term.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] The PTs that were included in each grouped term are listed in Table 2.1.

[b] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by adjudication committee.

Source: Module 5.3.5.3 SCS Tables 1.2.1.3, 1.2.2.1, and 1.2.4.1

Table 2.4: Drug-Related Treatment-Emergent Adverse Events Reported in at Least 5% of Subjects in the HER2-positive GC T-DXd 6.4 mg/kg Pool, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-Positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any drug-related TEAE	122 (97.6)	56 (90.3)	74 (93.7)	221 (96.5)
Nausea	72 (57.6)	25 (40.3)	46 (58.2)	137 (59.8)
Neutropenia [a]	80 (64.0)	22 (35.5)	20 (25.3)	112 (48.9)
Fatigue [a]	66 (52.8)	24 (38.7)	37 (46.8)	111 (48.5)
Decreased appetite	66 (52.8)	25 (40.3)	18 (22.8)	106 (46.3)
Anaemia [a]	51 (40.8)	13 (21.0)	15 (19.0)	78 (34.1)
Thrombocytopenia [a]	49 (39.2)	4 (6.5)	15 (19.0)	76 (33.2)
Leukopenia [a]	48 (38.4)	22 (35.5)	7 (8.9)	66 (28.8)
Vomiting	26 (20.8)	4 (6.5)	26 (32.9)	59 (25.8)
Diarrhoea	32 (25.6)	18 (29.0)	22 (27.8)	58 (25.3)
Alopecia	28 (22.4)	9 (14.5)	17 (21.5)	49 (21.4)
Lymphopenia [a]	29 (23.2)	1 (1.6)	4 (5.1)	37 (16.2)
Constipation	11 (8.8)	8 (12.9)	10 (12.7)	26 (11.4)
Interstitial lung disease [b]	16 (12.8)	0	6 (7.6)	25 (10.9)
Weight decreased	16 (12.8)	4 (6.5)	8 (10.1)	24 (10.5)
Pyrexia	11 (8.8)	3 (4.8)	1 (1.3)	16 (7.0)
Aspartate aminotransferase increased	6 (4.8)	0	5 (6.3)	14 (6.1)
Dysgeusia	8 (6.4)	4 (6.5)	3 (3.8)	14 (6.1)
Stomatitis [a]	10 (8.0)	3 (4.8)	1 (1.3)	14 (6.1)
Hypoalbuminaemia	5 (4.0)	1 (1.6)	3 (3.8)	12 (5.2)
Hypokalaemia	5 (4.0)	1 (1.6)	5 (6.3)	12 (5.2)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SMQ = Standardised MedDRA Query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

Table 4: Treatment-emergent Adverse Events of at Least CTCAE Grade 3 Reported in at Least 2% of Subjects (in Any Column) by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any TEAE ≥Grade 3	107 (85.6)	35 (56.5)	42 (53.2)	169 (73.8)
Neutrophil count decreased	62 (49.6)	14 (22.6)	6 (7.6)	77 (33.6)
Anaemia	48 (38.4)	14 (22.6)	11 (13.9)	68 (29.7)
White blood cells count decreased	26 (20.8)	7 (11.3)	4 (5.1)	37 (16.2)
Decreased appetite	21 (16.8)	8 (12.9)	4 (5.1)	28 (12.2)
Lymphocyte count decreased	15 (12.0)	1 (1.6)	2 (2.5)	21 (9.2)
Platelet count decreased	14 (11.2)	2 (3.2)	2 (2.5)	21 (9.2)
Nausea	7 (5.6)	1 (1.6)	6 (7.6)	14 (6.1)
Fatigue	9 (7.2)	2 (3.2)	3 (3.8)	12 (5.2)
Febrile neutropenia	6 (4.8)	2 (3.2)	2 (2.5)	9 (3.9)
Hypokalaemia	5 (4.0)	4 (6.5)	1 (1.3)	9 (3.9)
Pneumonia	4 (3.2)	0	2 (2.5)	7 (3.1)
Disease progression	3 (2.4)	2 (3.2)	2 (2.5)	6 (2.6)
Hyponatraemia	3 (2.4)	3 (4.8)	0	6 (2.6)
Neutropenia	2 (1.6)	1 (1.6)	4 (5.1)	6 (2.6)
Ascites	3 (2.4)	1 (1.6)	2 (2.5)	5 (2.2)
Blood alkaline phosphatase increased	4 (3.2)	0	1 (1.3)	5 (2.2)
Aspartate aminotransferase increased	3 (2.4)	0	1 (1.3)	4 (1.7)
Diarrhoea	3 (2.4)	1 (1.6)	1 (1.3)	4 (1.7)
Hepatic function abnormal	4 (3.2)	1 (1.6)	0	4 (1.7)
Hypoalbuminaemia	4 (3.2)	3 (4.8)	0	4 (1.7)
Jaundice cholestatic	4 (3.2)	1 (1.6)	0	4 (1.7)
Tumour haemorrhage	3 (2.4)	0	1 (1.3)	4 (1.7)
Weight decreased	1 (0.8)	1 (1.6)	3 (3.8)	4 (1.7)
ILD[a]	3 (2.4)	0	1 (1.3)	4 (1.7)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Abdominal pain	1 (0.8)	2 (3.2)	2 (2.5)	3 (1.3)
Acute kidney injury	1 (0.8)	0	2 (2.5)	3 (1.3)
COVID-19	0	0	3 (3.8)	3 (1.3)
Dehydration	3 (2.4)	1 (1.6)	0	3 (1.3)
Dysphagia	0	0	3 (3.8)	3 (1.3)
Embolism	1 (0.8)	0	2 (2.5)	3 (1.3)
Hypertension	0	2 (3.2)	1 (1.3)	2 (0.9)
Hypophosphataemia	0	1 (1.6)	2 (2.5)	2 (0.9)
Malignant neoplasm progression	0	0	2 (2.5)	2 (0.9)
Pulmonary embolism	0	0	2 (2.5)	2 (0.9)
Vomiting	0	0	2 (2.5)	2 (0.9)

AC = adjudication committee; CTCAE = Common Terminology Criteria for Adverse Events; COVID-19 = coronavirus disease 2019; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])
The HER2-positive GC T-DXd 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
[a] All adjudicated ILD considered as drug-related events by the ILD AC.
Source: Module 5.3.5.3 SCS Tables 1.2.1.5 and 1.2.4.1

2.5.3.1. Adverse events of special interest

Table 2.18: Selected Preferred Terms in Adverse Events of Special Interest

Category	Selected Preferred Terms for Review
ILD/pneumonitis	Events of ILD/pneumonitis from PTs triggering adjudication, based on the MedDRA Version 23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure
Left ventricular dysfunction (LV dysfunction)	Acute left ventricular failure Acute right ventricular failure Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Chronic left ventricular failure Chronic right ventricular failure Ejection fraction decreased Left ventricular dysfunction Left ventricular failure Right ventricular failure Ventricular failure

ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardised MedDRA Query

Interstitial Lung Disease (ILD)/Pneumonitis

After the first suspected fatal ILD case occurred, the Sponsor established an **external ILD Adjudication Committee (AC).**

The ILD AC adjudicated **each potential ILD event** with regard to whether it was ILD and whether it was related to T-DXd (regardless of the determination made by the investigator) and determined **onset dates** and adjudicated **grades** for events that the AC considered to be ILD. In June 2019, a **global ILD awareness campaign** was initiated to educate both investigators and subjects with the goal of reducing the risk of severe ILD (including fatal cases) by proactively detecting and intensively managing ILD at an early stage.

A total of 27/229 (**11.8%**) subjects in HER2-positive GC Pool experienced events adjudicated as ILD, including 25/229 (**10.9%**) subjects who experienced events adjudicated as being **drug-related ILD**.

Adjudicated drug-related ILD was associated with the outcome of **death in 1/79 (1.3%)** subject from Study U205 and in none of the subjects from the Study J202.

The **median time to adjudicated onset** date of the first drug-related adjudicated ILD event in the HER2-positive GC Pool was **85 days** (range: 36 to 638).

Table 2.19: Interstitial Lung Disease Events by Adjudicated Outcome and Adjudicated Grade (Safety Analysis Set)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee [a]	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any event of potential ILD, n (%)	20 (16.0)	0	9 (11.4)	34 (14.8)
Adjudicated as ILD	16 (12.8)	0	7 (8.9)	27 (11.8)
Grade 1	4 (3.2)	0	2 (2.5)	6 (2.6)
Grade 2	9 (7.2)	0	4 (5.1)	16 (7.0)
Grade 3	2 (1.6)	0	0	3 (1.3)
Grade 4	1 (0.8)	0	0	1 (0.4)
Grade 5	0	0	1 (1.3)	1 (0.4)
Adjudicated as drug-related ILD	16 (12.8)	0	6 (7.6)	25 (10.9)
Grade 1	4 (3.2)	0	2 (2.5)	6 (2.6)
Grade 2	9 (7.2)	0	3 (3.8)	15 (6.6)
Grade 3	2 (1.6)	0	0	2 (0.9)
Grade 4	1 (0.8)	0	0	1 (0.4)
Grade 5	0	0	1 (1.3)	1 (0.4)
Adjudicated as not drug-related ILD	0	0	1 (1.3)	2 (0.9)
Grade 1	0	0	0	0
Grade 2	0	0	1 (1.3)	1 (0.4)
Grade 3	0	0	0	1 (0.4)
Grade 4	0	0	0	0
Grade 5	0	0	0	0

AC = Adjudication Committee; CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages are calculated using the number of subjects in the Safety Analysis Set as the denominator.
Table includes all events that were submitted to the ILD AC.
If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade.
[a] The ILD AC assigned grades to those events that were determined to be ILD.
Source: Module 5.3.5.3 SCS Table 1.2.5.1

Table 2.20: Overview of Adjudicated Drug-related Interstitial Lung Disease Events (Safety Analysis Set)

Parameter	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any event adjudicated as drug-related ILD	16 (12.8)	0	6 (7.6)	25 (10.9)
ILD CTCAE ≥Grade 3 [a]	3 (2.4)	0	1 (1.3)	4 (1.7)
Serious ILD	7 (5.6)	0	2 (2.5)	9 (3.9)
ILD associated with discontinuation of study drug	8 (6.4)	0	5 (6.3)	15 (6.6)
ILD associated with dose reduction	0	0	1 (1.3)	1 (0.4)
ILD associated with study drug interruption	6 (4.8)	0	0	8 (3.5)
ILD associated with outcome of death	0	0	1 (1.3)	1 (0.4)

AC = Adjudicated Committee; CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] The ILD AC assigned grades to those events that were determined to be ILD. A subject was counted once at the maximum severity.
Adjudicated drug-related ILD associated with death is derived based on adjudicated CTCAE Grade 5 events.
Source: Module 5.3.5.3 SCS Tables 1.2.4.1, 1.2.4.2, 1.2.4.3, 1.2.4.4, 1.2.4.5, and 1.2.4.6

Among the 25/229 subjects in the HER2-positive GC Pool who experienced adjudicated drug-related ILD, 16/25 (64.0%) received **steroids**, 9/25 (36.0%) received **antibiotics**, and 8/25 (32.0%) received both **steroids and antibiotics**.

Table 2.21: Outcome of Events Adjudicated as Drug-Related Interstitial Lung Disease (Safety Analysis Set)

Outcome of Event	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any event adjudicated as drug-related ILD, n (%)	16 (12.8)	0	6 (7.6)	25 (10.9)
Recovered/resolved	6 (37.5)	0	2 (33.3)	9 (36.0)
Not recovered/not resolved	6 (37.5)	0	1 (16.7)	9 (36.0)
Recovering/resolving	4 (25.0)	0	1 (16.7)	5 (20.0)
Recovered/resolved with sequelae	0	0	1 (16.7)	1 (4.0)
Fatal	0	0	1 (16.7)	1 (4.0)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of treated subjects; n = number of patients; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentage for adjudicated drug-related ILD was calculated using the number of subjects in the Safety Analysis Set as the denominator.
Percentages were calculated using the number of subjects who had adjudicated drug-related ILD as the denominator.
Source: Module 5.3.5.3 SCS Table 1.2.5.4

Left ventricular dysfunction

Among the 13 relevant PTs included in the case definition of LV dysfunction (Table 2.18), only **1 subject** in the HER2-positive GC Pool, with grade 3 ejection fraction decrease, met the criteria for LV dysfunction. **No subjects** from Studies J202 and U205 had events of potential LV dysfunction reported.

Measurements of LVEF from laboratory data (every 2 cycles in Study J101 and every 4 cycles in Study J202 and Study U205) were graded as follows **per CTCAE** Version 4.03 (or Version 5.0), with each LVEF measurement being assigned a CTCAE grade:

- Grade 2: Resting LVEF 50% to 40%; 10% to 19% decrease from baseline
- Grade 3: Resting LVEF 39% to 20%; ≥20% decrease from baseline
- Grade 4: Resting LVEF <20%.

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It should be noted that instructions given to the study sites regarding dose modification due to AEs of LVEF decrease were different from the CTCAE grading above, as they were based on the following **guidelines for anti-HER2 therapy**

- LVEF of 40% to ≤45% with <10% decrease from baseline required no dose modification.
- LVEF of 40% to ≤45% with ≥10% decrease from baseline and LVEF <40% or >20% decrease from baseline **required study drug interruption with discontinuation** of study drug if the value had not improved upon repeat measurement within 3 weeks.

Table 2.22: Summary of Left Ventricular Ejection Fraction Decrease Based on Laboratory Data (Safety Analysis Set)

Parameter	Study J202 HER2-positive GC (Primary Cohort) T-DXd 6.4 mg/kg (N = 125)	Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-Positive GC T-DXd 6.4 mg/kg Pool (N = 229)
Subjects with Worst LVEF CTCAE Grade Post-Baseline, n (%)			
Non-missing, n [a]	117	57	199
Grade 2	11 (9.4)	2 (3.5)	14 (7.0)
Subjects with LVEF Measurement since Worst Grade	6	1	8
Recovered from Worst Grade to ≥90% of Baseline, n (%) [b,c]	3 (50.0)	1 (100)	4 (50.0)
Grade 3	0	0	1 (0.5)
Subjects with LVEF Measurement since Worst Grade	0	0	0
Recovered from Worst Grade to ≥90% of Baseline, n (%) [b,c]	0	0	0
Lowest LVEF measurement post-baseline			
Non-missing, n [a]	117	57	199
Median	65.0	60.0	63.0
Range	45, 78	41, 82	41, 82
40% - 49%	1 (0.8)	1 (1.3)	2 (0.9)
20% - 39%	0	0	0
<20%	0	0	0
Maximum LVEF decrease from baseline			
Non-missing, n [a]	117	57	199
Median	-1.0	0	-1.0
Range	-17, 14	-17, 9	-27, 14
10% - 19% decrease	11 (8.8)	1 (1.3)	13 (5.7)
≥20% decrease	0	0	1 (0.4)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/ gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; EF = ejection fraction; N = total number of subjects; n = number of subjects; Std Dev = standard deviation; T-DXd = trastuzumab deruxtecan

HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the non-missing n as the denominator.
For study J202 physician's choice group, LVEF is only collected at screening visit per protocol.
LVEF was defined as follows: Grade 2 = resting EF of ≥40% to <50%, or a 10% to <20% decrease from baseline; Grade 3 = resting EF of ≥20 to <40%, or a ≥20% decrease from baseline; and Grade 4 = resting EF <20%.
[a] Non-missing n was the number of subjects with both baseline and postbaseline data.
[b] ≥90% baseline since worst grade was defined as the highest postbaseline LVEF after the measurement with worst grade that was ≥90% of the baseline LVEF value.
[c] Percentages were calculated using the number of subjects having worst postbaseline LVEF at the specific grade. If there was no LVEF measurement after the worst grade of LVEF, the subject was not included in the denominator.
Source: Module 5.3.5.3 SCS Table 1.2.6.8.1

2.5.4. Serious adverse event/deaths/other significant events

2.5.4.1. SAEs

Table 5: Treatment-emergent Serious Adverse Events by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with any serious TEAE	56 (44.8)	16 (25.8)	29 (36.7)	92 (40.2)
Decreased appetite	13 (10.4)	1 (1.6)	0	16 (7.0)
ILD[a]	7 (5.6)	0	2 (2.5)	9 (3.9)
Pneumonia	5 (4.0)	0	2 (2.5)	9 (3.9)
Disease progression	3 (2.4)	2 (3.2)	2 (2.5)	6 (2.6)
Cholangitis	3 (2.4)	1 (1.6)	0	5 (2.2)
Nausea	1 (0.8)	0	4 (5.1)	5 (2.2)
Anaemia	4 (3.2)	2 (3.2)	0	4 (1.7)
Dehydration	4 (3.2)	0	0	4 (1.7)
Tumour haemorrhage	3 (2.4)	0	1 (1.3)	4 (1.7)
Vomiting	1 (0.8)	0	3 (3.8)	4 (1.7)
Abdominal pain	1 (0.8)	0	2 (2.5)	3 (1.3)
Acute kidney injury	1 (0.8)	1 (1.6)	2 (2.5)	3 (1.3)
Diarrhoea	2 (1.6)	0	1 (1.3)	3 (1.3)
Jaundice cholestatic	3 (2.4)	1 (1.6)	0	3 (1.3)
Pyrexia	3 (2.4)	1 (1.6)	0	3 (1.3)
Bacteraemia	1 (0.8)	0	0	2 (0.9)
COVID-19	0	0	2 (2.5)	2 (0.9)
Gastric stenosis	2 (1.6)	0	0	2 (0.9)
Hydronephrosis	1 (0.8)	1 (1.6)	1 (1.3)	2 (0.9)
Hypotension	2 (1.6)	0	0	2 (0.9)
Malignant neoplasm progression	0	0	2 (2.5)	2 (0.9)
Neoplasm progression	2 (1.6)	1 (1.6)	0	2 (0.9)
Platelet count decreased	1 (0.8)	0	0	2 (0.9)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Sepsis	2 (1.6)	0	0	2 (0.9)
Abdominal distension	1 (0.8)	0	0	1 (0.4)
Acute coronary syndrome	1 (0.8)	0	0	1 (0.4)
Anal stenosis	1 (0.8)	0	0	1 (0.4)
Animal bite	0	0	1 (1.3)	1 (0.4)
Bacterial sepsis	0	0	1 (1.3)	1 (0.4)
Basal ganglia infarction	0	0	1 (1.3)	1 (0.4)
Biliary obstruction	1 (0.8)	0	0	1 (0.4)
Bile duct stenosis	0	0	1 (1.3)	1 (0.4)
Bile duct stone	1 (0.8)	0	0	1 (0.4)
Biliary sepsis	1 (0.8)	0	0	1 (0.4)
Biliary tract infection	1 (0.8)	0	0	1 (0.4)
COVID-19 pneumonia	0	0	1 (1.3)	1 (0.4)
Cerebrovascular accident	0	0	1 (1.3)	1 (0.4)
Cholangitis acute	1 (0.8)	0	0	1 (0.4)
Cholangitis infective	1 (0.8)	0	0	1 (0.4)
Colitis	0	0	1 (1.3)	1 (0.4)
Condition aggravated	1 (0.8)	0	0	1 (0.4)
Device occlusion	0	0	1 (1.3)	1 (0.4)
Device related infection	0	0	1 (1.3)	1 (0.4)
Disseminated intravascular coagulation	1 (0.8)	0	0	1 (0.4)
Dysphagia	0	0	1 (1.3)	1 (0.4)
Enteritis	0	0	1 (1.3)	1 (0.4)
Exposure to communicable disease	0	0	1 (1.3)	1 (0.4)
Fatigue	1 (0.8)	1 (1.6)	0	1 (0.4)
Febrile neutropenia	1 (0.8)	1 (1.6)	0	1 (0.4)
Gastric haemorrhage	1 (0.8)	0	0	1 (0.4)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Gastrointestinal obstruction	1 (0.8)	1 (1.6)	0	1 (0.4)
General physical health deterioration	1 (0.8)	0	0	1 (0.4)
Generalised tonic-clonic seizure	0	0	1 (1.3)	1 (0.4)
Haematemesis	0	0	1 (1.3)	1 (0.4)
Hemiplegia	1 (0.8)	0	0	1 (0.4)
Hepatic function abnormal	1 (0.8)	1 (1.6)	0	1 (0.4)
Hepatotoxicity	0	0	1 (1.3)	1 (0.4)
Hyperpyrexia	0	0	1 (1.3)	1 (0.4)
Hypophagia	1 (0.8)	0	0	1 (0.4)
Inguinal hernia	1 (0.8)	0	0	1 (0.4)
Intestinal obstruction	0	0	1 (1.3)	1 (0.4)
Large intestine perforation	1 (0.8)	0	0	1 (0.4)
Liver injury	1 (0.8)	0	0	1 (0.4)
Lymphangiosis carcinomatosa	0	0	1 (1.3)	1 (0.4)
Neck pain	1 (0.8)	0	0	1 (0.4)
Oesophageal stenosis	1 (0.8)	0	0	1 (0.4)
Pancreatitis	1 (0.8)	0	0	1 (0.4)
Pericardial effusion	1 (0.8)	0	0	1 (0.4)
Pericarditis malignant	1 (0.8)	0	0	1 (0.4)
Pneumonia aspiration	1 (0.8)	1 (1.6)	0	1 (0.4)
Pneumonia bacterial	1 (0.8)	0	0	1 (0.4)
Presyncope	1 (0.8)	0	0	1 (0.4)
Pulmonary embolism	0	0	1 (1.3)	1 (0.4)
Pyloric stenosis	1 (0.8)	0	0	1 (0.4)
Staphylococcal infection	0	0	1 (1.3)	1 (0.4)
Stomatitis	1 (0.8)	0	0	1 (0.4)
Stress cardiomyopathy	1 (0.8)	0	0	1 (0.4)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Upper gastrointestinal haemorrhage	1 (0.8)	0	0	1 (0.4)
Urinary tract infection	0	0	1 (1.3)	1 (0.4)
Urinary tract obstruction	0	0	1 (1.3)	1 (0.4)
Vascular device infection	1 (0.8)	0	0	1 (0.4)
Wound infection	0	0	1 (1.3)	1 (0.4)
Asthenia	0	1 (1.6)	0	0
Blood creatinine increased	0	2 (3.2)	0	0
Cancer pain	0	1 (1.6)	0	0
Cerebral infarction	0	1 (1.6)	0	0
Dizziness	0	1 (1.6)	0	0
Infectious pleural effusion	0	1 (1.6)	0	0
Liver disorder	0	1 (1.6)	0	0
Neutropenia	0	1 (1.6)	0	0
Neutrophil count decreased	0	1 (1.6)	0	0
White blood cell count decreased	0	1 (1.6)	0	0

AC = adjudication committee; COVID-19 = coronavirus disease 2019; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 24.0; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])
The HER2-positive GC T-DXd 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
[a] All serious adjudicated ILD considered as drug-related events by the ILD AC.
Source: Module 5.3.5.3 SCS Tables 1.2.1.8 and 1.2.4.2

Table 6: Number of Subjects with One or Multiple Serious Adverse Events in the HER2-positive GC T-DXd 6.4 mg/kg Pool (Safety Analysis Set)

	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79) n (%)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229) n (%)
	T-DXd 6.4 mg/kg (N = 125) n (%)	TPC (N = 62) n (%)		
Any TESAE	56 (44.8)	16 (25.8)	29 (36.7)	92 (40.2)
1 event	29 (23.2)	9 (14.5)	17 (21.5)	49 (21.4)
2 events	10 (8.0)	4 (6.5)	6 (7.6)	19 (8.3)
3 events	4 (3.2)	0	3 (3.8)	8 (3.5)
4 events	7 (5.6)	2 (3.2)	0	7 (3.1)
≥5 events	6 (4.8)	1 (1.6)	3 (3.8)	9 (3.9)

GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; PT = preferred term; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TESAE = treatment-emergent serious adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])
The HER2-positive GC 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Multiple occurrences of the same PT were counted as different events.
Source: Module 5.3.5.3 SCS Table 1.2.1.1.1; Appendix 1 Table 2

Ethnic differences in toxicity profile

Ethnic differences in drug toxicity are becoming increasingly recognized and are well documented in the scientific literature. In particular, higher hematologic toxicity has been described for Asian vs. Western cancer subjects. Although factors underlying such differences have not been precisely identified, various intrinsic and extrinsic factors such as variation in PK, genetic, and lifestyle factors are considered to be responsible for ethnic specific drug safety profiles.

While hematologic events were the most common TEAEs and drug-related TEAEs in both studies, the following grouped terms were more frequent in the T-DXd arm of Study J202 than in Study U205 (Module 5.3.5.3 SCS Tables 1.2.2.1 and 1.2.2.2):

- Anaemia (PTs: anaemia, haemoglobin decreased, haematocrit decreased, red blood cell count decreased): 57.6% vs. 34.2%; considered as drug-related, 40.8% vs. 19.0%.
- Neutropenia (PTs: neutropenia, neutrophil count decreased): 64.8% vs. 25.3%; considered as drug-related, 64.0% vs. 25.3%.
- Thrombocytopenia (PTs: thrombocytopenia, platelet count decreased): 40.0% vs. 21.5%; considered as drug-related, 39.2% vs. 20.3%.
- Leukopenia (PTs: leukopenia, white blood cell count decreased): 38.4% vs. 10.1%; considered as drug-related, 38.4% vs. 10.1%.
- Lymphopenia (PTs: lymphopenia, lymphocyte count decreased): 23.2% vs. 5.1%; considered as drug-related, 23.2% vs. 5.1%.

The higher hematologic toxicity observed in the T-DXd arm of Study J202 (Asian population) vs. Study U205 (Western population) is consistent with what has been reported in T-DXd studies in BC, other clinical studies of drugs for subjects with advanced GC, and other observations from the literature. The

exact factors responsible for the more pronounced hematologic toxicity observed in the Japanese and Asian population are not known.

2.5.4.2. Deaths

This section summarizes data on all reported deaths, including the following:

- On-study deaths, defined as **any death that occurred from the date of the first dose** up to 28 days (for Study J101) or up to 47 days (for Studies J202 and U205) after the last dose of study drug (as defined in the respective protocols)
- **Deaths that occurred after** the 28-day (for Study J101) or 47-day (for Studies J202 and U205) follow-up period

Table 2.7: Primary Cause of Any Deaths and On-Treatment Deaths (Safety Analysis Set)

Primary Cause of Death	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-Positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Any Death	84 (67.2)	49 (79.0)	22 (27.8)	115 (50.2)
Disease Progression	80 (64.0)	46 (74.2)	12 (15.2)	100 (43.7)
Adverse Event	3 (2.4)	1 (1.6)	7 (8.9)	11 (4.8) [a]
Other	0	2 (3.2)	1 (1.3)	1 (0.4) [b]
Unknown	1 (0.8)	0	2 (2.5)	3 (1.3)
On-treatment Death [c]	8 (6.4)	7 (11.3)	9 (11.4)	18 (7.9)
Disease Progression	5 (4.0)	7 (11.3)	5 (6.3)	11 (4.8)
Adverse Event	3 (2.4)	0	4 (5.1)	7 (3.1) [d]
Other	0	0	0	0
Unknown	0	0	0	0

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] Adverse events with outcome of death were "Disseminated intravascular coagulation" for subject DS8201-A-J202-[redacted], "Large intestine perforation" for subject DS8201-A-J202-82042213, "Pneumonia" for subject DS8201-A-J202-[redacted] "Interstitial lung disease" for subject DS8201-A-U205-[redacted] "Cerebrovascular accident" for subject DS8201-A-U205-[redacted] "COVID-19" for subject DS8201-A-U205-[redacted] and DS8201-A-U205-[redacted] "Encephalopathy" for subject DS8201-A-U205-[redacted] "Lymphangiosis carcinomatosa" for subject DS8201-A-U205-[redacted] "Intestinal obstruction" for subject DS8201-A-U205-[redacted] and "Extradural haematoma" and "Traumatic intracranial haemorrhage" for subject DS8201-A-J101-[redacted]
[b] The investigator recorded a primary cause of death as "Other: PT sustained traumatic brain injury during car accident 07 Oct 2020 which was determined to be the cause of death" for subject DS8201-A-U205-[redacted]
[c] On-treatment death was defined as any death that occurred from the date of the first dose up to 28 days (for Study J101) or up to 47 days (for Study J202 and Study U205) after the last dose of study drug.
[d] Adverse events with outcome of death were "Disseminated intravascular coagulation" for subject DS8201-A-J202-[redacted], "Large intestine perforation" for subject DS8201-A-J202-[redacted] "Pneumonia" for subject DS8201-A-J202-[redacted] "Cerebrovascular accident" for subject DS8201-A-U205-[redacted] "Lymphangiosis carcinomatosa" for subject DS8201-A-U205[redacted], "Intestinal obstruction" for subject DS8201-A-U205-[redacted], and "COVID-19" for subject DS8201-A-U205-[redacted]
Source: Module 5.3.5.3 SCS Table 1.2.7, Listing 1.1, and Listing 1.2

Table 2.8: Treatment-Emergent Adverse Events Associated with Outcome of Death, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-Positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Any Subject with TEAE Associated with Outcome of Death	8 (6.4)	2 (3.2)	10 (12.7)	19 (8.3)
Disease progression	3 (2.4)	1 (1.6)	2 (2.5)	6 (2.6)
COVID-19	0	0	2 (2.5)	2 (0.9)
Malignant neoplasm progression	0	0	2 (2.5)	2 (0.9)
Neoplasm progression	2 (1.6)	1 (1.6)	0	2 (0.9)
Cerebrovascular accident	0	0	1 (1.3)	1 (0.4)
Disseminated intravascular coagulation	1 (0.8)	0	0	1 (0.4)
Interstitial lung disease	0	0	1 (1.3)	1 (0.4)
Intestinal obstruction	0	0	1 (1.3)	1 (0.4)
Large intestine perforation	1 (0.8)	0	0	1 (0.4)
Lymphangiosis carcinomatosa	0	0	1 (1.3)	1 (0.4)
Pneumonia	1 (0.8)	0	0	1 (0.4)

COVID-19 = coronavirus disease 2019; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Preferred terms are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
Source: Module 5.3.5.3 SCS Table 1.2.1.16

According to the SCS Table 2.8, a total of 10 subjects in Study J202 experienced a fatal TEAE: 8 subjects in the T-DXd arm and 2 subjects in the TPC arm. In the tabular list of narratives in the J202 CSR, there were 18 subjects marked with a "Y" in the death column. Eight of these 18 subjects are not included in the SCS Table 2.8 for the following reasons:

- Three subjects were from the exploratory cohorts and therefore were not included in the Safety Analysis Set (ie, Subjects No. [redacted] and [redacted] from the exploratory cohort 1 and Subject No.-[redacted]-from the exploratory cohort 2).

- Five subjects in the TPC cohort died due to disease progression not reported as a TEAE (ie, Subjects No. [redacted]).

To conclude, there were a total of 19 subjects treated with T-DXd who experienced fatal TEAEs, as reported in the HER2-positive GC Pool column of the SCS Table 2.8:

- Eight subjects in Study J202 (all on-study deaths).

- Ten subjects in Study U205 (8 on-study deaths and 2 off-study deaths).

- One subject in Study J101 (on-study death).

2.5.4.3. Other significant events

Time to onset of TEAEs and outcome (resolved/not resolved)

The time to onset of all the relevant TEAEs in Study J202, Study U205, and the HER2-positive GC Pool is presented in Table 7. The relevant TEAEs include the selected TEAEs, ILD, and left ventricular dysfunction.

Table 7: Time to Onset of Relevant Treatment-emergent Adverse Events (Safety Analysis Set)

	Time to First Onset (Days)[b]							
	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	
	T-DXd 6.4 mg/kg (N = 125)		TPC (N = 62)					
	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)
Nausea	79	4.0 (1, 177)	29	8.0 (1, 92)	52	4.0 (1, 173)	150	4.0 (1, 177)
Decreased appetite	76	5.0 (1, 520)	28	8.5 (1, 183)	26	23.5 (1, 310)	124	6.0 (1, 520)
Fatigue[a]	69	8.0 (1, 294)	27	11.0 (1, 141)	44	4.0 (1, 175)	121	7.0 (1, 294)
Vomiting	33	6.0 (1, 291)	5	19.0 (3, 44)	33	7.0 (1, 153)	74	7.0 (1, 291)
Thrombocytopenia[a]	50	8.0 (7, 298)	4	13.5 (9, 16)	17	8.0 (5, 232)	79	8.0 (5, 298)
Diarrhoea	41	9.0 (2, 395)	20	9.0 (2, 94)	28	7.5 (2, 363)	74	9.0 (2, 395)
Lymphopenia[a]	29	14.0 (1, 269)	2	72.0 (59, 85)	4	8.0 (7, 8)	37	9.0 (1, 269)
Leukopenia[a]	48	16.0 (7, 248)	22	14.0 (7, 85)	8	41.5 (15, 337)	67	16.0 (2, 337)
Neutropenia[a]	81	16.0 (6, 756)	22	14.5 (7, 86)	20	15.0 (8, 142)	113	16.0 (6, 756)

	Time to First Onset (Days)[b]							
	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	
	T-DXd 6.4 mg/kg (N = 125)		TPC (N = 62)					
	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)
Anaemia[a]	72	18.0 (2, 444)	19	19.0 (8, 86)	27	20.0 (1, 299)	113	22.0 (1, 444)
Headache[a]	4	18.5 (4, 84)	4	56.5 (6, 94)	7	40.0 (22, 151)	11	26.0 (4, 151)
Ejection fraction decreased	0	0	0	0	0	0	1	26.0 (26, 26)
Constipation	31	42.0 (1, 777)	15	10.0 (1, 397)	21	24.0 (2, 287)	59	30.0 (1, 777)
Febrile neutropenia	6	24.5 (13, 77)	2	9.0 (9, 9)	2	25.5 (12, 39)	9	31.0 (12, 103)
Stomatitis[a]	14	29.0 (2, 512)	3	16.0 (7, 79)	1	81.0 (81, 81)	19	33.0 (2, 512)
Rash[a]	7	43.0 (4, 618)	3	14.0 (5, 22)	1	62.0 (62, 62)	9	47.0 (4, 618)
Upper respiratory tract infection[a]	9	78.0 (21, 294)	3	73.0 (34, 243)	1	13.0 (13, 13)	12	69.0 (13, 294)
Abdominal pain[a]	19	120.0 (1, 354)	9	9.0 (1, 168)	16	29.0 (3, 146)	35	85.0 (1, 354)
ILD[c]	16	102.5 (36, 638)	0	0	6	68.5 (42, 85)	25	85.0 (36, 638)

AC = Adjudication Committee; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; n = number of subjects with the specific selected TEAE within the treatment arm or pool; N = total number of subjects treated; PT = preferred term; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7]).
The HER2-positive GC 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Results are presented in ascending order of time to onset within the HER2-positive GC T-DXd 6.4 mg/kg Pool.
[a] For the PTs that were included in each grouped term
[b] Time to first onset (days) = date of onset of the subject's first post-dose selected TEAE - date of the first dose + 1. Time to first onset of adjudicated drug-related ILD (days) = onset date of first ILD adjudicated as drug-related - first dose date + 1.
[c] ILD events include all adjudicated and considered as drug related events by the ILD AC.
Source: Module 5.3.5.3 SCS Tables 1.2.2.1, 1.2.5.4, and 1.2.6.7

The time to first worsening grade of LVEF decrease from Baseline based on laboratory data in the T-DXd arm of Study J202, Study U205, and the HER2-positive GC T-DXd 6.4 mg/kg Pool is summarized in Table 8.

Table 8: Time to First Worsening Grade of LVEF Decrease from Baseline Based on Laboratory Data (Safety Analysis Set)

	Time to First Onset (Days)		
	Study J202 HER2-positive GC (Primary Cohort) T-DXd 6.4 mg/kg (N = 125)	**Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)**	**HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)**
n	11	2	15
Median	168.0	78.5	166.0
Range	82, 681	78, 79	26, 681

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; n = number of subjects with non-missing observation; N = total subjects; T-DXd = trastuzumab deruxtecan
The HER2-positive GC 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Per CTCAE, Grade 2 LVEF decrease is defined by a resting ejection fraction of ≥40% to <50%, or a 10% to <20% drop from Baseline. Grade 3 LVEF decrease is defined by a resting ejection fraction of ≥20% to <40% or a ≥20% drop from Baseline. Grade 4 LVEF decrease is defined by a resting ejection fraction <20%.
Time to first worsening of LVEF = onset date of first worsening grade of laboratory LVEF decrease - date of the first dose + 1.
Source: Appendix 1 Table 3

The outcome of all relevant TEAEs (including the selected TEAEs, ILD, and left ventricular dysfunction) is presented in Table 9 (Study J202) and Table 10 (Study U205 and HER2-positive GC Pool).

Table 9: Outcome of Relevant Treatment-emergent Adverse Events in Study J202 (Safety Analysis Set)

	Study J202 HER2-positive GC (Primary Cohort)									
	T-DXd 6.4 mg/kg (N = 125)					TPC (N = 62)				
	n	Number (%) of Subjects				n	Number (%) of Subjects			
		Resolved	Resolved with Sequelae	Resolving	Not Resolved		Resolved	Resolved with Sequelae	Resolving	Not Resolved
Neutropenia[a]	81	70 (86.4)	0	0	11 (13.6)	22	17 (77.3)	0	0	5 (22.7)
Nausea	79	46 (58.2)	0	0	30 (38.0)	29	17 (58.6)	0	0	12 (41.4)
Decreased appetite	76	26 (34.2)	0	0	47 (61.8)	28	11 (39.3)	0	0	17 (60.7)
Anaemia[a]	72	31 (43.1)	0	2 (2.8)	38 (52.8)	19	8 (42.1)	0	1 (5.3)	10 (52.6)
Fatigue[a]	69	19 (27.5)	0	1 (1.4)	46 (66.7)	27	7 (25.9)	0	0	20 (74.1)
Thrombocytopenia[a]	50	30 (60.0)	0	0	18 (36.0)	4	2 (50.0)	0	0	2 (50.0)
Leukopenia[a]	48	36 (75.0)	0	0	12 (25.0)	22	15 (68.2)	0	0	7 (31.8)
Diarrhoea	41	34 (82.9)	0	0	7 (17.1)	20	15 (75.0)	0	0	5 (25.0)

	Study J202 HER2-positive GC (Primary Cohort)									
	T-DXd 6.4 mg/kg (N = 125)					TPC (N = 62)				
	n	Number (%) of Subjects				n	Number (%) of Subjects			
		Resolved	Resolved with Sequelae	Resolving	Not Resolved		Resolved	Resolved with Sequelae	Resolving	Not Resolved
Vomiting	33	27 (81.8)	0	0	6 (18.2)	5	3 (60.0)	0	0	2 (40.0)
Constipation	31	12 (38.7)	0	1 (3.2)	14 (45.2)	15	9 (60.0)	0	0	6 (40.0)
Lymphopenia[a]	29	18 (62.1)	0	0	10 (34.5)	2	1 (50.0)	0	0	1 (50.0)
Abdominal pain[a]	19	8 (42.1)	0	0	11 (57.9)	9	3 (33.3)	0	0	6 (66.7)
ILD[a]	16	6 (37.5)	0	4 (25.0)	6 (37.5)	0	0	0	0	0
Stomatitis[a]	14	6 (42.9)	0	0	7 (50.0)	3	3 (100)	0	0	0
Upper respiratory tract infection[a]	9	9 (100)	0	0	0	3	1 (33.3)	0	0	2 (66.7)
Rash[a]	7	6 (85.7)	0	1 (14.3)	0	3	1 (33.3)	0	0	2 (66.7)
Febrile neutropenia	6	6 (100)	0	0	0	2	2 (100)	0	0	0
Headache[a]	4	2 (50.0)	0	0	2 (50.0)	4	3 (75.0)	0	0	1 (25.0)

AC = Adjudication Committee; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; n = number of subjects with the specific selected TEAE within the treatment arm; N = number of subjects treated; PT = preferred term; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])

Percentages were calculated using the number of subjects with the specific selected TEAE within the treatment arm a s the denominator. The denominator for outcome of the worst ILD event is the number of subjects with adjudicated drug-related ILD.

Some subjects have "Missing/Unknown" outcomes for the specific selected TEAE (not included in the table).

TEAEs are presented in descending order of frequency in the T-DXd arm.

[a] For the PTs that were included in each grouped term

[b] All adjudicated ILD considered as drug-related events by the ILD AC.

Source: Module 5.3.5.3 SCS Tables 1.2.2.1 and 1.2.5.4

Table 10: Outcome of Relevant Treatment-emergent Adverse Events in Study U205 and the HER2-positive Gastric Cancer Pool (Safety Analysis Set)

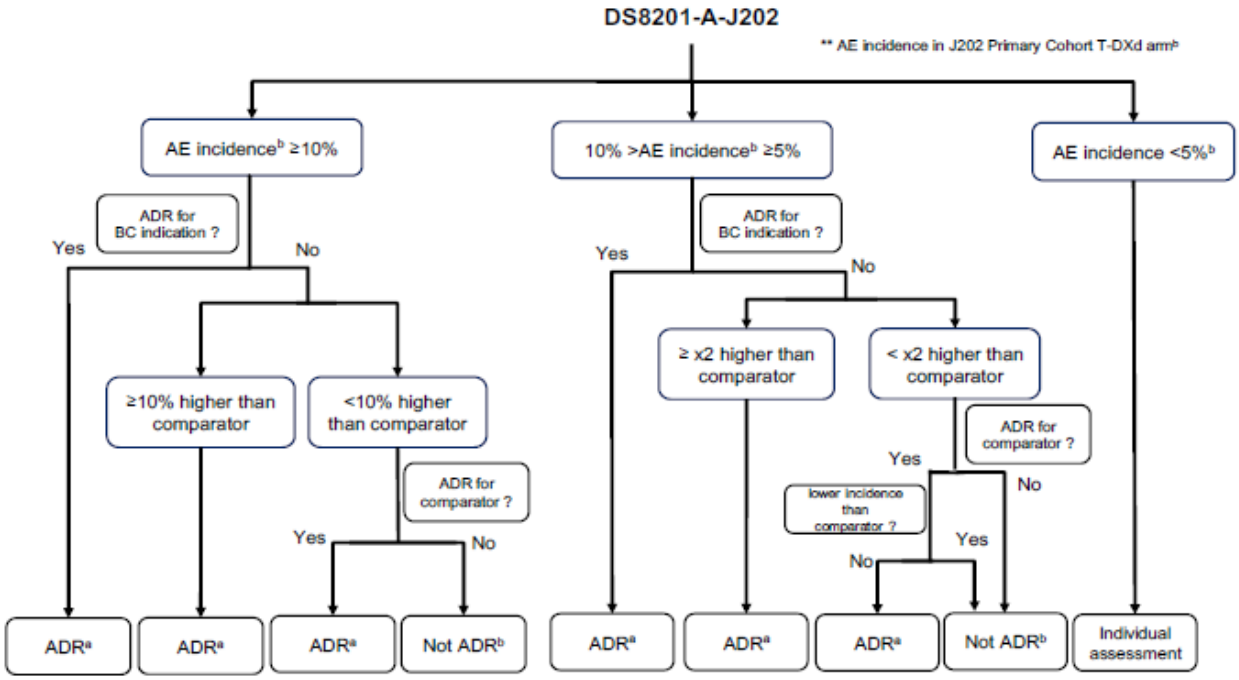
	Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)					HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 229)				
	n	Number (%) of Subjects				n	Number (%) of Subjects			
		Resolved	Resolved with Sequelae	Resolving	Not Resolved		Resolved	Resolved with Sequelae	Resolving	Not Resolved
Nausea	52	28 (53.8)	0	6 (11.5)	16 (30.8)	150	83 (55.3)	0	7 (4.7)	55 (36.7)
Decreased appetite	26	10 (38.5)	0	3 (11.5)	11 (42.3)	124	46 (37.1)	0	5 (4.0)	68 (54.8)
Fatigue[a]	44	20 (45.5)	2 (4.5)	5 (11.4)	16 (36.4)	121	44 (36.4)	2 (1.7)	6 (5.0)	65 (53.7)
Anaemia[a]	27	15 (55.6)	2 (7.4)	2 (7.4)	6 (22.2)	113	53 (46.9)	2 (1.8)	4 (3.5)	51 (45.1)
Neutropenia[a]	20	16 (80.0)	0	0	3 (15.0)	113	97 (85.8)	0	1 (0.9)	14 (12.4)
Thrombocytopenia[a]	17	10 (58.8)	0	1 (5.9)	5 (29.4)	79	50 (63.3)	0	2 (2.5)	24 (30.4)
Vomiting	33	23 (69.7)	0	4 (12.1)	6 (18.2)	74	58 (78.4)	0	4 (5.4)	12 (16.2)
Diarrhoea	28	23 (82.1)	0	0	5 (17.9)	74	61 (82.4)	0	0	13 (17.6)
Leukopenia[a]	8	6 (75.0)	0	0	2 (25.0)	67	50 (74.6)	0	0	17 (25.4)
Constipation	21	13 (61.9)	0	1 (4.8)	5 (23.8)	59	29 (49.2)	0	2 (3.4)	22 (37.3)
Lymphopenia[a]	4	4 (100)	0	0	0	37	23 (62.2)	0	1 (2.7)	12 (32.4)
Abdominal pain[a]	16	8 (50.0)	0	1 (6.3)	7 (43.8)	35	16 (45.7)	0	1 (2.9)	18 (51.4)
ILD[b]	6	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	25	9 (36.0)	1 (4.0)	5 (20.0)	9 (36.0)
Stomatitis[a]	1	1 (100)	0	0	0	19	8 (42.1)	0	0	10 (52.6)
Upper respiratory tract infection[a]	1	1 (100)	0	0	0	12	12 (100)	0	0	0
Headache[a]	7	3 (42.9)	0	1 (14.3)	2 (28.6)	11	5 (45.5)	0	1 (9.1)	4 (36.4)
Febrile neutropenia	2	2 (100)	0	0	0	9	9 (100)	0	0	0
Rash[a]	1	1 (100)	0	0	0	9	8 (88.9)	0	1 (11.1)	0
Ejection fraction decreased	0	0	0	0	0	1	0	0	0	1 (100.0)

AC = Adjudication Committee; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease. n = number of subjects with the specific selected TEAE within the treatment arm; N = number of subjects treated; PT = preferred term; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

The HER2-positive GC 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects with the specific selected TEAE within the study or pool a s the denominator. The denominator for outcome of the worst ILD event is the number of subjects with adjudicated drug-related ILD.
TEAEs are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool.
Some subjects have "Missing/Unknown" outcomes for the specific selected TEAE (not included in the table).
[a] For the PTs that were included in each grouped term
[b] All adjudicated ILD considered as drug-related events by the ILD AC. Of note, there was 1 fatal event of ILD in Study U205. Source: Module 5.3.5.3 SCS Tables 1.2.2.1 and 1.2.5.4, and Listing 1.2

2.5.4.4. Adverse drug reactions

Figure 4.1: Methodology of ADR Determination for HER2-Positive GC Population



ADR = adverse drug reaction; AE = adverse event; BC = breast cancer; T-DXd = trastuzumab deruxtecan
Comparator is defined as treatment of physician's choice
Based on the review of individual events:
[a] If evidence suggests that the event is due to the underlying disease or has an alternative etiology, it may be determined as NOT an ADR
[b] If there is a causal relationship between the event and study drug, it may be determined as an ADR

Table 10.1: All Adverse Drug Reactions by MedDRA System Organ Class and Preferred term/Grouped Term in the HER2-positive GC T-DXd 6.4 mg/kg Pool (Safety Analysis Set)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects, by CTCAE Grade							
	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	
	T-DXd 6.4 mg/kg (N = 125)		TPC (N = 62)					
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Subjects with any ADR	124 (99.2)	100 (80.0)	60 (96.8)	31 (50.0)	77 (97.5)	31 (39.2)	226 (98.7)	146 (63.8)
Blood and lymphatic system disorders								
Anaemia [a]	72 (57.6)	48 (38.4)	19 (30.6)	14 (22.6)	27 (34.2)	11 (13.9)	113 (49.3)	68 (29.7)
Neutropenia [b]	81 (64.8)	64 (51.2)	22 (35.5)	15 (24.2)	20 (25.3)	9 (11.4)	113 (49.3)	82 (35.8)
Thrombocytopenia [c]	50 (40.0)	14 (11.2)	4 (6.5)	2 (3.2)	16 (20.3)	3 (3.8)	78 (34.1)	22 (9.6)
Leukopenia [d]	48 (38.4)	26 (20.8)	22 (35.5)	7 (11.3)	7 (8.9)	4 (5.1)	66 (28.8)	37 (16.2)
Lymphopenia [e]	29 (23.2)	15 (12.0)	2 (3.2)	1 (1.6)	4 (5.1)	3 (3.8)	37 (16.2)	22 (9.6)
Febrile neutropenia	6 (4.8)	6 (4.8)	2 (3.2)	2 (3.2)	2 (2.5)	2 (2.5)	9 (3.9)	9 (3.9)
Gastrointestinal disorders								
Nausea	79 (63.2)	7 (5.6)	29 (46.8)	1 (1.6)	52 (65.8)	6 (7.6)	150 (65.5)	14 (6.1)
Vomiting	33 (26.4)	0	5 (8.1)	0	33 (41.8)	2 (2.5)	74 (32.3)	2 (0.9)
Diarrhoea	41 (32.8)	3 (2.4)	20 (32.3)	1 (1.6)	27 (34.2)	1 (1.3)	73 (31.9)	4 (1.7)
Constipation	31 (24.8)	0	15 (24.2)	0	21 (26.6)	0	59 (25.8)	0
Abdominal pain [f]	19 (15.2)	1 (0.8)	9 (14.5)	2 (3.2)	16 (20.3)	2 (2.5)	35 (15.3)	3 (1.3)
Stomatitis [g]	14 (11.2)	2 (1.6)	3 (4.8)	0	1 (1.3)	0	19 (8.3)	2 (0.9)
General disorders and administration site conditions								
Fatigue [h]	69 (55.2)	11 (8.8)	27 (43.5)	3 (4.8)	44 (55.7)	4 (5.1)	121 (52.8)	15 (6.6)
Pyrexia	31 (24.8)	0	10 (16.1)	0	8 (10.1)	0	47 (20.5)	0
Oedema peripheral	14 (11.2)	0	0	0	4 (5.1)	0	19 (8.3)	0
Hepatobiliary disorders								
Hepatic function abnormal	11 (8.8)	4 (3.2)	1 (1.6)	1 (1.6)	0	0	14 (6.1)	4 (1.7)
Infections and infestations								
Upper respiratory tract infection [i]	21 (16.8)	1 (0.8)	8 (12.9)	0	1 (1.3)	0	27 (11.8)	1 (0.4)
Pneumonia	13 (10.4)	3 (2.4)	1 (1.6)	0	2 (2.5)	2 (2.5)	20 (8.7)	6 (2.6)
Injury, poisoning and procedural complications								
Infusion-related reaction [j]	2 (1.6)	0	0	0	0	0	2 (0.9)	0
Investigations								
Aspartate aminotransferase increased	12 (9.6)	3 (2.4)	3 (4.8)	0	9 (11.4)	1 (1.3)	24 (10.5)	4 (1.7)
Alanine aminotransferase increased	9 (7.2)	2 (1.6)	3 (4.8)	0	6 (7.6)	1 (1.3)	18 (7.9)	3 (1.3)
Blood alkaline phosphatase increased	11 (8.8)	4 (3.2)	2 (3.2)	0	6 (7.6)	1 (1.3)	18 (7.9)	5 (2.2)
Blood bilirubin increased	10 (8.0)	1 (0.8)	0	0	4 (5.1)	1 (1.3)	15 (6.6)	3 (1.3)

MedDRA System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects, by CTCAE Grade							
	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	
	T-DXd 6.4 mg/kg (N = 125)		TPC (N = 62)					
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Metabolism and nutrition disorders								
Decreased appetite	76 (60.8)	21 (16.8)	28 (45.2)	8 (12.9)	26 (32.9)	4 (5.1)	124 (54.1)	28 (12.2)
Hypokalaemia	10 (8.0)	5 (4.0)	4 (6.5)	4 (6.5)	12 (15.2)	1 (1.3)	25 (10.9)	9 (3.9)
Dehydration	8 (6.4)	3 (2.4)	2 (3.2)	1 (1.6)	2 (2.5)	0	10 (4.4)	3 (1.3)
Respiratory, thoracic and mediastinal disorders								
Interstitial lung disease [k]	16 (12.8)	3 (2.4)	0	0	6 (7.6)	0	25 (10.9)	3 (1.3)
Cough	6 (4.8)	0	2 (3.2)	0	6 (7.6)	1 (1.3)	13 (5.7)	1 (0.4)
Epistaxis	4 (3.2)	0	0	0	6 (7.6)	0	13 (5.7)	0
Dyspnoea	1 (0.8)	0	1 (1.6)	0	7 (8.9)	1 (1.3)	8 (3.5)	1 (0.4)
Skin and subcutaneous tissue disorders								
Alopecia	28 (22.4)	0	9 (14.5)	0	19 (24.1)	0	51 (22.3)	0
Pruritus	10 (8.0)	0	2 (3.2)	0	2 (2.5)	0	13 (5.7)	0
Rash [l]	7 (5.6)	0	3 (4.8)	0	1 (1.3)	0	9 (3.9)	0

ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, version 23.0; N = number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2 positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202 and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

System Organ Class are sorted by alphabetic order. PT/Grouped terms are sorted by descending frequency in 'All Grades' column of HER2-positive GC T-DXd 6.4 mg/kg Pool.

[a] Anaemia (grouped term) includes PTs of Anaemia, Haemoglobin decreased, Haematocrit decreased, and Red blood cell count decreased.

[b] Neutropenia (grouped term) includes PTs of Neutropenia and Neutrophil count decreased.

[c] Thrombocytopenia (grouped term) includes PTs of Thrombocytopenia and Platelet count decreased.

[d] Leukopenia (grouped term) includes PTs of Leukopenia and White blood cell count decreased.

[e] Lymphopenia (grouped term) includes PTs of Lymphopenia and Lymphocyte count decreased.

[f] Abdominal pain (grouped term) includes PTs of Abdominal pain, Abdominal discomfort, Gastrointestinal pain, Abdominal pain lower, and Abdominal pain upper.

[g] Stomatitis (grouped term) includes PTs of Stomatitis, Aphthous ulcer, Mouth ulceration, Oral mucosa erosion, and Oral mucosal blistering.

[h] Fatigue (grouped term) includes PTs of Fatigue, Asthenia, and Malaise.

[i] Upper respiratory tract infection (grouped term) includes PTs Upper respiratory tract infection, Influenza, and Influenza-like illness. Grouped term Upper respiratory tract infection is updated from the original definition for CSR/SCS, with addition of PTs of nasopharyngitis, pharyngitis, sinusitis, rhinitis. The updated definition is used for summary of ADRs only.

[j] Cases of infusion-related reactions include Infusion related reaction (n = 2). Cases of infusion-related reactions are based on safety review of pre-specified PTs and additional PT of 'infusion site extravasation'.

[k] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by the adjudication committee.

[l] Rash (grouped term) includes PTs of Rash, Rash pustular, and Rash maculo-papular.

2.5.5. Laboratory findings

Table 2.24: Selected Laboratory Abnormalities (Safety Analysis Set)

Laboratory Abnormality	Number (%) of Subjects, by CTCAE Grade							
	Study J202 with HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	
	T-DXd 6.4 mg/kg (N = 125)		TPC (N = 62)					
	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4
Hematology								
Hemoglobin decreased	96 (76.8)	50 (40.0)	33 (55.0)	14 (23.3)	39 (49.4)	7 (8.9)	152 (66.4)	66 (28.8)
White blood cell count decreased	94 (75.2)	36 (28.8)	32 (53.3)	8 (13.3)	48 (60.8)	7 (8.9)	159 (69.4)	50 (21.8)
Neutrophil count decreased	91 (72.8)	64 (51.2)	27 (45.0)	14 (23.3)	42 (53.2)	9 (11.4)	148 (64.6)	82 (35.8)
Lymphocyte count decreased	92 (73.6)	37 (29.6)	32 (54.2)	7 (11.9)	42 (53.2)	12 (15.2)	156 (68.1)	58 (25.3)
Platelet count decreased	88 (70.4)	15 (12.0)	7 (11.7)	3 (5.0)	35 (44.3)	1 (1.3)	141 (61.6)	21 (9.2)
Chemistry								
Aspartate aminotransferase increased	72 (57.6)	11 (8.8)	20 (33.3)	6 (10.0)	25 (31.6)	2 (2.5)	111 (48.5)	14 (6.1)
Blood alkaline phosphatase increased	73 (58.4)	11 (8.8)	21 (35.6)	6 (10.2)	15 (19.2)	1 (1.3)	100 (43.9)	12 (5.3)
Alanine aminotransferase increased	62 (49.6)	11 (8.8)	11 (18.3)	2 (3.3)	18 (22.8)	1 (1.3)	91 (39.7)	12 (5.2)
Hypokalemia	44 (35.2)	6 (4.8)	12 (20.0)	5 (8.3)	22 (27.8)	4 (5.1)	77 (33.6)	13 (5.7)
Blood bilirubin increased	32 (25.6)	10 (8.0)	4 (6.8)	2 (3.4)	11 (14.1)	0	46 (20.2)	11 (4.8)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects with both baseline and post-treatment measurements as the denominator, based on CTCAE grade-derived laboratory abnormalities of subjects whose post-baseline grades worse than baseline grades.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.

2.5.5.1. Hematology

Hematology parameters measured in the clinical studies included: platelets, hemoglobin, white blood cell count, absolute neutrophil count, and lymphocytes.

Blood chemistry parameters included: sodium, magnesium, potassium, calcium, AST (aspartate aminotransferase) , ALT (alanine aminotransferase), serum creatinine, TBL (total bilirubin), albumin, and ALP (alkaline phosphatase).

Anemia

Table 3.1: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Anemia (Hemoglobin Decreased) (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	0	4 (3.2)	5 (4.0)	3 (2.4)	0	12 (9.6)
	1	0	14 (11.2)	37 (29.6)	20 (16.0)	0	71 (56.8)
	2	0	0	14 (11.2)	27 (21.6)	0	41 (32.8)

	3	0	0	0	1 (0.8)	0	1 (0.8)
	4	0	0	0	0	0	0
	Total	0	18 (14.4)	56 (44.8)	51 (40.8)	0	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	0	**7 (11.7)**	**2 (3.3)**	**1 (1.7)**	0	10 (16.7)
	1	0	18 (30.0)	**10 (16.7)**	**5 (8.3)**	0	33 (55.0)
	2	0	1 (1.7)	8 (13.3)	**8 (13.3)**	0	17 (28.3)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	0	26 (43.3)	20 (33.3)	14 (23.3)	0	60 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	5 (6.3)	**13 (16.5)**	**2 (2.5)**	0	0	20 (25.3)
	1	0	26 (32.9)	**17 (21.5)**	**4 (5.1)**	0	47 (59.5)
	2	0	0	9 (11.4)	**3 (3.8)**	0	12 (15.2)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	5 (6.3)	39 (49.4)	28 (35.4)	7 (8.9)	0	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	6 (2.6)	**17 (7.4)**	**8 (3.5)**	**3 (1.3)**	0	34 (14.8)
	1	0	42 (18.3)	**61 (26.6)**	**29 (12.7)**	0	132 (57.6)
	2	0	0	28 (12.2)	**34 (14.8)**	0	62 (27.1)
	3	0	0	0	1 (0.4)	0	1 (0.4)
	4	0	0	0	0	0	0
	Total	6 (2.6)	59 (25.8)	97 (42.4)	67 (29.3)	0	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.1

Platelet count

Study J202 subject no. [redacted] and study U205 subject no. [redacted] experienced an event of **major bleeding** (tumour haemorrhage) within 14 days of the onset of ≥Grade 3 thrombocytopenia. Of note, 52/229 (22.7%) subjects in the HER2-positive GC Pool received a **transfusion** within

28 days after the onset of a TEAE of anemia or thrombocytopenia.

Table 3.2: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Platelet Count (Decrease) (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	30 (24.0)	**54 (43.2)**	**13 (10.4)**	**7 (5.6)**	**2 (1.6)**	106 (84.8)
	1	0	7 (5.6)	**6 (4.8)**	**5 (4.0)**	**1 (0.8)**	19 (15.2)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	30 (24.0)	61 (48.8)	19 (15.2)	12 (9.6)	3 (2.4)	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	47 (78.3)	**4 (6.7)**	0	**2 (3.3)**	**1 (1.7)**	54 (90.0)
	1	1 (1.7)	5 (8.3)	0	0	0	6 (10.0)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	48 (80.0)	9 (15.0)	0	2 (3.3)	1 (1.7)	60 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	38 (48.1)	**27 (34.2)**	**4 (5.1)**	**1 (1.3)**	0	70 (88.6)
	1	1 (1.3)	5 (6.3)	**3 (3.8)**	0	0	9 (11.4)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	39 (49.4)	32 (40.5)	7 (8.9)	1 (1.3)	0	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	75 (32.8)	**91 (39.7)**	**19 (8.3)**	**11 (4.8)**	**4 (1.7)**	200 (87.3)
	1	1 (0.4)	12 (5.2)	**10 (4.4)**	**5 (2.2)**	**1 (0.4)**	29 (12.7)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	76 (33.2)	103 (45.0)	29 (12.7)	16 (7.0)	5 (2.2)	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.1

Table 11: Number and Percentage of Subjects with Events of Bleeding and Thrombocytopenia (Grouped Term) (Safety Analysis Set)

MedDRA PT	Study J202 HER2-positive GC (Primary Cohort)				Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79) n (%)		HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229) n (%)	
	T-DXd 6.4 mg/kg (N = 125) n (%)		TPC (N = 62) n (%)					
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with any bleeding event with any event of thrombocytopenia (grouped term)	**12 (9.6)**	**3 (2.4)**	**0**	**0**	**3 (3.8)**	**1 (1.3)**	**17 (7.4)**	**4 (1.7)**
Epistaxis	3 (2.4)	0	0	0	2 (2.5)	0	7 (3.1)	0
Disseminated intravascular coagulation	2 (1.6)	2 (1.6)	0	0	0	0	2 (0.9)	2 (0.9)
Upper gastrointestinal haemorrhage	2 (1.6)	0	0	0	0	0	2 (0.9)	0
Gastric haemorrhage	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Haematemesis	0	0	0	0	1 (1.3)	1 (1.3)	1 (0.4)	1 (0.4)
Haematuria	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Haemorrhage subcutaneous	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Haemorrhoidal haemorrhage	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Melaena	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Retinal haemorrhage	1 (0.8)	0	0	0	0	0	1 (0.4)	0
Tumour haemorrhage	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.4)
Outcome of event of bleeding in subjects with any event of thrombocytopenia (grouped term)								
Fatal	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)	1 (0.4)
Not Recovered/Not Resolved	6 (4.8)	2 (1.6)	0	0	1 (1.3)	0	9 (3.9)	2 (0.9)
Recovering/Resolving	0	0	0	0	0	0	0	0
Recovered/Resolved with Sequelae	0	0	0	0	0	0	0	0
Recovered/Resolved	5 (4.0)	0	0	0	2 (2.5)	1 (1.3)	7 (3.1)	1 (0.4)

In the HER2-positive GC Pool, there were a total of 52 (22.7%) patients who received a transfusion within 28 days after the onset of a TEAE of anaemia or thrombocytopenia (Module 5.3.5.3 SCS Table 1.2.3.2). The reasons for the transfusion were as follows (Module 5.3.5.3 SCS Listing 1.8):

- Anaemia, n = 42.
- Anaemia and platelet count decreased, n = 7.
- Platelet count decreased, n = 3.

Neutrophil count decrease

Two subjects in Study J202 experienced a ≥Grade 3 event of **sepsis** within 14 days of the onset of neutropenia (grouped term) or febrile neutropenia.

A total of 35/229 (15.3%) subjects in the **HER2-positive GC Pool** were **treated with G-CSF** within 28 days after onset of neutropenia or febrile neutropenia, with similar proportion of subjects between the T-DXd and the TPC arm of Study J202.

Table 3.3: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Neutrophil Count Decreased (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	33 (26.4)	**6 (4.8)**	**21 (16.8)**	**48 (38.4)**	**15 (12.0)**	123 (98.4)
	1	0	0	0	**1 (0.8)**	0	1 (0.8)
	2	0	0	1 (0.8)	0	0	1 (0.8)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	33 (26.4)	6 (4.8)	22 (17.6)	49 (39.2)	15 (12.0)	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	33 (55.0)	**3 (5.0)**	**10 (16.7)**	**8 (13.3)**	**5 (8.3)**	59 (98.3)
	1	0	0	0	**1 (1.7)**	0	1 (1.7)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	33 (55.0)	3 (5.0)	10 (16.7)	9 (15.0)	5 (8.3)	60 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	37 (46.8)	**12 (15.2)**	**21 (26.6)**	**5 (6.3)**	**4 (5.1)**	79 (100)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0

	4	0	0	0	0	0	0
	Total	37 (46.8)	12 (15.2)	21 (26.6)	5 (6.3)	4 (5.1)	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	80 (34.9)	**18 (7.9)**	**48 (21.0)**	**59 (25.8)**	**21 (9.2)**	226 (98.7)
	1	0	0	0	**2 (0.9)**	0	2 (0.9)
	2	0	0	1 (0.4)	0	0	1 (0.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	80 (34.9)	18 (7.9)	49 (21.4)	61 (26.6)	21 (9.2)	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Bolded values represent worsening from baseline.
Source: Module 5.3.5.3 SCS Table 1.3.1.1

The MAH has reviewed all subjects who received G-CSF during T-DXd treatment and identified 38 (16.6%) subjects in the HER2-positive Pool who received G-CSF as either prophylaxis or treatment. Subjects who received G-CSF as treatment are presented in Appendix 2 Listing 3. Two of the 38 subjects received G-CSF as primary prophylaxis for neutropenia (Subject No. [redacted] in Study J202 and Subject No. [redacted]–in Study U205). In addition, 2 subjects in Study U205 received G-CSF as secondary prophylaxis for neutropenia (Subject Nos. [redacted] and [redacted]). Given the limited use of G-CSF as prophylaxis, the MAH considers that the overall incidence of these events is a true reflection of the toxicity profile in neutropenia and febrile neutropenia. Based on these observations, the MAH considers that neutropenia and febrile neutropenia can be managed by following the guidance on dose modification provided in the SmPC and through standard clinical practice.

Lymphocyte count decrease

Table 3.4: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Lymphocyte Count Decreased (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	15 (12.0)	**13 (10.4)**	**20 (16.0)**	**9 (7.2)**	**1 (0.8)**	58 (46.4)
	1	1 (0.8)	12 (9.6)	**22 (17.6)**	**13 (10.4)**	0	48 (38.4)
	2	0	0	3 (2.4)	**8 (6.4)**	**4 (3.2)**	15 (12.0)
	3	0	0	0	2 (1.6)	**2 (1.6)**	4 (3.2)
	4	0	0	0	0	0	0
	Total	16 (12.8)	25 (20.0)	45 (36.0)	32 (25.6)	7 (5.6)	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	11 (18.6)	**10 (16.9)**	**4 (6.8)**	**1 (1.7)**	0	26 (44.1)
	1	1 (1.7)	10 (16.9)	**11 (18.6)**	**3 (5.1)**	**1 (1.7)**	26 (44.1)
	2	0	2 (3.4)	1 (1.7)	**1 (1.7)**	**1 (1.7)**	5 (8.5)
	3	0	0	1 (1.7)	1 (1.7)	0	2 (3.4)
	4	0	0	0	0	0	0
	Total	12 (20.3)	22 (37.3)	17 (28.8)	6 (10.2)	2 (3.4)	59 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	27 (34.2)	**13 (16.5)**	**7 (8.9)**	**5 (6.3)**	0	52 (65.8)
	1	0	2 (2.5)	**10 (12.7)**	**1 (1.3)**	0	13 (16.5)
	2	0	0	7 (8.9)	**6 (7.6)**	0	13 (16.5)
	3	0	0	0	1 (1.3)	0	1 (1.3)
	4	0	0	0	0	0	0
	Total	27 (34.2)	15 (19.0)	24 (30.4)	13 (16.5)	0	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	45 (19.7)	**31 (13.5)**	**33 (14.4)**	**18 (7.9)**	**2 (0.9)**	129 (56.3)
	1	1 (0.4)	14 (6.1)	**34 (14.8)**	**15 (6.6)**	**1 (0.4)**	65 (28.4)
	2	0	0	10 (4.4)	**16 (7.0)**	**4 (1.7)**	30 (13.1)
	3	0	0	0	3 (1.3)	**2 (0.9)**	5 (2.2)
	4	0	0	0	0	0	0
	Total	46 (20.1)	45 (19.7)	77 (33.6)	52 (22.7)	9 (3.9)	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.1

2.5.5.2. Blood chemistry

Renal function – serum creatinine increase

Table 3.5: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Serum Creatinine Increased (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	3 (2.4)	**98 (78.4)**	**8 (6.4)**	**1 (0.8)**	0	110 (88.0)
	1	2 (1.6)	8 (6.4)	**4 (3.2)**	0	0	14 (11.2)
	2	0	0	1 (0.8)	0	0	1 (0.8)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	5 (4.0)	106 (84.8)	13 (10.4)	1 (0.8)	0	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	8 (13.6)	**37 (62.7)**	0	**1 (1.7)**	**1 (1.7)**	47 (79.7)
	1	2 (3.4)	7 (11.9)	**2 (3.4)**	0	0	11 (18.6)
	2	0	0	1 (1.7)	0	0	1 (1.7)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	10 (16.9)	44 (74.6)	3 (5.1)	1 (1.7)	1 (1.7)	59 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	62 (78.5)	**7 (8.9)**	0	**1 (1.3)**	0	70 (88.6)
	1	0	9 (11.4)	0	0	0	9 (11.4)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	62 (78.5)	16 (20.3)	0	1 (1.3)	0	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	65 (28.4)	**122 (53.3)**	**12 (5.2)**	**2 (0.9)**	0	201 (87.8)
	1	2 (0.9)	20 (8.7)	**5 (2.2)**	0	0	27 (11.8)
	2	0	0	1 (0.4)	0	0	1 (0.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	67 (29.3)	142 (62.0)	18 (7.9)	2 (0.9)	0	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.2

Renal function – creatinine clearance

Creatinine clearance is defined using the Cockcroft-Gault equation.

Table 3.6: Renal Function Abnormalities (Safety Analysis Set)

Creatinine Clearance (mL/min) [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Non-missing n [b]	125	59	63	212
Minimum post-baseline				
<30	6 (4.8)	4 (6.8)	0	7 (3.3)
30 - <60	54 (43.2)	24 (40.7)	10 (15.9)	81 (38.2)
60 - <90	51 (40.8)	25 (42.4)	26 (41.3)	83 (39.2)
≥90	14 (11.2)	6 (10.2)	27 (42.9)	41 (19.3)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the non-missing n as the denominator.

[a] Creatinine clearance computed by the calculation by each site.

[b] Non-missing n is the number of subjects with both baseline and post-baseline data.

Source: Module 5.3.5.3 SCS Table 1.3.1.4

Renal function - potassium decrease

Table 3.7: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Potassium Decreased (Hypokalemia) (Safety Analysis Set)

Group	Baseline CTCAE	Number (%) of Subjects with Worst Post-Baseline CTCAE Grade					
	Grade	Normal	1	2	3	4	Total
Study J202 with HER2-positive GC (primary cohort) T-DXd 6.4 mg/kg (N = 125)	Normal	80 (64.0)	0	**38 (30.4)**	**6 (4.8)**	0	124 (99.2)
	1	0	0	0	0	0	0
	2	0	0	1 (0.8)	0	0	1 (0.8)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	80 (64.0)	0	39 (31.2)	6 (4.8)	0	125 (100)
Study J202 with HER2-positive GC (primary cohort) TPC (N = 62)	Normal	47 (78.3)	0	**7 (11.7)**	**3 (5.0)**	**1 (1.7)**	58 (96.7)
	1	0	0	0	0	0	0
	2	0	0	1 (1.7)	**1 (1.7)**	0	2 (3.3)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	47 (78.3)	0	8 (13.3)	4 (6.7)	1 (1.7)	60 (100)
Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	Normal	53 (67.1)	**18 (22.8)**	0	**3 (3.8)**	**1 (1.3)**	75 (94.9)
	1	1 (1.3)	3 (3.8)	0	0	0	4 (5.1)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	54 (68.4)	21 (26.6)	0	3 (3.8)	1 (1.3)	79 (100)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Normal	147 (64.2)	**18 (7.9)**	**46 (20.1)**	**11 (4.8)**	**2 (0.9)**	224 (97.8)
	1	1 (0.4)	3 (1.3)	0	0	0	4 (1.7)
	2	0	0	1 (0.4)	0	0	1 (0.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	148 (64.6)	21 (9.2)	47 (20.5)	11 (4.8)	2 (0.9)	229 (100)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER 2 = human epidermal growth factor receptor 2; N = **total** number of treated subjects; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

For each group, percentages were based on the number of subjects in the Safety Analysis Set who had a baseline and at least 1 post-baseline assessment.

Baseline value was defined as the last non-missing value prior to the first dose of study drug.

Bolded values represent worsening from baseline.

Source: Module 5.3.5.3 SCS Table 1.3.1.2

Liver function test (LFT)

At enrollment, a total of 57/229 (24.9%) subjects in the HER2-positive GC Pool had mild and 1/229 (0.4%) had moderate **hepatic impairment.**

A total of 130/229 (56.8%) subjects in the HER2-positive GC Pool had **liver metastases.**

In the HER2-positive GC Pool, 8/229 (**5.3%**) subjects had post-baseline LFT values that met the biochemical criteria for potential **Hy's Law** (ALT or AST ≥3 × ULN and TBL ≥2 × ULN), of which 6/125

(4.8%) subjects were in the Study J202 T-DXd arm and none in Study U205 (Table 3.8). Additionally, 3/59 (**5.1%**) in the J202 TPC arm met the biochemical criteria of potential Hy's Law.

In all 11 subjects, the events of potential Hy's Law were determined **not to be causally associated with study drug** due to alternative etiologies at the time of occurrence of the events, the most common of which were biliary duct/drainage issues (5 events) and progressive disease (3 events)

Table 3.8: Hepatic Function Abnormalities (Safety Analysis Set)

Hepatic Function Laboratory Parameter	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positiveGC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Alanine aminotransferase (ALT)				
Non-missing n[a]	125	60	79	229
Baseline ≥ULN	15 (12.0)	8 (13.3)	7 (8.9)	25 (10.9)
Maximum post-baseline value				
≥3 × ULN	15 (12.0)	7 (11.7)	3 (3.8)	19 (8.3)
≥5 × ULN	11 (8.8)	2 (3.3)	1 (1.3)	12 (5.2)
≥8 × ULN	3 (2.4)	1 (1.7)	1 (1.3)	4 (1.7)
≥10 × ULN	3 (2.4)	1 (1.7)	1 (1.3)	4 (1.7)
≥20 × ULN	2 (1.6)	0	0	2 (0.9)
Aspartate aminotransferase (AST)				
Non-missing n[a]	125	60	79	229
Baseline ≥ULN	36 (28.8)	14 (23.3)	14 (17.7)	58 (25.3)
Maximum post-baseline value				
≥3 × ULN	23 (18.4)	10 (16.7)	7 (8.9)	35 (15.3)
≥5 × ULN	11 (8.8)	6 (10.0)	3 (3.8)	15 (6.6)
≥8 × ULN	6 (4.8)	2 (3.3)	0	6 (2.6)
≥10 × ULN	5 (4.0)	1 (1.7)	0	5 (2.2)
≥20 × ULN	0	1 (1.7)	0	0
ALT or AST				
Non-missing n[a]	125	60	79	229
Baseline ≥ULN	37 (29.6)	14 (23.3)	16 (20.3)	62 (27.1)

Hepatic Function Laboratory Parameter	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positiveGC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Maximum post-baseline value				
≥3 × ULN	27 (21.6)	10 (16.7)	9 (11.4)	41 (17.9)
≥5 × ULN	13 (10.4)	6 (10.0)	3 (3.8)	17 (7.4)
≥8 × ULN	6 (4.8)	2 (3.3)	1 (1.3)	7 (3.1)
≥10 × ULN	5 (4.0)	1 (1.7)	1 (1.3)	6 (2.6)
≥20 × ULN	2 (1.6)	1 (1.7)	0	2 (0.9)
Total bilirubin (TBL)				
Non-missing n[a]	125	59	78	228
Baseline ≥ULN	5 (4.0)	1 (1.7)	1 (1.3)	6 (2.6)
Maximum post-baseline value				
≥1.5 × ULN	16 (12.8)	4 (6.8)	5 (6.4)	23 (10.1)
≥2 × ULN	13 (10.4)	3 (5.1)	1 (1.3)	16 (7.0)
≥3 × ULN	10 (8.0)	2 (3.4)	0	12 (5.3)
Alkaline phosphatase (ALP)				
Non-missing n[a]	125	59	78	228
Baseline ≥ULN	47 (37.6)	18 (30.5)	28 (35.9)	82 (36.0)
Maximum post-baseline value				
≥1.5 × ULN	68 (54.4)	21 (35.6)	24 (30.8)	104 (45.6)
≥2 × ULN	44 (35.2)	14 (23.7)	16 (20.5)	69 (30.3)
Concurrent TBL elevation with ALT or AST elevation[b]				
Non-missing n[a]	125	59	0	150
ALT or AST ≥3 × ULN and TBL ≥2 × ULN	6 (4.8)	3 (5.1)	0	8 (5.3)
Concurrent TBL elevation with ALT or AST elevation and ALP <2 × ULN[b]				
Non-missing n [a]	125	59	0	150
ALT or AST ≥3 × ULN and TBL ≥2 × ULN and ALP <2 × ULN	3 (2.4)	2 (3.4)	0	3 (2.0)

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2;

N = total number of treated subjects; T-DXd = trastuzumab deruxtecan; TBL = total bilirubin; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]); ULN = upper limit of normal.

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the non-missing n as the denominator.

Each subject was counted for only the worst case observed post-baseline.

[a] Non-missing n is the number of subjects with both baseline and post-baseline data.

[b] "Concurrent" means these abnormalities occurred within a 28-day window.

Source: Module 5.3.5.3 SCS Table 1.3.1.3

None of the 11 cases of potential Hy's Law were considered to be drug-related by the investigators. In all instances, at the time of meeting potential Hy's Law biochemical criteria, ALP was >2 × ULN suggesting an obstructive etiology caused the elevated LFT results. The alternative etiology for meeting biochemical Hy's Law criteria included the following: liver metastases, biliary dilatation requiring stenting, stent revision, or biliary drainage, bile stone, cholangitis, biliary sepsis, and disease progression.

2.5.5.3. Other observations related to safety

Vital signs

Table 1.3.2 Notable Vital Sign Values
(Safety Analysis Set)

	Number (%) of Subjects in Study			Number (%) of Subjects in Pool	
	J202 HER2 positive GC (primary cohort)		U205 HER2		
Vital Sign Parameter Criteria	T-DXd 6.4 mg/kg (N=125)	TPC (N=62)	positive GC 6.4 mg/kg (N=79)	HER2 positive GC 6.4 mg/kg Pool (N=229)	All Tumor Types T-DXd >= 5.4 mg/kg Pool (N=962)
Systolic Blood Pressure (mmHg)					
Non-missing n [1]	125	60	79	229	962
>= 180 mmHg and increase >= 20 mmHg from baseline	0	0	0	0	8 (0.8)
<= 90 mmHg and decrease >= 20 mmHg from baseline	9 (7.2)	5 (8.3)	3 (3.8)	14 (6.1)	104 (10.8)
Diastolic Blood Pressure (mmHg)					
Non-missing n [1]	125	60	79	229	962
>= 105 mmHg and increase >= 15 mmHg from baseline	1 (0.8)	2 (3.3)	1 (1.3)	3 (1.3)	9 (0.9)
<= 50 mmHg and decrease >= 15 mmHg from baseline	17 (13.6)	2 (3.3)	5 (6.3)	25 (10.9)	107 (11.1)
Heart Rate (beats/min)					
Non-missing n [1]	125	59	79	229	962
>= 120 bpm and increase from baseline>= 15%	8 (6.4)	5 (8.5)	1 (1.3)	10 (4.4)	43 (4.5)
<= 50 bpm and decrease from baseline>= 15%	11 (8.8)	0	3 (3.8)	16 (7.0)	34 (3.5)
Temperature (C)					
Non-missing n [1]	125	61	79	229	960
> 39	7 (5.6)	1 (1.6)	0	8 (3.5)	12 (1.3)
< 36	50 (40.0)	10 (16.4)	28 (35.4)	88 (38.4)	345 (35.9)
SpO2 (%)					
Non-missing n [1]	124	59	78	227	947
< 90%	1 (0.8)	0	0	2 (0.9)	25 (2.6)

Note: The pooled analysis group is based on tumor type and first dose received for subjects in each study.
The baseline value is defined as the last non-missing value before initial administration of study treatment.
HER2 positive GC 6.4 mg/kg Pool include data from studies: DS8201-A-J101, DS8201-A-J202 and DS8201-A-U205.
All Tumor Types T-DXd >= 5.4 mg/kg Pooled Data: DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205.
[1] Non-missing n is the number of subjects with both baseline and post-baseline data. Percentages are calculated using the non-missing n as denominator.

ECG

Table 4.1: Summary of QTcF Intervals (Safety Analysis Set)

QTcF Interval	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Non-missing n [a]	124	59	74	223
New >470 ms (female) or >450 ms (male) [b]	20 (16.1)	5 (8.5)	8 (10.8)	35 (15.7)
New >480 ms [b]	5 (4.0)	2 (3.4)	4 (5.4)	11 (4.9)
New >500 ms [b]	2 (1.6)	2 (3.4)	1 (1.4)	4 (1.8)
>30 ms increase from baseline [c]	13 (10.5)	5 (8.5)	16 (21.6)	32 (14.3)
>60 ms increase from baseline [c]	4 (3.2)	2 (3.4)	3 (4.1)	9 (4.0)

ECG = electrocardiogram; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; ms = millisecond; QTcF = QT interval corrected for heart rate using Fridericia's correction formula; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2 positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202 and DS8201-A-U205.
Percentages were calculated using the non-missing n as the denominator.
[a] Non-missing n is the number of subjects with both baseline and post-baseline data.
[b] A new ECG abnormality was defined as an abnormal ECG finding post-baseline that was not present at baseline.
[c] The baseline value was defined as the last non-missing value before first dose of study drug. If multiple ECG measurements were taken at baseline, the average of all baseline values was used as baseline.

2.5.6. Safety in special populations

2.5.6.1. Intrinsic factors

TEAEs were evaluated for the following intrinsic factors: **age** (<65, ≥65 years and <75, and ≥75 years), **race** (White, Asian, and Other), **sex** (male, female), ECOG PS (0, 1), **renal function** at baseline (normal function, mild impairment, and moderate impairment), and **hepatic function** at baseline (normal function, mild impairment).

Age

One notable difference for the category **TEAEs with an outcome of death** was reported, with a higher proportion of subjects in the age group of <65 years.

In the HER2-positive GC Pool, events in the following categories were reported in a higher proportion of subjects ≥75 years of age (n = 24) than in subjects <75 years of age (n = 205):

- **≥Grade 3 TEAEs** (20/24 [83.3%] vs.147/205 [71.7%])
- TEAEs associated with study **drug interruption** (14/24 [58.3%] vs. 95/205 [46.3%])
- TEAEs associated with **dose reduction** (10/24 [41.7%] vs. 58/205 [28.3%])
- **SAEs** (12/24 [50.0%] vs. 80/205 [39.0%])

A similar pattern was seen in the TPC arm.

Table 5.1: Overall Summary of Treatment-Emergent Adverse Events by Age Group (Safety Analysis Set)

Parameter	Age Group <65 years				Age Group ≥65 years			
	Number (%) of Subjects				Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 46)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 109)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 33)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 120)
	T-DXd 6.4 mg/kg (N = 55)	TPC (N = 27)			T-DXd 6.4 mg/kg (N = 70)	TPC (N = 35)		
Duration of treatment (months)								
Median	5.22	2.76	4.24	4.37	4.48	2.76	5.16	4.60
Range	0.7, 25.4	0.5, 7.1	0.7, 15.4	0.7, 25.4	0.7, 29.7	0.5, 13.1	0.7, 15.9	0.7, 29.7
Subjects with any TEAE, n (%)	55 (100)	27 (100)	46 (100)	109 (100)	70 (100)	34 (97.1)	33 (100)	120 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	52 (94.5)	16 (59.3)	27 (58.7)	85 (78.0)	55 (78.6)	19 (54.3)	13 (39.4)	82 (68.3)
Serious TEAEs	24 (43.6)	7 (25.9)	18 (39.1)	43 (39.4)	32 (45.7)	9 (25.7)	11 (33.3)	49 (40.8)
TEAEs associated with study drug discontinuation	7 (12.7)	0	7 (15.2)	14 (12.8)	15 (21.4)	4 (11.4)	5 (15.2)	24 (20.0)
TEAEs associated with dose reduction	17 (30.9)	10 (37.0)	14 (30.4)	33 (30.3)	23 (32.9)	11 (31.4)	5 (15.2)	35 (29.2)
TEAEs associated with study drug interruption	33 (60.0)	10 (37.0)	10 (21.7)	47 (43.1)	46 (65.7)	13 (37.1)	7 (21.2)	62 (51.7)
TEAEs associated with an outcome of death[b]	4 (7.3)	0	9 (19.6)	13 (11.9)	4 (5.7)	2 (5.7)	1 (3.0)	6 (5.0)
Subjects with any drug-related TEAE, n (%)[c]	54 (98.2)	25 (92.6)	43 (93.5)	105 (96.3)	68 (97.1)	31 (88.6)	31 (93.9)	116 (96.7)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	44 (80.0)	13 (48.1)	14 (30.4)	62 (56.9)	50 (71.4)	14 (40.0)	7 (21.2)	69 (57.5)
Drug-related serious TEAEs	10 (18.2)	3 (11.1)	4 (8.7)	15 (13.8)	20 (28.6)	2 (5.7)	4 (12.1)	26 (21.7)
Drug-related TEAEs associated with study drug discontinuation	5 (9.1)	0	3 (6.5)	8 (7.3)	9 (12.9)	3 (8.6)	4 (12.1)	16 (13.3)
Drug-related TEAEs associated with dose reduction	17 (30.9)	10 (37.0)	10 (21.7)	29 (26.6)	21 (30.0)	11 (31.4)	5 (15.2)	33 (27.5)
Drug-related TEAEs associated with study drug interruption	26 (47.3)	8 (29.6)	6 (13.0)	36 (33.0)	39 (55.7)	11 (31.4)	1 (3.0)	47 (39.2)
Drug-related TEAEs associated with an outcome of death[b]	0	0	1 (2.2)	1 (0.9)	1 (1.4)	0	0	1 (0.8)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.

[c] If relationship was missing, the TEAE was considered to be related to the drug.

Source: Module 5.3.5.3 SCS Tables 1.4.2 and 1.4.3

Table 12: Treatment-emergent Serious Adverse Events, Treatment-emergent Adverse Events Associated with Dose Reduction, Treatment-emergent Adverse Events Associated with an Outcome of Death (All and Drug-related Events) by Age (Safety Analysis Set)

	Age Group <65 years				Age Group ≥65 years			
	Number (%) of Subjects				Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 46)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 109)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 33)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 120)
	T-DXd 6.4 mg/kg (N = 55)	TPC (N = 27)			T-DXd 6.4 mg/kg (N = 70)	TPC (N = 35)		
Treatment-emergent SAEs	24 (43.6)	7 (25.9)	18 (39.1)	43 (39.4)	32 (45.7)	9 (25.7)	11 (33.3)	49 (40.8)
Drug-related treatment-emergent SAEs[a]	10 (18.2)	3 (11.1)	4 (8.7)	15 (13.8)	20 (28.6)	2 (5.7)	4 (12.1)	26 (21.7)
TEAEs associated with dose reduction	17 (30.9)	10 (37.0)	12 (26.1)	31 (28.4)	23 (32.9)	11 (31.4)	5 (15.2)	35 (29.2)
Drug-related TEAEs associated with dose reduction	17 (30.9)	10 (37.0)	9 (19.6)	28 (25.7)	21 (30.0)	11 (31.4)	5 (15.2)	33 (27.5)
TEAEs associated with an outcome of death	4 (7.3)	0	9 (19.6)	13 (11.9)	4 (5.7)	2 (5.7)	1 (3.0)	6 (5.0)
Drug-related TEAEs associated with an outcome of death	0	0	1 (2.2)	1 (0.9)	1 (1.4)	0	0	1 (0.8)

GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; PTX = paclitaxel; SAE = serious adverse event; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])
The HER2-positive GC T-DXd 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] If relationship was missing, the AE was also considered to be drug-related

Source: Module 5.3.5.3 SCS Table 1.4.3

Sex

Within the HER2-positive GC Pool, notable differences in the frequency of events in the following categories were observed when comparing male subjects (n = 172) and female subjects (n = 57) subjects:

a higher proportion of **male** subjects compared to female subjects experienced:

- Drug-related TEAEs associated with study drug discontinuation (21/172 [12.2%] vs. 3/57 [5.3%])

a higher proportion of **female** subjects compared to male subjects experienced:

- SAEs (28/57 [49.1%] vs. 64/172 [37.2%])

Table 1.4.3 Subgroup Analysis of Overall Summary of Treatment-Emergent Adverse Events
(Safety Analysis Set)

Gender: Female

	Number (%) of Subjects in Study			Number (%) of
	J202 HER2 positive GC (primary cohort)		U205 HER2 positive GC	
	T-DXd 6.4 mg/kg (N = 30)	TPC (N = 15)	6.4 mg/kg (N = 22)	HER2 positive GC 6.4 mg/kg Pool (N = 57)
Treatment-Emergent Adverse Events (TEAE)	30 (100)	15 (100)	22 (100)	57 (100)
TEAE with CTCAE Grade >= 3	26 (86.7)	6 (40.0)	12 (54.5)	42 (73.7)
TEAE associated with an outcome of death	3 (10.0)	0	1 (4.5)	4 (7.0)
TEAE associated with study drug discontinuation	6 (20.0)	1 (6.7)	2 (9.1)	10 (17.5)
TEAE associated with study drug interruption	16 (53.3)	6 (40.0)	5 (22.7)	23 (40.4)
TEAE associated with dose reduction	11 (36.7)	5 (33.3)	5 (22.7)	18 (31.6)
Drug-Related TEAE (Related TEAE)	29 (96.7)	13 (86.7)	22 (100)	56 (98.2)
Related TEAE with CTCAE Grade >= 3	23 (76.7)	4 (26.7)	8 (36.4)	35 (61.4)
Related TEAE associated with an outcome of death	0	0	0	0
Related TEAE associated with study drug discontinuation	1 (3.3)	1 (6.7)	0	3 (5.3)
Related TEAE associated with study drug interruption	13 (43.3)	4 (26.7)	3 (13.6)	18 (31.6)
Related TEAE associated with dose reduction	10 (33.3)	5 (33.3)	3 (13.6)	15 (26.3)
Treatment-Emergent Serious Adverse Events (SAE)	17 (56.7)	2 (13.3)	9 (40.9)	28 (49.1)
SAE with CTCAE Grade >= 3	15 (50.0)	2 (13.3)	7 (31.8)	24 (42.1)
SAE associated with an outcome of death	3 (10.0)	0	1 (4.5)	4 (7.0)
SAE associated with study drug discontinuation	5 (16.7)	0	1 (4.5)	7 (12.3)
SAE associated with study drug interruption	3 (10.0)	2 (13.3)	1 (4.5)	5 (8.8)
SAE associated with dose reduction	6 (20.0)	0	0	6 (10.5)
Drug-Related SAE (Related SAE)	11 (36.7)	0	2 (9.1)	14 (24.6)
Related SAE with CTCAE Grade >= 3	8 (26.7)	0	1 (4.5)	10 (17.5)
Related SAE associated with an outcome of death	0	0	0	0
Related SAE associated with study drug discontinuation	0	0	0	1 (1.8)
Related SAE associated with study drug interruption	2 (6.7)	0	0	2 (3.5)
Related SAE associated with dose reduction	5 (16.7)	0	0	5 (8.8)

Table 1.4.3 Subgroup Analysis of Overall Summary of Treatment-Emergent Adverse Events
(Safety Analysis Set)

Gender: Male

	Number (%) of Subjects in Study			Number (%) of S
	J202 HER2 positive GC (primary cohort)		U205 HER2 positive GC	
	T-DXd 6.4 mg/kg (N = 95)	TPC (N = 47)	6.4 mg/kg (N = 57)	HER2 positive GC 6.4 mg/kg Pool (N = 172)
Treatment-Emergent Adverse Events (TEAE)	95 (100)	46 (97.9)	57 (100)	172 (100)
TEAE with CTCAE Grade >= 3	81 (85.3)	29 (61.7)	28 (49.1)	125 (72.7)
TEAE associated with an outcome of death	5 (5.3)	2 (4.3)	9 (15.8)	15 (8.7)
TEAE associated with study drug discontinuation	16 (16.8)	3 (6.4)	10 (17.5)	28 (16.3)
TEAE associated with study drug interruption	63 (66.3)	17 (36.2)	12 (21.1)	86 (50.0)
TEAE associated with dose reduction	29 (30.5)	16 (34.0)	14 (24.6)	50 (29.1)
Drug-Related TEAE (Related TEAE)	93 (97.9)	43 (91.5)	52 (91.2)	165 (95.9)
Related TEAE with CTCAE Grade >= 3	71 (74.7)	23 (48.9)	13 (22.8)	96 (55.8)
Related TEAE associated with an outcome of death	1 (1.1)	0	1 (1.8)	2 (1.2)
Related TEAE associated with study drug discontinuation	13 (13.7)	2 (4.3)	7 (12.3)	21 (12.2)
Related TEAE associated with study drug interruption	52 (54.7)	15 (31.9)	4 (7.0)	65 (37.8)
Related TEAE associated with dose reduction	28 (29.5)	16 (34.0)	12 (21.1)	47 (27.3)
Treatment-Emergent Serious Adverse Events (SAE)	39 (41.1)	14 (29.8)	20 (35.1)	64 (37.2)
SAE with CTCAE Grade >= 3	32 (33.7)	13 (27.7)	17 (29.8)	53 (30.8)
SAE associated with an outcome of death	5 (5.3)	2 (4.3)	9 (15.8)	15 (8.7)
SAE associated with study drug discontinuation	6 (6.3)	1 (2.1)	7 (12.3)	15 (8.7)
SAE associated with study drug interruption	16 (16.8)	2 (4.3)	6 (10.5)	25 (14.5)
SAE associated with dose reduction	0	1 (2.1)	2 (3.5)	2 (1.2)
Drug-Related SAE (Related SAE)	19 (20.0)	5 (10.6)	6 (10.5)	27 (15.7)
Related SAE with CTCAE Grade >= 3	10 (10.5)	4 (8.5)	5 (8.8)	17 (9.9)
Related SAE associated with an outcome of death	1 (1.1)	0	1 (1.8)	2 (1.2)
Related SAE associated with study drug discontinuation	4 (4.2)	0	4 (7.0)	9 (5.2)
Related SAE associated with study drug interruption	5 (5.3)	2 (4.3)	1 (1.8)	7 (4.1)
Related SAE associated with dose reduction	0	1 (2.1)	0	0

Table 13: Treatment-emergent Serious Adverse Events Considered as Drug-related, of Grade ⩾3 (All Events), Associated with Dose Reduction (All and Drug-related Events), and Associated with an Outcome of Death (All and Drug-related Events) by Sex (Safety Analysis Set)

	Male					Female				
	Number (%) of Subjects					Number (%) of Subjects				
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 57)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 172)	ATT T-DXd ≥5.4 mg/kg Pool (N = 331)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 22)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 57)	ATT T-DXd ≥5.4 mg/kg Pool (N = 631)
	T-DXd 6.4 mg/kg (N = 95)	TPC (N = 47)				T-DXd 6.4 mg/kg (N = 30)	TPC (N = 15)			
Drug-related treatment-emergent SAEs[a]	19 (20.0)	5 (10.6)	6 (10.5)	27 (15.7)	50 (15.1)	11 (36.7)	0	2 (9.1)	14 (24.6)	104 (16.5)
Treatment-emergent SAEs of Grade ≥3[b]	32 (33.7)	13 (27.7)	17 (29.8)	53 (30.8)	105 (31.7)	15 (50.0)	2 (13.3)	7 (31.8)	24 (42.1)	175 (27.7)
Treatment-emergent SAEs associated with dose reduction	0	1 (2.1)	2 (3.5)	2 (1.2)	7 (2.1)	6 (20.0)	0	0	6 (10.5)	21 (3.3)
Drug-related treatment-emergent SAEs associated with dose reduction	0	1 (2.1)	0	0	4 (1.2)	5 (16.7)	0	0	5 (8.8)	17 (2.7)
Treatment-emergent SAEs associated with an outcome of death	5 (5.3)	2 (4.3)	9 (15.8)	15 (8.7)	33 (10.0)	3 (10.0)	0	1 (4.5)	4 (7.0)	43 (6.8)
Drug-related treatment-emergent SAEs associated with an outcome of death	1 (1.1)	0	1 (1.8)	2 (1.2)	4 (1.2)	0	0	0	0	12 (1.9)

ATT = all tumor types; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; PTX = paclitaxel; SAE = serious adverse event; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or PTX [n = 7])

The HER2-positive GC T-DXd 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] If relationship was missing, the AE was also considered to be drug-related.

[b] A subject was counted once at the maximum severity.

Source: Module 5.3.5.3 SCS Table 1.4.3

ECOG performance status

Table 5.2: Overall Summary of Treatment-Emergent Adverse Events by ECOG Performance Status (Safety Analysis Set)

Parameter	Baseline ECOG PS = 0				Baseline ECOG PS = 1			
	Number (%) of Subjects				Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 29)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 110)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 50)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 119)
	T-DXd 6.4 mg/kg (N = 62)	TPC (N = 30)			T-DXd 6.4 mg/kg (N = 63)	TPC (N = 32)		
Duration of treatment (months)								
Median	5.96	2.74	4.34	5.63	4.27	2.81	4.25	4.27
Range	1.4, 29.7	0.5, 13.1	1.4, 12.6	1.4, 29.7	0.7, 16.8	0.5, 11.3	0.7, 15.9	0.7, 16.8
Subjects with any TEAE, n (%)	62 (100)	30 (100)	29 (100)	110 (100)	63 (100)	31 (96.9)	50 (100)	119 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	50 (80.6)	15 (50.0)	8 (27.6)	74 (67.3)	57 (90.5)	20 (62.5)	32 (64.0)	93 (78.2)
Serious TEAEs	20 (32.3)	4 (13.3)	4 (13.8)	30 (27.3)	36 (57.1)	12 (37.5)	25 (50.0)	62 (52.1)
TEAEs associated with study drug discontinuation	9 (14.5)	2 (6.7)	3 (10.3)	15 (13.6)	13 (20.6)	2 (6.3)	9 (18.0)	23 (19.3)
TEAEs associated with dose reduction	20 (32.3)	11 (36.7)	3 (10.3)	30 (27.3)	20 (31.7)	10 (31.3)	16 (32.0)	38 (31.9)
TEAEs associated with study drug interruption	45 (72.6)	11 (36.7)	5 (17.2)	60 (54.5)	34 (54.0)	12 (37.5)	12 (24.0)	49 (41.2)
TEAEs associated with an outcome of death [b]	3 (4.8)	1 (3.3)	2 (6.9)	6 (5.5)	5 (7.9)	1 (3.1)	8 (16.0)	13 (10.9)
Subjects with any drug-related TEAE, n (%)[c]	62 (100)	28 (93.3)	28 (96.6)	109 (99.1)	60 (95.2)	28 (87.5)	46 (92.0)	112 (94.1)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	45 (72.6)	12 (40.0)	3 (10.3)	60 (54.5)	49 (77.8)	15 (46.9)	18 (36.0)	71 (59.7)
Drug-related serious TEAEs	9 (14.5)	0	0	11 (10.0)	21 (33.3)	5 (15.6)	8 (16.0)	30 (25.2)
Drug-related TEAEs associated with study drug discontinuation	6 (9.7)	2 (6.7)	2 (6.9)	10 (9.1)	8 (12.7)	1 (3.1)	5 (10.0)	14 (11.8)
Drug-related TEAEs associated with dose reduction	20 (32.3)	11 (36.7)	3 (10.3)	30 (27.3)	18 (28.6)	10 (31.3)	12 (24.0)	32 (26.9)
Drug-related TEAEs associated with study drug interruption	38 (61.3)	10 (33.3)	2 (6.9)	49 (44.5)	27 (42.9)	9 (28.1)	5 (10.0)	34 (28.6)
Drug-related TEAEs associated with an outcome of death[b]	0	0	0	0	1 (1.6)	0	1 (2.0)	2 (1.7)

CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] A subject was counted once at the maximum severity.

[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.

[c] If relationship was missing, the TEAE was considered to be related to the drug.

Source: Module 5.3.5.3 SCS Tables 1.4.2 and 1.4.3

Renal function at baseline

Subjects were categorized into groups of baseline renal function, calculated using the Cockcroft-Gault equation of serum creatinine clearance:

- **Normal** function: CrCl ≥90 mL/min
- **Mild** impairment: CrCl ≥60 and <90 mL/min
- **Moderate** impairment: CrCl ≥30 and <60 mL/min
- **Severe** impairment: CrCl ≥15 and <30 mL/min
- **End stage** renal disease: CrCl <15 mL/min not on dialysis or requiring dialysis

Studies J202, U205, and J101 **excluded** subjects with severe renal impairment or end-stage renal disease.

A relatively higher incidence of adjudicated **drug-related ILD** was seen in subjects with moderate renal impairment (14.3%) when compared to subjects with mild renal impairment (9.8%) and subjects with normal renal function (11.8%) in the HER2-positive GC Pool. Subjects with moderate renal impairment also presented with a higher incidence of **≥Grade 3 adjudicated drug-related ILD** when compared to subjects with mild renal impairment and normal renal function (3.6% vs. 1.1% vs. 1.5%, respectively).

Table 5.3: Overall Summary of Treatment-Emergent Adverse Events by Baseline Renal Function (Safety Analysis Set)

Parameter	Normal Renal Function				Mild Renal Impairment				Moderate Renal Impairment			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 32)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 68)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 25)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 91)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 8)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 56)
	T-DXd 6.4 mg/kg (N = 33)	TPC (N = 13)			T-DXd 6.4 mg/kg (N = 53)	TPC (N = 28)			T-DXd 6.4 mg/kg (N = 39)	TPC (N = 20)		
Duration of treatment (months)												
Median	5.52	2.73	3.43	4.14	4.37	2.30	4.37	4.37	4.60	2.99	5.91	5.29
Range	1.4, 29.7	0.9, 4.6	0.7, 15.4	0.7, 29.7	0.7, 25.5	0.5, 13.1	0.7, 15.2	0.7, 25.5	0.7, 18.6	0.5, 6.7	1.3, 15.9	0.7, 18.6
Subjects with any TEAE, n (%)	33 (100)	13 (100)	32 (100)	68 (100)	53 (100)	28 (100)	25 (100)	91 (100)	39 (100)	19 (95.0)	8 (100)	56 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	31 (93.9)	6 (46.2)	16 (50.0)	50 (73.5)	44 (83.0)	19 (67.9)	8 (32.0)	62 (68.1)	32 (82.1)	9 (45.0)	6 (75.0)	45 (80.4)
Serious TEAEs	11 (33.3)	2 (15.4)	12 (37.5)	24 (35.3)	25 (47.2)	10 (35.7)	6 (24.0)	34 (37.4)	20 (51.3)	3 (15.0)	5 (62.5)	28 (50.0)
TEAEs associated with study drug discontinuation	3 (9.1)	1 (7.7)	6 (18.8)	9 (13.2)	10 (18.9)	1 (3.6)	2 (8.0)	14 (15.4)	9 (23.1)	2 (10.0)	1 (12.5)	12 (21.4)
TEAEs associated with dose reduction	12 (36.4)	5 (38.5)	9 (28.1)	22 (32.4)	15 (28.3)	10 (35.7)	3 (12.0)	23 (25.3)	13 (33.3)	6 (30.0)	2 (25.0)	18 (32.1)
TEAEs associated with study drug interruption	17 (51.5)	6 (46.2)	7 (21.9)	26 (38.2)	36 (67.9)	8 (28.6)	4 (16.0)	47 (51.6)	26 (66.7)	8 (40.0)	3 (37.5)	33 (58.9)
TEAEs associated with an outcome of death[b]	3 (9.1)	0	7 (21.9)	10 (14.7)	3 (5.7)	1 (3.6)	1 (4.0)	4 (4.4)	2 (5.1)	1 (5.0)	1 (12.5)	4 (7.1)
Subjects with any drug-related TEAE, n (%)[c]	33 (100)	12 (92.3)	29 (90.6)	65 (95.6)	52 (98.1)	24 (85.7)	23 (92.0)	88 (96.7)	37 (94.9)	19 (95.0)	8 (100)	54 (96.4)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	27 (81.8)	6 (46.2)	8 (25.0)	37 (54.4)	39 (73.6)	15 (53.6)	3 (12.0)	50 (54.9)	28 (71.8)	6 (30.0)	3 (37.5)	37 (66.1)
Drug-related serious TEAEs	6 (18.2)	0	4 (12.5)	10 (14.7)	14 (26.4)	4 (14.3)	1 (4.0)	16 (17.6)	10 (25.6)	1 (5.0)	2 (25.0)	14 (25.0)
Drug-related TEAEs associated with study drug discontinuation	1 (3.0)	1 (7.7)	5 (15.6)	6 (8.8)	7 (13.2)	0	2 (8.0)	10 (11.0)	6 (15.4)	2 (10.0)	0	8 (14.3)
Drug-related TEAEs associated with dose reduction	12 (36.4)	5 (38.5)	7 (21.9)	20 (29.4)	14 (26.4)	10 (35.7)	3 (12.0)	22 (24.2)	12 (30.8)	6 (30.0)	1 (12.5)	16 (28.6)
Drug-related TEAEs associated with study drug interruption	14 (42.4)	4 (30.8)	3 (9.4)	18 (26.5)	29 (54.7)	8 (28.6)	1 (4.0)	37 (40.7)	22 (56.4)	7 (35.0)	1 (12.5)	26 (46.4)

Drug-related TEAEs associated with an outcome of death[b]	0	0	1 (3.1)	1 (1.5)	1 (1.9)	0	0	1 (1.1)	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] A subject was counted once at the maximum severity.
[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.
[c] If relationship was missing, the TEAE was considered to be related to the drug.
Source: Module 5.3.5.3 SCS Tables 1.4.2 and 1.4.3

Table 14: Treatment-emergent Adverse Events of Grade ≥3, Drug-related Treatment-emergent Adverse Events, and Treatment-emergent Serious Adverse Events (All and Drug-related) by Baseline Renal Function (Safety Analysis Set)

	Normal Renal Function				**Mild Renal Impairment**				**Moderate Renal Impairment**			
	Number (%) of Subjects				**Number (%) of Subjects**				**Number (%) of Subjects**			
	Study J202 HER2-positive GC (Primary Cohort)		**Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 32)**	**HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 68)**	**Study J202 HER2-positive GC (Primary Cohort)**		**Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 25)**	**HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 91)**	**Study J202 HER2-positive GC (Primary Cohort)**		**Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 8)**	**HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 56)**
	T-DXd 6.4 mg/kg (N = 33)	**TPC (N = 13)**			**T-DXd 6.4 mg/kg (N = 53)**	**TPC (N = 28)**			**T-DXd 6.4 mg/kg (N = 39)**	**TPC (N = 20)**		
TEAEs with CTCAE ≥Grade 3[a]	31 (93.9)	6 (46.2)	16 (50.0)	50 (73.5)	44 (83.0)	19 (67.9)	10 (40.0)	64 (70.3)	32 (82.1)	9 (45.0)	6 (75.0)	45 (80.4)
Drug-related TEAEs	33 (100)	12 (92.3)	30 (93.8)	66 (97.1)	52 (98.1)	24 (85.7)	23 (92.0)	88 (96.7)	37 (94.9)	19 (95.0)	8 (100)	54 (96.4)
Treatment-emergent SAEs	11 (33.3)	2 (15.4)	12 (37.5)	24 (35.3)	25 (47.2)	10 (35.7)	6 (24.0)	34 (37.4)	20 (51.3)	3 (15.0)	5 (62.5)	28 (50.0)
Drug-related treatment-emergent SAEs	6 (18.2)	0	4 (12.5)	10 (14.7)	14 (26.4)	4 (14.3)	1 (4.0)	16 (17.6)	10 (25.6)	1 (5.0)	2 (25.0)	14 (25.0)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric cancer/gastric or gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; PTX = paclitaxel; SCS = Summary of Clinical Safety; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice
(includes subjects who received irinotecan [n = 55] or PTX [n = 7])
The HER2-positive GC T-DXd 6.4 mg/kg Pool includes data from Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] A subject was counted once at the maximum severity.
Source: Module 5.3.5.3 SCS Table 1.4.3

Hepatic function at baseline

Subjects were categorized into groups based on baseline hepatic function per the NCI criteria:

- **Normal function**: TBL ≤ULN and AST ≤ULN except for subjects with Gilbert syndrome and TBL ≤3.0 × ULN and AST ≤ULN for subjects with Gilbert syndrome
- **Mild impairment**: TBL >ULN, ≤1.5 × ULN and any AST except for subjects with Gilbert syndrome; TBL >ULN, ≤3.0 × ULN and AST >ULN for subjects with Gilbert syndrome; and TBL ≤ULN and AST >ULN regardless of Gilbert syndrome
- **Moderate** impairment: TBL >1.5 × ULN, ≤3.0 × ULN and any AST except for subjects with Gilbert syndrome
- **Severe** impairment: TBL >3.0 × ULN and any AST regardless of Gilbert syndrome

No subject entered the study with **severe hepatic impairment**. **One** subject entered with **moderate hepatic impairment** at screening.

Table 5.4: Overall Summary of Treatment-Emergent Adverse Events by Baseline Hepatic Function (Safety Analysis Set)

Parameter	Normal Hepatic Function				Mild Hepatic Impairment			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 65)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 170)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 13)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 57)
	T-DXd 6.4 mg/kg (N = 88)	TPC (N = 47)			T-DXd 6.4 mg/kg (N = 36)	TPC (N = 15)		
Duration of treatment (months)								
Median	5.52	2.76	4.37	4.71	2.91	2.73	4.14	4.04
Range	0.7, 25.5	0.5, 13.1	0.7, 15.9	0.7, 25.5	0.7, 29.7	0.5, 11.3	0.7, 11.0	0.7, 29.7
Subjects with any TEAE, n (%)	88 (100)	46 (97.9)	65 (100)	170 (100)	36 (100)	15 (100)	13 (100)	57 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	75 (85.2)	26 (55.3)	30 (46.2)	117 (68.8)	31 (86.1)	9 (60.0)	9 (69.2)	48 (84.2)
Serious TEAEs	39 (44.3)	12 (25.5)	21 (32.3)	66 (38.8)	17 (47.2)	4 (26.7)	7 (53.8)	25 (43.9)
TEAEs associated with study drug discontinuation	16 (18.2)	3 (6.4)	8 (12.3)	27 (15.9)	6 (16.7)	1 (6.7)	4 (30.8)	11 (19.3)
TEAEs associated with dose reduction	30 (34.1)	18 (38.3)	14 (21.5)	50 (29.4)	10 (27.8)	3 (20.0)	5 (38.5)	18 (31.6)
TEAEs associated with study drug interruption	59 (67.0)	15 (31.9)	14 (21.5)	80 (47.1)	19 (52.8)	8 (53.3)	3 (23.1)	28 (49.1)
TEAEs associated with an outcome of death[b]	5 (5.7)	1 (2.1)	4 (6.2)	10 (5.9)	3 (8.3)	1 (6.7)	6 (46.2)	9 (15.8)
Subjects with any drug-related TEAE, n (%)[c]	87 (98.9)	43 (91.5)	61 (93.8)	165 (97.1)	34 (94.4)	13 (86.7)	12 (92.3)	54 (94.7)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	65 (73.9)	20 (42.6)	14 (21.5)	88 (51.8)	28 (77.8)	7 (46.7)	6 (46.2)	41 (71.9)
Drug-related serious TEAEs	20 (22.7)	4 (8.5)	5 (7.7)	27 (15.9)	10 (27.8)	1 (6.7)	2 (15.4)	13 (22.8)
Drug-related TEAEs associated with study drug discontinuation	13 (14.8)	2 (4.3)	5 (7.7)	20 (11.8)	1 (2.8)	1 (6.7)	2 (15.4)	4 (7.0)
Drug-related TEAEs associated with dose reduction	28 (31.8)	18 (38.3)	11 (16.9)	45 (26.5)	10 (27.8)	3 (20.0)	4 (30.8)	17 (29.8)
Drug-related TEAEs associated with study drug interruption	50 (56.8)	11 (23.4)	5 (7.7)	61 (35.9)	14 (38.9)	8 (53.3)	2 (15.4)	21 (36.8)
Drug-related TEAEs associated with an outcome of death[b]	1 (1.1)	0	0	1 (0.6)	0	0	1 (7.7)	1 (1.8)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] A subject was counted once at the maximum severity.
[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.
[c] If relationship was missing, the TEAE was considered to be related to the drug.
Source: Module 5.3.5.3 SCS Tables 1.4.2 and 1.4.3

2.5.6.2. Extrinsic factors

TEAEs were evaluated for geographic **region** (Asia, North America, and Europe) and **country** (Japan and countries other than Japan).

Geographic region

Table 5.5: Overall Summary of Treatment-Emergent Adverse Events by Region (Asia, North America, and Europe) (Safety Analysis Set)

Parameter	Asia				North America				Europe			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 [d] HER2-positive GC T-DXd 6.4 mg/kg (N = 0)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 150)	Study J202 [e] HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 34)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 34)	Study J202 [e] HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 45)	HER2-positive GC T-DXd 6.4 mg/kg GC Pool (N = 45)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)			T-DXd 6.4 mg/kg (N = 0)	TPC (N = 0)			T-DXd 6.4 mg/kg (N = 0)	TPC (N = 0)		
Duration of treatment (months)												
Median	4.60	2.76	N/A	4.60	N/A	N/A	3.89	3.89	N/A	N/A	5.16	5.16
Range	0.7, 29.7	0.5, 13.1	N/A	0.7, 29.7	N/A	N/A	0.7, 15.9	0.7, 15.9	N/A	N/A	0.7, 12.9	0.7, 12.9
Subjects with any TEAE, n (%)	125 (100)	61 (98.4)	N/A	150 (100)	N/A	N/A	34 (100)	34 (100)	N/A	N/A	45 (100)	45 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	107 (85.6)	35 (56.5)	N/A	127 (84.7)	N/A	N/A	17 (50.0)	17 (50.0)	N/A	N/A	23 (51.1)	23 (51.1)
Serious TEAEs	56 (44.8)	16 (25.8)	N/A	63 (42.0)	N/A	N/A	13 (38.2)	13 (38.2)	N/A	N/A	16 (35.6)	16 (35.6)
TEAEs associated with study drug discontinuation	22 (17.6)	4 (6.5)	N/A	26 (17.3)	N/A	N/A	7 (20.6)	7 (20.6)	N/A	N/A	5 (11.1)	5 (11.1)
TEAEs associated with dose reduction	40 (32.0)	21 (33.9)	N/A	49 (32.7)	N/A	N/A	9 (26.5)	9 (26.5)	N/A	N/A	10 (22.2)	10 (22.2)
TEAEs associated with study drug interruption	79 (63.2)	23 (37.1)	N/A	92 (61.3)	N/A	N/A	6 (17.6)	6 (17.6)	N/A	N/A	11 (24.4)	11 (24.4)
TEAEs associated with an outcome of death[b]	8 (6.4)	2 (3.2)	N/A	9 (6.0)	N/A	N/A	5 (14.7)	5 (14.7)	N/A	N/A	5 (11.1)	5 (11.1)
Subjects with any drug-related TEAE, n (%)[c]	122 (97.6)	56 (90.3)	N/A	147 (98.0)	N/A	N/A	31 (91.2)	31 (91.2)	N/A	N/A	43 (95.6)	43 (95.6)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	94 (75.2)	27 (43.5)	N/A	110 (73.3)	N/A	N/A	6 (17.6)	6 (17.6)	N/A	N/A	15 (33.3)	15 (33.3)
Drug-related serious TEAEs	30 (24.0)	5 (8.1)	N/A	33 (22.0)	N/A	N/A	2 (5.9)	2 (5.9)	N/A	N/A	6 (13.3)	6 (13.3)
Drug-related TEAEs associated with study drug discontinuation	14 (11.2)	3 (4.8)	N/A	17 (11.3)	N/A	N/A	3 (8.8)	3 (8.8)	N/A	N/A	4 (8.9)	4 (8.9)
Drug-related TEAEs associated with dose reduction	38 (30.4)	21 (33.9)	N/A	47 (31.3)	N/A	N/A	7 (20.6)	7 (20.6)	N/A	N/A	8 (17.8)	8 (17.8)
Drug-related TEAEs associated with study drug interruption	65 (52.0)	19 (30.6)	N/A	76 (50.7)	N/A	N/A	2 (5.9)	2 (5.9)	N/A	N/A	5 (11.1)	5 (11.1)

Drug-related TEAEs associated with an outcome of death[b]	1 (0.8)	0	N/A	1 (0.7)	N/A	N/A	1 (2.9)	1 (2.9)	N/A	N/A	0	0

CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; GC = gastric/gastroesophageal junction cancer; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] A subject was counted once at the maximum severity.
[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.
[c] If relationship was missing, the TEAE was considered to be related to the drug.
[d] Study U205 is not conducted in Asia, therefore no applicable data.
[e] Study J202 is not conducted in North America and Europe, therefore no applicable data.
Source: Module 5.3.5.3 SCS Tables 1.4.2 and 1.4.3

Country

Within the HER2-positive GC Pool, notable differences in the frequency of events in the following categories were observed when comparing subjects from Japan (n = 124) with subjects from countries other than Japan (n = 105) (Table 5.5):

- ≥Grade 3 TEAEs (overall and drug-related) and TEAEs associated with study drug interruption (overall and drug-related) were reported in a higher proportion of subjects from Japan than non-Japan.
- TEAEs associated with an outcome of death were reported in a proportion at least twice as high in subjects from non-Japan countries (12/105 [11.4%]) than from Japan (7/124 [5.6%]).

Table 5.6: Overall Summary of Treatment-Emergent Adverse Events by Country (Japan, Non-Japan) (Safety Analysis Set)

Parameter	Japan				Non-Japan			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205[d] HER2-positive GC	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 124)	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 105)
	T-DXd 6.4 mg/kg (N = 99)	TPC (N = 50)	T-DXd 6.4 mg/kg (N = 0)		T-DXd 6.4 mg/kg (N = 26)	TPC (N = 12)	T-DXd 6.4 mg/kg (N = 79)	
Duration of treatment (months)								
Median	4.99	2.76	N/A	4.80	4.48	2.10	4.34	4.37
Range	0.7, 29.7	0.5, 13.1	N/A	0.7, 29.7	0.7, 16.8	0.5, 7.1	0.7, 15.9	0.7, 16.8
Subjects with any TEAE, n (%)	99 (100)	50 (100)	N/A	124 (100)	26 (100)	11 (91.7)	79 (100)	105 (100)
TEAEs with worst CTCAE ≥Grade 3[a]	84 (84.8)	29 (58.0)	N/A	104 (83.9)	23 (88.5)	6 (50.0)	40 (50.6)	63 (60.0)
Serious TEAEs	42 (42.4)	12 (24.0)	N/A	49 (39.5)	14 (53.8)	4 (33.3)	29 (36.7)	43 (41.0)
TEAEs associated with study drug discontinuation	16 (16.2)	3 (6.0)	N/A	20 (16.1)	6 (23.1)	1 (8.3)	12 (15.2)	18 (17.1)
TEAEs associated with dose reduction	31 (31.3)	17 (34.0)	N/A	40 (32.3)	9 (34.6)	4 (33.3)	19 (24.1)	28 (26.7)
TEAEs associated with study drug interruption	68 (68.7)	19 (38.0)	N/A	81 (65.3)	11 (42.3)	4 (33.3)	17 (21.5)	28 (26.7)
TEAEs associated with an outcome of death[b]	6 (6.1)	1 (2.0)	N/A	7 (5.6)	2 (7.7)	1 (8.3)	10 (12.7)	12 (11.4)
Subjects with any drug-related TEAE, n (%)[c]	98 (99.0)	46 (92.0)	N/A	123 (99.2)	24 (92.3)	10 (83.3)	74 (93.7)	98 (93.3)
Drug-related TEAEs with worst CTCAE ≥Grade 3[a]	77 (77.8)	21 (42.0)	N/A	93 (75.0)	17 (65.4)	6 (50.0)	21 (26.6)	38 (36.2)
Drug-related serious TEAEs	24 (24.2)	2 (4.0)	N/A	27 (21.8)	6 (23.1)	3 (25.0)	8 (10.1)	14 (13.3)

Drug-related TEAEs associated with study drug discontinuation	10 (10.1)	2 (4.0)	N/A	13 (10.5)	4 (15.4)	1 (8.3)	7 (8.9)	11 (10.5)
Drug-related TEAEs associated with dose reduction	30 (30.3)	17 (34.0)	N/A	39 (31.5)	8 (30.8)	4 (33.3)	15 (19.0)	23 (21.9)
Drug-related TEAEs associated with study drug interruption	57 (57.6)	16 (32.0)	N/A	68 (54.8)	8 (30.8)	3 (25.0)	7 (8.9)	15 (14.3)
Drug-related TEAEs associated with an outcome of death[b]	0	0	N/A	0	1 (3.8)	0	1 (1.3)	2 (1.9)

CTCAE = Common Terminology Criteria for Adverse Events; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of treated subjects; n = number of subjects; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])
HER2-positive GC 6.4 mg/kg Pool includes data from studies: DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
[a] A subject was counted once at the maximum severity.
[b] For specific TEAEs associated with outcome of death, refer to Table 2.8.
[c] If relationship was missing, the TEAE was considered to be related to the drug.
[d] Study U205 is not conducted in Japan, therefore no applicable data.
Source: Module 5.3.5.3 SCS Tables 1.4.2, and 1.4.3

The higher frequency of TEAEs associated with an outcome of death in Study U205 vs. the T-DXd arm of Study J202 (ie, 10 [12.7%] vs. 8 [6.4%]) was mostly attributable to a greater proportion of deaths due to COVID-19 (2 [2.5%] vs. 0) and TEAEs related to disease progression (5 [6.3%] vs. 6 [4.8%]). Importantly, there were no differences between the 2 studies in terms of drug-related TEAEs associated with an outcome of death; indeed, such events were reported only in 1 subject in each study (ILD in Study U205 and pneumonia in the T-DXd arm of Study J202).

The higher frequency of hematologic toxicity in Asian vs. Western subjects, and more particularly in Japanese vs. non-Japanese subjects, is not surprising as it has been already observed in studies in HER2-positive BC conducted by the Applicant, as well as in published reports of clinical studies investigating drugs for the treatment of subjects with HER2-positive metastatic GC, and other observations from the literature.

2.5.7. Safety related to drug-drug interactions and other interactions

2.5.7.1. Drug-drug interactions

Although no drug-drug interaction (DDI) studies have been performed in subjects with GC, no interactions with strong cytochrome P450 (CYP)3A and organic anion transporting polypeptide 1B inhibitors were observed in a dedicated DDI study with ritonavir and itraconazole in subjects with HER2-expressing advanced solid malignant tumors. No new information on drug interactions is available since the time of Study DS8201-A-A104 (DCO of 26 Sep 2018).

2.5.7.2. Other interactions

Infusion-related reactions

T-DXd was not associated with severe **infusion-related reactions (IRR).**

In the T-DXd arm of **Study J202**, 12/125 (9.6%) subjects were antidrug-antibodies (ADA) positive at baseline. No subjects were ADA-positive at both baseline and post-baseline. A total of 9/123 (7.3%) subjects were identified as having treatment-emergent ADAs.

In **Study U205**, a similar proportion of subjects who had a baseline assessment were ADA positive at baseline (5/76 (6.6%)). No subjects were ADA-positive at both baseline and post-baseline. A total of

2/73 (2.7%) subjects were identified as having treatment-emergent ADAs (defined as having ADA-positive samples post-baseline and a negative or missing baseline result).

After comprehensive review of each potential IRR event in the HER2-positive GC Pool, 2 subjects in the T-DXd arm of Study J202 were considered to have experienced IRR events. Both subjects were ADA-negative at baseline and post-baseline.

2.5.8. Discontinuation due to adverse events

In the HER2-positive GC Pool, 38/229 (16.6%) subjects experienced any TEAE associated with **study drug discontinuation**, with the most commonly reported TEAE being ILD (15/229 [6.6%]).

Table 2.10: Treatment-Emergent Adverse Events Associated with Study Drug Discontinuation Reported in Any Subject, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with Any TEAE Associated with Study Drug Discontinuation	22 (17.6)	4 (6.5)	12 (15.2)	38 (16.6)
Interstitial lung disease [b]	8 (6.4)	0	5 (6.3)	15 (6.6)
Pneumonia	2 (1.6)	0	0	3 (1.3)
Anaemia [a]	2 (1.6)	0	0	2 (0.9)
Fatigue [a]	2 (1.6)	1 (1.6)	0	2 (0.9)
COVID-19	0	0	1 (1.3)	1 (0.4)
COVID-19 pneumonia	0	0	1 (1.3)	1 (0.4)
Cerebrovascular accident	0	0	1 (1.3)	1 (0.4)
Cholangitis	1 (0.8)	0	0	1 (0.4)
Colitis	0	0	1 (1.3)	1 (0.4)
Decreased appetite	0	0	0	1 (0.4)
Gastrointestinal obstruction	1 (0.8)	0	0	1 (0.4)
Hemiplegia	1 (0.8)	0	0	1 (0.4)
Hepatic function abnormal	1 (0.8)	0	0	1 (0.4)
Hepatotoxicity	0	0	1 (1.3)	1 (0.4)
Hyponatraemia	1 (0.8)	0	0	1 (0.4)
Large intestine perforation	1 (0.8)	0	0	1 (0.4)
Nausea	0	0	1 (1.3)	1 (0.4)
Pneumonia bacterial	1 (0.8)	0	0	1 (0.4)
Sepsis	1 (0.8)	0	0	1 (0.4)
Thrombocytopenia [a]	0	0	0	1 (0.4)
Weight decreased	0	0	1 (1.3)	1 (0.4)
Cerebral infarction	0	1 (1.6)	0	0
Neutropenia [a]	0	2 (3.2)	0	0

COVID-19 = coronavirus disease 2019; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SMQ = Standardised MedDRA Query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
PT/grouped terms are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] The PTs that were included in each grouped term are listed in Table 2.1.
[b] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by adjudication committee.
Source: Module 5.3.5.3 SCS Tables 1.2.1.10, 1.2.2.4, and 1.2.4.3

A similar proportion of subjects in the Study J202 T-DXd arm (40/125 [32.0%]) and the TPC arm (21/62 [33.9%]) experienced TEAEs associated with **dose reduction** except for leukopenia (grouped term), of which the incidence was at least twice as high in the TPC arm than in the T-DXd arm (3/62 [4.8%] vs. 2/125 [1.6%], respectively) (Table 2.11).

Table 2.11: Treatment-Emergent Adverse Events Associated with Dose Reduction Reported in at Least 1% of Subjects in the HER2-positive GC T-DXd 6.4 mg/kg Pool, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with Any TEAE Associated with Dose Reduction	40 (32.0)	21 (33.9)	19 (24.1)	68 (29.7)
Neutropenia [a]	16 (12.8)	7 (11.3)	4 (5.1)	21 (9.2)
Decreased appetite	12 (9.6)	3 (4.8)	2 (2.5)	19 (8.3)
Nausea	7 (5.6)	5 (8.1)	7 (8.9)	15 (6.6)
Fatigue [a]	10 (8.0)	4 (6.5)	3 (3.8)	13 (5.7)
Febrile neutropenia	3 (2.4)	1 (1.6)	2 (2.5)	5 (2.2)
Thrombocytopenia [a]	1 (0.8)	0	0	4 (1.7)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Weight decreased	0	2 (3.2)	4 (5.1)	4 (1.7)
Diarrhoea	1 (0.8)	1 (1.6)	1 (1.3)	3 (1.3)
Leukopenia [a]	2 (1.6)	3 (4.8)	0	3 (1.3)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7]).
HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.
PT/grouped terms are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] The PTs that were included in each grouped term are listed in Table 2.1.
Source: Module 5.3.5.3 SCS Tables 1.2.1.14 and 1.2.2.5

A total of 109/229 (47.6%) subjects in the HER2-positive GC Pool experienced TEAEs associated with study **drug interruption**, with a notably higher incidence in the Study J202 T-DXd arm (79/125 [63.2%]) than in Study U205 (17/79 [21.5%]) (Table 2.12).

Table 2.12: Treatment-Emergent Adverse Events Associated with Study Drug Interruption Reported in at Least 1% of Subjects in the HER2-positive GC T-DXd 6.4 mg/kg Pool, by Preferred Term/Grouped Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Subjects with Any TEAE Associated with Study Drug Interruption	79 (63.2)	23 (37.1)	17 (21.5)	109 (47.6)

MedDRA Preferred Term/ Grouped Term [a]	Number (%) of Subjects			
	Study J202 HER2-positive GC (Primary Cohort)		Study U205 HER2-positive GC T-DXd 6.4 mg/kg (N = 79)	HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)
	T-DXd 6.4 mg/kg (N = 125)	TPC (N = 62)		
Neutropenia [a]	35 (28.0)	7 (11.3)	1 (1.3)	41 (17.9)
Anaemia [a]	15 (12.0)	2 (3.2)	3 (3.8)	19 (8.3)
Decreased appetite	11 (8.8)	2 (3.2)	0	16 (7.0)
Leukopenia [a]	11 (8.8)	8 (12.9)	1 (1.3)	12 (5.2)
Fatigue [a]	9 (7.2)	4 (6.5)	1 (1.3)	10 (4.4)
Interstitial lung disease [b]	6 (4.8)	0	0	8 (3.5)
Pneumonia	6 (4.8)	0	0	8 (3.5)
Thrombocytopenia [a]	5 (4.0)	0	0	6 (2.6)
Lymphopenia [a]	4 (3.2)	0	0	4 (1.7)
Upper respiratory tract infection [a]	4 (3.2)	0	0	4 (1.7)
Cholangitis	1 (0.8)	0	0	3 (1.3)
Diarrhoea	3 (2.4)	1 (1.6)	0	3 (1.3)
Hypokalaemia	3 (2.4)	0	0	3 (1.3)
Vomiting	0	0	3 (3.8)	3 (1.3)

GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, Version 23.0; N = total number of treated subjects; PT = preferred term; SMQ = Standardised MedDRA Query; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice (includes subjects who received irinotecan [n = 55] or paclitaxel [n = 7])

HER2-positive GC 6.4 mg/kg Pool includes data from studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

PT/grouped terms are presented in descending order of frequency in the HER2-positive GC T-DXd 6.4 mg/kg Pool. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] The PTs that were included in each grouped term are listed in Table 2.1.

[b] Interstitial lung disease includes events that were adjudicated as ILD and considered study drug related by adjudication committee.

Source: Module 5.3.5.3 SCS Tables 1.2.1.12, 1.2.2.6, and 1.2.4.5

2.5.9. Post marketing experience

Based on review of data from 20 Dec 2019 (first approval of T-DXd in the US) through 01 Aug 2021, no new safety findings have been identified from spontaneous reports during the post-marketing period. The reported events were generally consistent with the known safety profile of T-DXd.

2.5.10. Discussion on clinical safety

The safety population consisted of in total 229 adult patients (**the HER2+ 6.4 mg/kg GC Pool**): 125 (J202, 3L+, Asians) + 79 (U205, 2L, Westerns) + 25 (J101, phase I, Asian) with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma, who had received a prior anti-HER2-based regimen. The number, demographics and baseline characteristics of these patients are considered relevant and the primary safety analysis is based on this pooled dataset. However, supplementary data from the confirmatory study DESTINY-Gastric04 (Specific Obligation) are awaited.

Median duration of treatment was 4.6 months in the T-DXd arm of study J202 and 4.34 months in study U205, but somewhat shorter in the TPC arm (2.76 months). In J202 16.8% and in U205 6.3% received treatment more than 12 months, whereas only 2 patients (3.2%) in the TPC arm of J202 received treatment more than 9 months. Median number of cycles (6 – 6) and mean relative dose intensity (89.67% – 93.52%) were comparable between the T-DXd arm of J202 and U205 and the **exposure** to T-DXd is considered sufficient to assess the safety profile.

At the safety data DCOs all (100%) T-DXd 6.4 mg/kg exposed patients had experienced **AEs**. 72.9% had experienced **≥grade 3 AEs**, 40.2% **SAEs**, 16.6% discontinuation of study-drug due to AEs and 8.3% AEs associated with the outcome of death. 96.5% of all T-DXd 6.4 mg/kg exposed patients experienced drug-related AEs, 57.2% drug-related ≥grade 3 AEs, 17.9% drug-related SAEs, 10.4% drug-related discontinuation and 0.9% drug-related AEs associated with the outcome of death. The majority of AEs and drug-related AEs in J202, U205 and in the HER2+ GC Pool were gastrointestinal or hematologic in nature. These are known adverse reactions to topoisomerase inhibitors and are in line with what is expected in this patient group in a 2L+ palliative setting from this ADC. The 10 most frequent AEs in the HER2+ 6.4 mg/kg GC pool were: nausea 65.5%, decreased appetite 54.1%, fatigue 52.8%, anemia 49.3%, neutropenia 49.3%, thrombocytopenia 34.1%, vomiting 32.3%, diarrhoea 31.9%, leukopenia 28.8%, constipation 25.8%. Within the 2L Western population (U205) there was, in comparison to the 3L+ Asian (J202) population, observed lower frequencies of **≥grade 3 AEs** (53.2% vs 85.6%), of **SAEs** (36.7% vs 44.8%) and less dose-reductions (24.1% vs 32.0%) but a higher degree of AEs associated with the outcome of death (12.7% va 6.4%). Furthermore, the 2L Western population had lower levels of hematologic and higher levels of GI associated AEs compared to the 3L+ Asian population. The higher incidence of hematologic events in the Asian/Japanese population is consistent with the scientific literature in which ethnic differences in drug toxicity are well documented. It has been observed in clinical studies in HER2-positive BC patients conducted by the MAH as well as in published reports of clinical studies investigating other treatments for HER2-positive metastatic GC.

ILD, the most important **AE of special interest**, is a frequent and well-known adverse event (11.8%) with almost all cases considered drug-related; ADR (10.9%), by the adjudicated independent committee, and strongly associated with T-DXd, as no patients in the TPC arm experienced ILD. The incidence, grade and resolution of ILD appears comparable to what is known from the BC population. Mostly grade 1-3, a few grade 4 and only one grade 5 ILDs were observed leading to dose discontinuation (in J202 predefined discontinuation if grade 2) in 6.6% of patients. The SmPC covers the ILD sufficiently in 4.2, 4.4, 4.8. LVEF decrease occurred with a low frequency (1.8%), was not fatal and mostly resolved.

In general, the frequency of **SAEs** is quite high in both J202 (44.8%), U205 (36.7%) and in the HER2+ 6.4 mg/kg GC pool (40.2%) and a notable number of patients experienced more than one SAE. The 3L+ Asian population has more decreased appetite (10.4% vs 0%), ILD (5.6% vs 2.5%), pneumonia (4% vs 2.5%), cholangitis (2.4% vs 0%), anemia3.2% vs 0%), dehydration (3.2% vs 0%), tumour haemorrhage (2.4% vs 1.3%), jaundice cholestatic (2.4% vs 0%) and pyrexia (2.4% vs 0%). The 2L Western population had more nausea (5.1% vs 0.8%), vomiting (3.8% vs 0.8%), abdominal pain (2.5% vs 0.8%) and acute kidney injury (2.5% vs 0.8%). This pattern of differences in frequencies of SAEs is equivalent to the pattern seen from AEs, which was expected.

In the HER2+ 6.4 mg/kg GC pool 8.3% experienced AEs associated with the outcome of **death**, hereof 2 (0.9%) considered drug-related. This is considered as a concerningly high frequency. The frequency was twice as high in the Western 2L compared to the Asian 3L+ (12.7% vs 6.4%) population, as was the on-treatment deaths (11.4% vs 6.4%). However, the main reason for deaths (6/10) in study U205 was disease progression or COVID-19 and as such not drug-related. Deaths due to AEs in the TPC arm of J202 was in comparison 3.2%.

The majority of **ADRs** were, as expected, gastrointestinal or hematologic in nature. The frequencies of all ADRs and grade 3 or 4 ADRs were in general high. The highest occurrence was seen in the T-DXd arm of J202A (all 99.2%, grade 3/4 80%), the lowest in U205 (all 97.5%, grade 3/4 39.2%). The TPC arm of J202 was in between (all 96.8%, grade 3/4 50%).

In the HER2+ 6.4 mg/kg GC pool, there were 113 (49.3%) subjects with neutropenia and 9 (3.9%) subjects with febrile neutropenia.

The Asian population (T-DXd arm of J202) had a ~2.5 times as high frequency (12 patients, 9.6%) of bleedings compared to the Western population (3 patients, 3.8%). This was anticipated considering the higher frequency of thrombocytopenia in the Asian population and is reflected in the SmPC.

All the patients fulfilling Hy's law had biochemical liver function tests suggesting an obstructive etiology. The etiologies for meeting biochemical Hy's Law criteria included liver metastases, biliary dilatation requiring stenting, stent revision, or biliary drainage, bile stone, cholangitis, biliary sepsis and disease progression. Mild hepatic impairment at baseline, primarily in study U205, was associated with a higher occurrence of AEs and SAEs, including, drug related AEs and AEs associated with death, compared to patients with normal hepatic liver function at baseline. However, the sample size was small (n=14) and 5/6 deaths were unrelated to hepatic impairment or study drug. The data do not suggest that T-DXd has a different safety profile in subjects with mild hepatic impairment at baselineIn the T-DXd arm of study J202 17.6% experienced **drug-discontinuation** due to AEs. In U205 this was 15.2% and in the HER2+ 6.4 mg/kg GC pool 16.6%. These discontinuation rates are rather high, but in the same range as what have been seen with 5.4 mg/kg.

In general, trastuzumab-deruxtecan has a different and more toxic safety profile than standard mono-chemotherapy, as is also seen with other ADCs. Although substantial, the toxicity of T-DXd was manageable.

Additional expert consultations

Not relevant.

2.5.11. Conclusions on clinical safety

In the populations of study J202 and U205, the majority and most common AEs were gastrointestinal or hematologic. Hematologic AEs were reported more frequently in the T-DXd arm of J202 than in U205, representing the main difference in toxicity profile between the 2 study populations.

Also, with regards to grade ≥3 AEs, the hematologic toxicity was far more pronounced in the Asian population compared to the Western and the primary reason for the notably higher degree of grade ≥3 AEs in the Asian (J202) population. These results are consistent with the scientific literature in which ethnic differences in drug toxicity are well documented, and with the observations from the clinical studies in HER2 positive BC patients conducted by the MAH, as well as published reports of clinical studies of other treatments for HER2-positive metastatic GC.

The incidence of SAEs was relatively high. The difference in occurence between the two studies was primarily due to higher frequency of decreased appetite and ILD in the Asian (J202) population. The discontinuation rate was relatively high but similar in the two studies and within the range of what is observed with targeted ADCs. AEs associated with an outcome of death were twice as high in U205 compared to the T-DXd arm of J202 but the majority of deaths were due to disease progression or COVID-19 and the difference is therefore acceptable. The frequency of ILD, an important identified risk factor associated with T-DXd treatment, was higher in the T-DXd arm of J202 than in U205. However, in both populations, the majority of drug-related ILD events were low grade, and the risk of and actions taken in case of ILD is sufficiently described in the SmPC.

In conclusion, the toxicity was manageable within both patient populations (T-DXd arm of J202 and U205) although with differences in the toxicity profile between the two groups. The differences were primarily due to expected higher hematologic toxicity in the Asian (mainly Japanese) population and due to the differences in baseline disease characteristics. Some differences were not obviously explainable. The toxicity profile of T-DXd 6.4 mg/kg is considered thoroughly described for both studies and was not worse or better for either group, but with somewhat different profiles. The median T-DXd treatment duration and median relative dose intensity were consistent in the T-DXd arm of J202 and U205, supporting that T-DXd was equally tolerated in the two study populations. Overall and across ethnicities and line of treatment, the toxicity profile of T-DXd is found to be challenging but considered manageable within the patient group encompassed by the sought and approved indication statement.
The important issues stated in the RMP will be addressed and the safety profile of Enhertu in the treatment of adult patients with advanced HER2+ GC will be confirmed in the ongoing confirmatory study DESTINY-Gastric 04 (DS-8201-A-U306) of which results are required as a special obligation for the CMA of the current extension of indication.

2.5.12. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable.

Safety concerns

Summary of safety concerns	
Important identified risks	• Interstitial lung disease/Pneumonitis • Left ventricular dysfunction
Important potential risks	• Embryo-foetal toxicity • Product confusion-related medication errors
Missing information	• Use in patients with moderate or severe hepatic impairment • Long-term safety

Pharmacovigilance plan

Study: **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 - Required additional pharmacovigilance activities				
Prescriber Survey preparations ongoing	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis	ILD	Final Report	Q2 2024
Phase 2 or 3 studies preparations ongoing	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies	Use in patients with moderate or severe hepatic impairment	Final report (for 10 subjects)	Q4 2023

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Interstitial Lung Disease/Pneumonitis	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Recommendations for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. Dose modification guidance and recommendation for corticosteroid treatment for managing the risk of ILD/pneumonitis are included in SmPC Section 4.2. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: Prescriber survey
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Continued)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

HCP = healthcare professional; ILD = interstitial lung disease; PK = pharmacokinetic; SmPC = Summary of Product Characteristics

2.7. Overall conclusion on the RMP

☒The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

2.8. Changes to the Product Information

As a result of this variation, section(s) 4.1, 4.2, 4.3, 4.8, 5.1, 5.2, and 6.6 of the SmPC are being updated to reflect the new applied indication and corresponding changes to relevant sections. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A full user test of the PL was done during the review of the initial Marketing Authorisation Application (MAA) for Enhertu in 2020. Enhertu is prescribed by a physician and administered intravenously under the supervision of a healthcare professional at a hospital/clinical setting. The posology for the applied indication is new however the mode of administration and method of reconstitution is unchanged. The updated PIL will be kept in an identical format size, colours and layout/design.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH for Enhertu (trastuzumab deruxtecan) has submitted a type II variation for an extension of indication. The final approved indication is:

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Patients treated with Enhertu for gastric or GEJ cancer should have documented HER2-positive tumour status, defined as a score of 3 + by IHC or a ratio of ≥ 2 by ISH or by FISH, assessed by a CE marked IVD medical device. If a CE marked IVD is not available, the HER2 status should be assessed by an alternate validated test.

The recommended dose of Enhertu is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

3.1.1. Disease or condition

Usually stomach (gastric) cancer (GC) starts in the lining of the stomach, growing slowly over the course of several years and causing few if any symptoms. Most patients (up to 95 percent) develop adenocarcinoma and are typically classified based on anatomic location (cardia/proximal, arising in the region adjoining the GEJ, or non-cardia/distal, arising in the lower portion of the stomach) and histologic type (diffuse, with undifferentiated tumour cells, or intestinal, with well-differentiated tumour cells). [11, 12] Overexpression or amplification of the HER2 gene or protein is reported in approximately 20% of patients with gastric adenocarcinoma, with higher rates of HER2 positivity seen in patients with intestinal histology than those with diffuse histology. Most patients present with inoperable advanced or metastatic disease requiring palliative treatment, although early detection is more common in Asia than in other regions. 5-year survival for advanced or metastatic gastric cancer is around 5–20%, with median overall survival being less than 1 year.

3.1.2. Available therapies and unmet medical need

Locally advanced or metastatic HER2-positive gastric adenocarcinoma remains an incurable disease. Once patients have progressed after a first-line regimen that includes anti-HER2 therapy, the disease outcomes are poor. [13]Ramucirumab (antiangiogenic monoclonal antibody) in combination with paclitaxel is approved for second line GC/GEJC regardless of HER2 expression. Other treatment options in the second-line or subsequent therapy settings include docetaxel, irinotecan and FOLFIRI (folinic acid, fluorouracil, and irinotecan). Currently, there is no approved targeted anti-HER2 therapy in the EU for the treatment of metastatic HER2-positive gastric adenocarcinoma in the second line or beyond settings, constituting a clear unmet need.

3.1.3. Main clinical studies

The pivotal study DESTINY-Gastric02 (U205) was a Phase 2, multicentre, single-arm, open-label study to evaluate the efficacy and safety of T-DXd (6.4 mg/kg as IV infusion Q3W) in 79 subjects with unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed during or after a trastuzumab-containing regimen (2L+ setting). The study was conducted in a Western

[11] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric cancer. Version 4.2021. 03 Aug 2021.
[12] Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterology Rev. 2019; 14(1):26-38.
[13] Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2016; 27 (suppl_5):v38-v49.

population at 24 sites in the US and Europe. The primary efficacy endpoint was confirmed ORR by ICR, while duration of response was a secondary endpoint.

The supportive study DESTINY-Gastric01 (J202) was a Phase 2, multicentre, open-label, 2:1 randomized study to evaluate efficacy and safety in subjects with advanced HER2-positive gastric or GEJ adenocarcinoma who had progressed on 2 or more prior regimens including a fluoropyrimidine agent (fluorouracil, capecitabine, or S-1) and a platinum agent (oxaliplatin or cisplatin) in addition to prior trastuzumab or a trastuzumab biosimilar (3L+ setting). The study was conducted in Japan and South Korea. Of focus in this assessment is the Primary Cohort (N=188), in which subjects were randomized to receive either T-DXd monotherapy at the proposed dose (6.4 mg/kg Q3W, n=126) or treatment of physician's choice (irinotecan or paclitaxel, n=62). The primary efficacy endpoint was unconfirmed ORR by ICR and the secondary endpoints were OS, PFS, mDoR and ORR by ICR.

3.2. Favourable effects

Pivotal U205 study in 2L US/European patients:

At initial DCO 09-APR-2021, confirmed ORR in this supportive SAT was 38.0% and mDoR was 8.1 months. At an updated DCO on 08-NOV-2021, confirmed ORR increased slightly to 41.8%. In this updated data, mDOR remained at 8.1 months.

Supportive J202 study in 3L Asian patients:

At DCO 08-NOV-2019, pivotal study J202 met its primary endpoint of improved response rate in the experimental arm: unconfirmed ORR by ICR was 48.4% in the T-DXd arm vs. 12.9% in the control irinotecan or paclitaxel arm. Confirmed response in the T-DXd arm was 38.0%. At DCO 03-JUN-2020, updated confirmed ORR by ICR remained stable at 39.7%.

In the last DCO, median DOR was 12.5 months in the T-DXd arm vs. 3.9 months in the control chemotherapy arm. Time-to-event endpoints also showed an advantage of T-DXd: mOS 12.5 vs. 8.9 months and mPFS 5.6 vs 3.5 months.

3.3. Uncertainties and limitations about favourable effects

In the absence of a control arm in the U205 study any conclusion based on indirect comparison lacks validity, as it cannot be readily assumed that the study populations are sufficiently similar to use the external comparison in support for extrapolation between lines of treatment. Despite compelling data from this single-arm trial, comprehensive data on the product are not available and as it is likely that the applicant will be able to provide these data, the on-going study DS8201-A-U306 (phase III RCT of trastuzumab deruxtecan versus ramucirumab + paclitaxel in the 2L population including EU and USA patients) constitutes a SOB in Annex II of the Opinion.

Due to better prognosis, Asian patients are treated with more lines of therapy for advanced disease than patients in the West. Therefore, comparison of results across the 3L+ Asian and the Western 2L+ setting is not straightforward because of intrinsic/extrinsic differences.

3.4. Unfavourable effects

At safety data DCOs (J202: 03-JUN-2020, U205: 09-APR-2021, J101: 01-AUG-2019) 73% of patients had experienced ≥grade 3 AEs, 40% SAEs, 17% discontinuation of study-drug due to AEs and 8% AEs associated with the outcome of death. The frequency of the same events in the physician's choice arm (mainly irinotecan, a few paclitaxel) of study J202 were all lower.

The 10 most frequent AEs in the HER2+ 6.4 mg/kg GC pool were: nausea 66%, decreased appetite 54%, fatigue 53%, anaemia 49%, neutropenia 49%, thrombocytopenia 34%, vomiting 32%, diarrhoea 32%, leukopenia 29%, and constipation 26%.

Within the 2L Western population (U205) there were, in comparison to the 3L+ Asian (J202) population, lower frequencies of ≥grade 3 AEs (53% vs 86%) and SAEs (37% vs 45%). The same frequency of dose-discontinuations was seen between the two populations. The hematologic toxicity was far more pronounced in the Asian population compared to the Western one, and the primary reason for the notably higher degree of grade ≥3 AEs in the Asian (J202) population. This ethnic difference in toxicity is well known and described across Oncology trials. The frequency of SAEs was relatively high; 40%, in the HER2+ 6.4 mg/kg GC pool (45% in J202 and 37% in U205). The difference between the two studies was primarily due to a higher frequency of decreased appetite and ILD in the Asian (J202) population. Nevertheless, it is acknowledged that hospitalisations in patients with GC/GEJC are quite frequent in view of clinical fragility and disease-associated factors.

The pattern of differences in frequencies of SAEs was equivalent to the pattern seen in AEs. In the T-DXd arm of study J202, 17.6% experienced drug-discontinuation due to an AE. In U205 this was 15.2% and in the HER2+ 6.4 mg/kg GC pool 16.6%. These discontinuation rates are rather high. ILD as reason for discontinuation occurred equally frequent in the two T-DXd exposed study populations (6.4% vs 6.3%) and was the primary cause of drug-discontinuation in both studies. The majority of drug-related ILD events were low grade (grade 1 or 2 in 13/16 subjects in the T-DXd arm of J202 and 5/6 subjects in U205), although a few fatal cases were observed.

In the HER2+ 6.4 mg/kg GC pool, 19/229 patients (8.3%), hereof 2 (0.9%) considered drug-related, experienced AEs associated with the outcome of death. The frequency of AEs associated with the outcome of death was twice as high in the Western 2L population compared to the Asian 3L+ (12.7% vs 6.4%), as was the on-treatment deaths (11.4% vs 6.4%), However, 6/10 deaths in U205 were due to disease progression or COVID-19 and the difference therefore acceptable. AEs with outcome of death in the physician choice arm of J202 occurred in 3.2%.

In the small group of patients ≥75 years of age from the TXD-d pool (24/229) compared to patients <75 years of age (n=204), there was a higher frequency of ≥grade 3 TEAEs (83.3 vs 71.7%), TEAEs associated with drug interruptions (58.3 vs 46.3%), dose reductions (41.7 vs 28.3%) and SAEs (50.0 vs 39%).

3.5. Uncertainties and limitations about unfavourable effects

The toxicity profiles of patients in study J202 T-DXd arm and study U205 are divergent with regard to the intrinsic factors age, sex, renal and hepatic function at baseline and with regards to the extrinsic factors concerning region and country. The frequencies of ≥grade 3 AEs, SAEs and AEs associated with death are also divergent, but to a large degree explainable. Differences in baseline disease characteristics and the well-established higher degree of hematologic toxicity in the Asian population, are some of the major reasons for the differences, but also the difference in study design, with one being a RCT (J202) and the other (U205) being a SAT, challenges the direct comparability of the safety profiles. Pooling data when the frequencies in quite a number of toxicity events are very far apart between the two populations is, to some degree, obscuring the data and the understandings that lead from them.

The safety evaluation in the HER2-positive GC pool is mainly based on data from the Asian population (n=150) with a smaller proportion of Western patients (n=79). Exposure-safety analyses indicated race-country as a covariate for most safety parameters indicating that the safety profile in study J202 cannot

easily be extrapolated to Western patients. In addition, the possibilities for extrapolation may be further impacted by the fact that the Asian patients included in study J202 were more heavily pre-treated than the European and US patients in studies U205, while having a better performance score.

The toxicity was manageable within both patient populations (T-DXd arm of J202 and U205) although with differences in the toxicity profile between the two groups. The differences were primarily due to expected higher hematologic toxicity in the Asian (mainly Japanese) population and due to the differences in baseline disease characteristics. Some differences were not obviously explainable. The toxicity profile of T-DXd 6.4 mg/kg is considered thoroughly displayed for both studies and could not be described as worse or better for either group, but as with different profiles.

The described uncertainties regarding the safety profile of T-DXd in the treatment of patients with GC will be further clarified by the fulfillment of the RMP. Additionally, a confirmation of the safety profile will be provided with the outcome of the ongoing confirmatory trial DESTINY-Gastric 04 required as a specific obligation. This is needed to guarantee comprehensiveness of the safety (and efficacy) data and by that to ensure a fully established safety profile.

3.6. Effects Table

Table 1. Effects Table for ENHERTU (Trastuzumab deruxtecan) as monotherapy for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior anti-HER2-based regimen in the pivotal phase 2 study U205 and the supportive study J202 (compared to TPC)(data cut-off: 08 Nov 2021/03 June 2020)

Effect	Short description	Unit	Treatment T-DXd N=79	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint for U205						
cORR by ICR	Confirmed overall response rate	% 95% CI	41.8 30.8, 53.4	NA		DCO 08 Nov 2021
Secondary endpoints for U205						
mDoR	Median duration of Response	Months 95% CI	8.1 5.9,NE	NA		DCO 08 Nov 2021
Effect	**Short description**	**Unit**	**Treatment T-DXd N=126**	**Control TPC N=62 total**	**Uncertainties / Strength of evidence**	**References**
Primary endpoint for J202						
ORR by ICR	Overall Response Rate Unconfirmed	%	48.4	12.9		DCO 08 Nov 2019
Secondary endpoints for J202						
mOS	Overall Survival	Months	12.5	8.9		DCO 03 Jun 2020
mPFS	Progression Free	Months	5.6	3.5		DCO 03 Jun 2020

Effect	Short description	Unit	Treatment T-DXd N=79	Control	Uncertainties / Strength of evidence	References
	Survival					
mDoR	Duration of Response	Months	12.5	3.9		DCO 03 Jun 2020
ORR by ICR	Overall Response Rate Confirmed	Months	39.7	11.3	Exploratory secondary endpoint	DCO 03 Jun 2020

Unfavourable Effects (HER2+ GC 6.4 mg/kg pool, n=229)

		HER2+ GC 6.4 mg/kg pool (n=229)	TPC arm J202 (Asian, n=62)	T-DXd arm J202 (Asian, n=125)	U205 (Western, n=79)	
Grade ≥3 AE	% (n)	72.9% (167)	56.5% (35)	85.6% (107)	53.2% (40)	
SAEs	% (n)	40.2% (92)	25.8% (16)	44.8% (56)	36.7% (29)	
AEs leading to discontinuation	% (n)	16.6% (38)	6.5% (4)	17.6% (22)	15.2% (12)	
AEs leading to death	% (n)	8.3% (19)	3.2% (2)	6.4% (8)	12.7% (10)	

Abbreviations: TPC=Treatment of Physicians Choice, T-DXd=Trastuzumab Deruxtecan, NA=Not available, NE=Not evaluable FAS=Full analysis set, ITT=Intention to treat analysis set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Locally advanced or metastatic HER2-positive gastric and gastroesophageal junction adenocarcinoma remain an incurable disease. Once patients have progressed after a first-line regimen that includes an anti-HER2 therapy, disease outcomes are poor. Currently, there is no approved targeted anti-HER2 therapy in the EU for the treatment of metastatic HER2-positive gastric adenocarcinoma in the second-line setting and beyond, which constitutes an unmet medical need.

Disease activity from T-DXd is evident from results in the pivotal trial and this preliminary promising efficacy is supported by the 3L+ Asian J202 trial, but it is not yet considered that comprehensive data for the intended 2L+ setting has been presented. To address this, the MAH has commited to providing results from the ongoing DESTINY-Gastric04 trial, currently imposed as a SOB in Annex II.

The majority of AEs and ADRs in J202, U205 and in the HER2+ GC Pool were gastrointestinal or hematologic in nature. Hematologic AEs were reported more frequently in the T-DXd arm of J202 than in U205, representing the main difference in toxicity profile between the 2 study populations.There were notable differences in the toxicity profile between the two patient groups. These were primarily due to expected higher hematologic toxicity in the Asian (mainly Japanese) population and due to the differences in baseline disease characteristics. The differences in baseline disease characteristics, ethnic differencies in toxicity profile and differences in study design challenges the comparability of the two

study populations' safety profiles. Pooling data when the frequencies in quite a number of toxicity events are very far apart between the two populations is, to some degree, obscuring the data and the understandings led from them. Still, the toxicity profile of T-DXd 6.4 mg/kg is considered thoroughly displayed for both studies and regarded as manageable within both patient populations. However, comprehensive data are awaited with the ongoing confirmatory phase 3 study DESTINY-Gastric 04 (DS-8201-A-U306).

However, the investigated patient group has metastatic gastric cancer, often symptomatic (and also leading to frequent hospitalisations) and many patients were heavily pre-treated. The targeted patient population are to an extent fragile and if left untreated, they have a very limited remaining life expectancy. Therefore, toxicity and treatment-related deaths can be considered acceptable in view of the potential efficacy benefits.

3.7.2. Balance of benefits and risks

The B/R of Enhertu for the intended 2L HER2+ GC/GEJC setting is positive in the context of a conditional approval.

3.7.3. Additional considerations on the benefit-risk balance

A SAG-O consultation concerning the remaining uncertainties of Enhertu for the proposed 2L HER2+ GC/GEJC was held on 03-NOV-2022. The SAG-O concluded that the activity and efficacy from T-DXd in the targeted population are sufficiently convincing to justify conditional approval even if the confirmatory data from the phase III trial in second-line are still outstanding. It was emphasised that the feasibility of the trial is the pillar for the considerations of the SAG-O.

Conditional marketing authorisation

Enhertu was initially, and currently is, approved as a conditional marketing authorisation (CMA). As comprehensive data on the product for this extension of indication are also not available, a conditional marketing authorisation was requested for this extension of indication.

Importantly, this extension of indication falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life- threatening disease. Furthermore, the CHMP considers that the new indication for this product fulfils the requirements for a conditional marketing authorisation:

• The benefit-risk balance of T-DXd is positive, as the results from studies U205 (pivotal study) and J202 (supportive study) are of clinical relevance in the applied indication, with confirmed objective response rates (ORR) by blinded independent central review of 41.8% in Study U205 and 39.7% in Study J202, both studies showed clinically meaningful median duration of response (DoR) (8.1 and 12.5 months, respectively).

• It is likely that the applicant will be able to provide comprehensive data.

The DESTINY-Gastric04 study is a Phase 3, multicenter, 2-arm, randomized, open-label study of T-DXd 6.4 mg/kg in subjects with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma who have progressed on or after a trastuzumab-containing regimen. The primary objective will assess OS and the secondary objectives will further assess efficacy, safety, PK, and immunogenicity of T-DXd compared with Ramucirumab + paclitaxel. As of 08 Nov 2022, 148 subjects have been enrolled and treated. Albeit recruitment might be impacted by approval in the EU, the MAH has substantiated the

feasibility of this study and as of 08 Nov 2022, 148 subjects have been enrolled and treated. There is planned ~490 subjects to be enrolled. Study U306 enrollment is projected to be completed by Dec 2024 and the CSR ready in Q4 of 2025. The study is currently being conducted in the following 22 countries: Argentina, Belgium, Brazil, Chile, China, France, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, South Korea, Poland, Portugal, Romania, Singapore, Spain, Taiwan, Turkey, and United Kingdom.

• T-DXd fulfils an unmet medical need as currently, for patients with locally advanced or metastatic HER2-positive GC, there is no approved HER2-targeted therapy after progression on chemotherapy with fluoropyrimidine + platinum agents plus trastuzumab (the standard of care in the first-line [1L] setting). The ORRs from currently approved treatments in 2L (PTX, docetaxel, irinotecan monotherapy, FOLFIRI [folinic acid, fluorouracil, and irinotecan] or ramucirumab + PTX or PTX-only) after a 1L regimen that includes an anti-HER2 therapy range from 3% to 28%. Median PFS ranges from approximately 1 month to 4 months and median OS ranges from approximately 4 months to 10 months in the 2L setting. While the limitations related to indirect comparisons between studies are acknowledged, T-DXd will act through a different mechanism of action, and is expected to bring a major therapeutic advantage to patients.

• The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Once the patient's GC has progressed on or after a 1L regimen that includes an anti-HER2 therapy, the disease outcomes are poor, with the 5-year survival rates ranging from 10% to approximately 30%. For those patients whose initial diagnosis is Stage IV disease, the prognosis is dismal in Asian and Western regions.

3.8. Conclusions

The overall B/R of trastuzumab-deruxtecan for the intended second line treatment of GC/GEJC is positive subject to the specific obligations and conditions imposed in order to obtain further clinical data to generate a comprehensive clinical data set. Consequently, the ongoing study DESTINY-Gastric04 (DS8201-A-U306) trial, a phase III RCT of trastuzumab deruxtecan versus ramucirumab + paclitaxel in the 2L population including EU and USA patients is imposed as a SOB in Annex II of the Opinion.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include monotherapy treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior

trastuzumab-based regimen for Enhertu based on final results from studies DS8201-A-U205 (DESTINY Gastric02) and DS8201 A J202 (DESTINY Gastric01); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Annex II and the Package Leaflet are updated in accordance. In addition, changes regarding the dosing recommendation for corticosteroid treatment and the protection of the infusion bag from light have been introduced. Version 3.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following additional measure:

Description	Due date
In order to confirm the efficacy and safety of Enhertu in the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen, the MAH should submit the final results of study DS-8201-A-U306, a phase 3, multicentre, 2-arm, randomised, open-label study of Enhertu in subjects with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen.	31 December 2025

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Enhertu II-0012