

EU Risk Management Plan for Enhertu (Trastuzumab Deruxtecan/T-DXd)

RMP version to be assessed as part of this application:

Data lock point for this
RMP

19 Dec 2022

RMP version number

8.0

Date of final sign off

10 Jan 2024

Rationale for submitting an updated RMP:

Update of missing information.

Summary of significant changes in this RMP:

Update of SVII.2 (New Safety Concerns and Reclassification with a Submission of an Updated RMP), removal of 'Use in Patients with Moderate Hepatic Impairment' as missing information in respective sections.

QPPV name:

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QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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1.8.2 Risk Management Plan
Trastuzumab deruxtecan

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PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	Trastuzumab deruxtecan (T-DXd)
Pharmacotherapeutic group(s) (ATC Code):	L01FD04
Marketing Authorisation Holder:	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers:	Trastuzumab deruxtecan (T-DXd)
Invented name(s) in the European Economic Area (EEA):	Enhertu
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class: Human epidermal growth factor receptor 2 (HER2)-targeted antibody and topoisomerase I inhibitor conjugate
	Summary of mode of action: Trastuzumab deruxtecan, hereafter referred to as T-DXd, is an antibody-drug conjugate (ADC) composed of 3 components: 1) a humanised anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, DXd, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.
	Important information about its composition: White to yellowish-white lyophilised powder in a single-dose vial for reconstitution and further dilution. The monoclonal antibody intermediate used in T-DXd is a humanized IgG1 mAb produced by mammalian (Chinese hamster ovary) cell culture.
Hyperlink to the Product Information:	Summary of Product Characteristics (SmPC)

Table Part I.1: Product Overview (Continued)

Indication(s) in the EEA:	Current: Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer (BC) who have received one or more prior anti-HER2-based regimens. Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low BC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Enhertu as monotherapy for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen. Enhertu as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum based chemotherapy with or without immunotherapy.
Dosage in the EEA	Current: Metastatic BC and NSCLC: 5.4 mg/kg given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Advanced gastric cancer (GC): 6.4 mg/kg given as an IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
Pharmaceutical form(s) and strengths	Current: 100 mg of T-DXd as a white to yellowish- white lyophilized powder for concentrate for solution for infusion in a single-dose vial. Must be reconstituted and diluted by a healthcare professional and administered as an IV infusion. T-DXd must not be administered as an IV push or bolus.
Is/will the product be subject to additional monitoring in the EU?	Yes

EU = European Union; HER2 = human epidermal growth factor receptor 2; INN = International Nonproprietary Name; RMP = Risk Management Plan

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1. HER2-positive Breast Cancer

SI1.1. Incidence and Prevalence

Approximately 11.7% of all new cancers are female BC, which has an annual incidence rate of 47.8 per 100,000 persons worldwide. Australia/New Zealand, Europe, and North America have the highest incidence by region.

BC is the most common cancer in women, accounting for 2.3 million new cases worldwide in 2020. In 2020, there were an estimated 7,790,717 women living with BC diagnosed in the last 5 years worldwide, with a 5-year prevalence proportion of 201.6 per 100,000.

Approximately 20% of patients with BC globally have HER2-positive tumours. HER2 positivity is associated with more aggressive disease. HER2-positive BC is also associated with negative hormone receptor (HR) status and a younger patient population. Among all BC cases in the Cortet study, 6.3% were HR-positive/HER2-positive and 3.7% were HR-negative/HER2-positive.

Crude and world- and Europe-standardised incidence rates for HER2-positive BC are compared to overall BC incidence rates in [Table Part II: Module SI.1](#).

Table Part II: Module SI.1: Incidence Rates for HER2-positive Breast Cancer Compared to Overall Breast Cancer

	Year of Diagnosis					
	2007	2008	2009	2010	2011	2012
Crude incidence rate						
Overall	170.99	166.88	159.45	177.99	170.83	171.37
HER2-positive/HR-positive	9.59	11.10	10.36	11.41	9.38	13.00
HER2-positive/HR-negative	5.65	5.28	5.65	6.75	6.59	6.45
World standardized incidence rate						
Overall	116.84	113.77	109.67	119.35	114.59	113.89
HER2-positive/HR-positive	6.70	8.26	8.37	8.74	7.26	10.03
HER2-positive/HR-negative	4.10	4.08	4.53	5.00	4.94	4.48
Europe standardized incidence rate						
Overall	154.27	149.78	142.02	157.86	150.87	149.10
HER2-positive/HR-positive	8.37	10.65	10.20	11.18	9.32	11.88
HER2-positive/HR-negative	4.90	4.99	5.35	6.33	6.09	5.61

Source: Cortet 2018

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor

European Union (EU):

In the 27 members of the EU (EU-27), 355,457 new cases of female BC were diagnosed in 2020, comprising approximately 12.1% of all cancers. The estimated annual age-standardised (worldwide) incidence rate of BC is 82.46 per 100,000 in the EU. In 2020, there were an estimated 1,457,608 women living with BC in the EU who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 640.6 per 100,000.

Among patients with metastatic BC, HER2 overexpression varies from 22% (France) to 34% (Italy). For Germany, Spain, and the United Kingdom (UK), the numbers were 32.4%, 26.3% and 28.4%, respectively. The study population comprised a total of 152,311 patients with metastatic BC in the UK, Germany, France, Spain, and Italy (EU-5) countries. HER2-positive/HR-negative BC was the least prevalent in France (9%) and most prevalent in Italy (13.5%). The proportion of HER2-positive/HR-positive patients ranged from 13.1% in France to 20.7% in Italy.

Breast cancer patients tested IHC 1+ or IHC 2+ without HER2 gene amplification are defined as HER2-low. An estimated 45% to 55% of all primary BC patients are HER2-low. The majority (65% to 83%) of the HER2-low BC patients have HR-positive tumours, which are mostly luminal subtype. The rest of the HER2-low BC patients are HR negative and are predominantly basal-like subtype. For the therapeutic purpose, patients with HER2-low BC are currently considered to have HER2-negative BC.

SI1.2. Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Sex: Breast cancer is mainly a disease in females, with 1% of cases occurring in males.

Age: In the EU-27, approximately 11.4% of BCs occur in women younger than 45 years of age. BCs are most commonly (47%) diagnosed among women 55 years to 75 years of age in the EU. Worldwide, 48% of the newly diagnosed patients with BC are 45 years to 64 years of age. BC incidence is much higher among adults and increases with age, with the highest incidence rate among those 65 years and older.

Among patients with metastatic BC, those with HER2-positive tumours are younger than those with HER2-negative tumours (including HER2-low). The youngest among a metastatic BC EU-5 population seemed to be those with HER2-positive HR-negative tumours, where 28% were younger than 50 years of age.

Race and/or Ethnicity: According to the Surveillance, Epidemiology, and End Results (SEER) cancer query system, age-adjusted incidence of BC is highest in White females (104.1 per 100,000). Incidence of BC in Black and Asian/Pacific Islander females is 99.2 and 85.4 per 100,000, respectively. BC risk is lower in Hispanic females, with an age-adjusted incidence rate of 80.3 per 100,000.

Family history: Women with a family history, especially a mother, sister, or daughter who has or had BC, have a higher risk of having BC. In western countries, genetic predisposition is the cause of up to 10% of BC cases. The most common inherited causes are mutation in the *BRCA1* and *BRCA2* genes.

Reproductive factors: Women who have early menarche (before age 12) or late menopause (after age 55) have a higher risk of developing BC. Nulliparous women and women who are over age 30 at their first birth may have a greater chance of developing BC.

Obesity: Obesity increases the risk of BC (possibly through an increase in oestrogen levels) in postmenopausal women. In premenopausal women, obesity is associated with a reduced incidence of BC.

Previous benign breast disease: Women with atypical epithelial hyperplasia have a higher risk (4 to 5 times) of developing BC.

Birth control pills: Oral contraceptive use may slightly increase the risk of developing BC. The risk decreases once the pills are stopped. Ten years after cessation of the oral contraceptive agent, there is no significantly increased risk of having BC.

Combined postmenopausal hormone therapy: Women who use combined hormone therapy after menopause have an increased risk of developing BC. There is a dose-response relationship, with larger risks corresponding with longer durations of combined hormonal therapy use.

Radiation exposure: Children or young adults exposed to radiation therapy to the chest area have a significantly increased risk of developing BC later in life.

SI1.3. The Main Existing Treatment Options

Although HER2-targeted drugs have been developed as molecularly targeted therapies, locally advanced and metastatic tumours invariably relapse with time.

HER2-positive Metastatic Breast Cancer

The first targeted agent for HER2 therapy, trastuzumab (HERCEPTIN®), is a humanized mAb directed against the extracellular domain of HER2. Other HER2-targeting agents have subsequently been approved, including the ADC KADCYLA® (T-DM1); the tyrosine kinase inhibitor NERLYNX® (neratinib) as monotherapy in early-stage BC and in combination with capecitabine in metastatic BC; the mAbs PERJETA® (pertuzumab) and MARGENZA® (margetuximab), and the tyrosine kinase inhibitors TYKERB® (lapatinib) and TUKYSA (tucatinib) each in combination with other chemotherapeutic agents. Although anti-HER2 targeted therapies have improved outcomes, they are not curative in the metastatic setting. The ADC T-DXd (Enhertu®) monotherapy was approved as a new treatment option in the United States (US), EU, Japan and a few other countries for patients with HER2-positive unresectable or metastatic BC who have received one or more prior anti-HER2-based regimens.

The current standard of care (SoC) for newly diagnosed HER2-positive metastatic BC in Europe is a combination of pertuzumab, trastuzumab, and taxane, per the European Society for Medical Oncology (ESMO), based on results from the CLEOPATRA study. T-DXd has been established as the standard of care for subsequent-line anti-HER2 therapy.

Tucatinib was approved based on the results from the HER2CLIMB study, in which subjects previously treated with trastuzumab, pertuzumab, and T-DM1 were randomised to receive trastuzumab plus capecitabine with or without tucatinib.

HER2-low Metastatic Breast Cancer

Current therapeutic guidelines for patients with BC exhibiting HER2-low expression are the same as those for patients with HER2-negative BC. For patients with metastatic HER2-negative BC, treatment recommendations from the National Comprehensive Cancer Network, ESMO, and the Japanese Breast Cancer Society clinical practice guidelines are based on tumour HR status, presence or absence of visceral crisis, and menopausal status.

HER2-low Hormone Receptor-Positive Metastatic Breast Cancer

In the first-line metastatic setting, in the absence of a visceral crisis, the SoC for patients with HER2-/HR+ BC is endocrine therapy (ET) with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.

In the second- and subsequent-line metastatic setting, preferred regimens include, but are not limited to, fulvestrant in combination with a CDK4/6 inhibitor if a CDK4/6 inhibitor was not previously used, ET plus everolimus, a nonsteroidal aromatase inhibitor, a steroidal aromatase inactivator, fulvestrant, and selective estrogen receptor modulators. For PIK3CA-mutated tumours, another option includes fulvestrant plus targeted therapy with alpelisib. Patients with deleterious or suspected deleterious germline BRCA mutations can be treated with poly adenosine diphosphate-ribose polymerase inhibitors.

Once tumours are refractory to ET, therapeutic guidelines recommend the use of sequential systemic single-agent chemotherapy. Preferred single-agent regimens in this setting include the anthracyclines doxorubicin and liposomal doxorubicin, the antimetabolites capecitabine and gemcitabine, the microtubule inhibitors vinorelbine and eribulin, and the taxane paclitaxel. Other recommended single agents are the taxanes docetaxel and nanoparticle albumin-bound (nab)-paclitaxel, the anthracycline epirubicin, and ixabepilone. Single-agent chemotherapy is preferred over combination therapy in this setting.

The most recent approved treatment for patients with HR-positive tumours refractory to ET who have received at least one prior line of chemotherapy is the CDK4/6 inhibitor abemaciclib, and the ADC sacituzumab govitecan. T-DXd is the first HER2-targeted therapy to demonstrate statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) over commonly used chemotherapeutic agents in adult patients with unresectable or metastatic HER2-low BC who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

HER2-negative Hormone Receptor-negative (Triple Negative) Breast Cancer

For patients with metastatic triple-negative breast cancer (TNBC), the treatment in the first-line metastatic setting is sequential single-agent chemotherapy, with the same preferred chemotherapeutic options as those for patients with HER2-/HR+ BCs who are refractory to ET. Regardless of BRCA status, for patients with TNBC previously treated with anthracyclines and taxanes in the adjuvant or neoadjuvant setting, platinum agents are the preferred option. For patients with BRCA1/2 mutations, the recommendation is to use poly adenosine diphosphate -ribose polymerase inhibitors (olaparib or talazoparib) or platinum agents.

For patients with metastatic TNBC with programmed death-ligand 1-positive disease, the preferred therapeutic option in the first-line setting is a programmed cell death protein 1-blocking antibody (pembrolizumab) in combination with chemotherapy.

For patients with TNBC who have received at least 2 previous regimens, including at least 1 of the treatment regimens in the metastatic setting, the ADC sacituzumab govitecan is approved.

Positive results from a small cohort of subjects with HR- BC led to approval of T-DXd as another targeted-therapy option for this segment of patients with a poor prognosis.

SI1.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

- According to Globocan data, approximately 684,996 women died from BC worldwide in 2020, with a 5-year age-adjusted mortality rate of 13.6 per 100,000. Data from 279 population-based cancer registries from 67 countries showed that the 5-year survival from BC is increasing in most developed countries.
- Metastatic BC is the third most common cause of death in Europeans after lung and colorectal cancer. The estimated number of deaths from BC in the EU was 91,826 in 2020. Overall, BC mortality rates in the EU declined by 15%, from 17.9% in 2002 to 15.2% per 100,000 in 2012. The mortality rate increased with increasing age and was highest among the oldest age group (70 years to 79 years). Triple negative and HER2-positive subtypes have the worst survival outcome.
- The 5-year relative survival rate for patients with BC in the US is 90.3%. Survival is higher among White patients than African American patients in all age groups. Survival also differs by cancer stage at diagnosis, with localised disease having a survival rate up to 99.0% and metastatic disease having a survival rate up to 29.0%. Overall, the 5-year relative survival for BC has been increasing from 74.5% in 1975 to 92.2% in 2019. In 2021, there were an estimated 43,600 deaths among patients with BC in the US. The mortality rate has been estimated to be 20.1 deaths per 100,000 persons per year based on the 2015 to 2019 data. The median age at death was 69 years.
- In 2020, Japan had an estimated 17,081 deaths due to BC, with a 5-year mortality rate of 9.9 per 100,000.
- Metastatic HER2-positive BC remains an incurable disease that is ultimately fatal. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive BC, the disease invariably progresses, with median survival being 2 to 4 years.

Events that Occur Frequently in Subjects with Metastatic Breast Cancer

Events that occur frequently in subjects with metastatic BC are described below. These include events associated with the disease or with therapies.

Bone metastases: Among patients with BC who had distant metastases, bone is the most common site for metastasis. The risk of developing bone metastases within 10 years after diagnosis was 7% to 9% according to a Canadian study. A retrospective study on 35,912 Danish patients with BC found that 4.2% of patients with BC develop bone metastasis within 5 years of diagnosis. Among patients with BC who had bone metastases, 47.7% developed skeletal-related events (SREs) defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopedic surgery.

Brain metastases: Brain metastasis (BM) was found in 5.1% of patients with BC. The symptoms most commonly associated with BM were headache (35%), vomiting (26%), nausea (23%), hemiparesis (22%), visual changes (13%), seizures (12%) and altered mental status (7%). In a retrospective study of clinical data of German patients with BC who had BM, median OS time after BM development was reported as 7.4 months, with a one-year survival rate of 37.7%. Patients with HER2-positive tumours had the longest median OS of 11.6 months (95% confidence interval: 10.0, 13.4) and those who received anti-HER2 therapy had a longer median OS (17.1 months).

Cardiotoxicity: Anthracyclines (eg, doxorubicin and epirubicin) used in the treatment of BC cause a dose-dependent, cumulative, progressive cardiac dysfunction that may ultimately lead to symptomatic congestive heart failure (CHF). Cardinale et al reported that in 1344 patients with BC receiving anthracycline-based therapy, the incidence of cardiac toxicity was 9.7% at a median follow-up of 5.2 years.

Trastuzumab treatment in patients with HER2-positive BC was associated with cardiac toxicity with heart failure incidence up to 4.7% and asymptomatic decline in left ventricular ejection fraction (LVEF) up to 20.6%.

Radiation exposure in patients with BC is associated with increased risk of ischemic heart disease with a magnitude of the risk of 7.4% per gray. There was no apparent threshold below which there was no risk. The risk was dose-dependent with a lag time of up to 20 years.

Hepatotoxicity/Liver metastases: Liver metastases develop in approximately half of the women with metastatic BC and represent a frequent cause of mortality among these patients. According to a UK study, the risk of developing liver metastasis in 6 years after BC diagnosis is 5.2%. Liver metastases were present in only 1.4% of overall patients with BC and 3.3% of patients with HER2-positive BC at the time of the initial BC diagnosis and are typically associated with metastases at other sites. In 78.6% of cases, the liver metastases were asymptomatic at the time of metastatic diagnosis. The remainder were symptomatic, presenting with epigastric pain or fullness (21.4%), palpable hepatomegaly (27.3%) and ascites (6.2%).

Pulmonary toxicity/Pulmonary metastases: In a systematic literature review of pneumonitis associated with BC therapy, the authors reported that most of the currently used BC treatments may induce pneumonitis with an incidence of 1% to 3%.

Approximately 31% of metastatic patients with BC suffer lung metastasis. Metastasis to the lung is associated with poor prognosis, with patients presenting with clinical symptoms such as pain, cough, haemoptysis, pleural effusion, and pulmonary dysfunction.

SI1.5. Important Comorbidities

Patients with BC who have comorbidities have overall higher mortality compared to patients without comorbidities.

Multiple registry studies have shown a correlation between the presence of comorbidities and higher mortality. A nationwide population-based cohort study of 9329 patients with BC of all ages in Denmark, a nationally representative cancer registry in Sweden including 42,646 patients with BC from 1992 to 2008, and a Dutch registry-based study of 9123 patients with BC all included similar proportions of patients with at least 1 comorbidity (22%, 13%, and 28%, respectively). In each of these studies, patients with at least 1 comorbid condition had a higher mortality rate than patients with no comorbidities.

In the US, a retrospective cohort study (N = 5186) in an elderly BC population found 22% of patients had at least 1 comorbidity at the time of BC diagnosis. Patients with comorbidities had a significantly higher mortality rate (risk ratio [RR] = 1.4 for patients with a single comorbidity and RR = 2.0 for patients with 2 or more comorbidities) compared to patients without any comorbidities.

A systematic review of 18 studies on BC survival and comorbid conditions demonstrated that the presence of comorbidities at baseline was an important independent prognostic factor and was associated with poorer BC survival. In this review population, hypertension was the most

common comorbidity. Other reported common comorbid conditions were cardiovascular disease, diabetes, previous cancer, cerebrovascular disease, and pulmonary disease.

Among patients in a study of 5 European countries, the majority of patients with HER2-positive BC had no comorbidities (Table Part II: Module SI.2).

Table Part II: Module SI.2: Summary of Important Comorbidities

	Number and Percentage of Patients					
	Metastatic BC (N = 152,311)		HER2-positive/ HR-positive (N = 27,159)		HER2-positive/ HR-negative (N = 16,870)	
Cardiac dysfunction	20,080	13.2	3164	11.7	1385	8.2
COPD	11,054	7.3	1605	5.9	816	4.8
Diabetes	22,690	14.9	3372	12.4	1442	8.5
None	108,295	71.1	20,530	75.6	13,477	79.9

BC = breast cancer; COPD = chronic obstructive pulmonary disease; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; UK = United Kingdom

Includes patients from UK, Germany, France, Spain and Italy

Source: DeKoven 2012

SI.2. HER2-positive Gastric Cancer

As there are limited epidemiological data in the literature for the HER2-positive GC population, data herein are presented on general GC, with HER2-positive GC data included where available.

SI.2.1. Incidence and Prevalence of HER2-positive Gastric Cancer Population

GC is the fifth most common cancer, accounting for 1.09 million new cases worldwide in 2020. Approximately 5.6% of all new cancers are GC, with an annual incidence rate of 11.1 per 100,000 persons worldwide. In 2020, there were an estimated 1,805,968 persons worldwide living with GC that had been diagnosed in last 5 years, with a 5-year prevalence proportion of 23.2 per 100,000. Almost 75.3% of new GC cases occur in Asia.

Overexpression of HER2 can be found in 8.2% to 29.5% of patients with GC. HER2 expression in GC varies based on the site of the primary tumour (gastric versus GEJ) and histological types. Reports of the relationship between HER2 overexpression and disease prognosis in patients with GC are inconsistent: some studies found HER2 positivity to be associated with more aggressive disease, with significantly shortened disease-free survival and OS, while other studies did not demonstrate such an association.

European Union: In the EU-27, approximately 75,443 new cases of GC were diagnosed in 2020, comprising approximately 3% of all cancers. The estimated annual incidence rate of GC was 6.8 per 100,000 persons in the EU. The incidence rate per 100,000 persons was highest in Lithuania (13.4), Estonia (12.6), and Latvia (12.1), and lowest in Sweden (3.3), Finland (3.8), and Denmark (4.4). In 2020, there were an estimated 119,887 patients in the EU living with GC that had been diagnosed in previous 5 years, with a 5-year prevalence proportion of 26.9 per 100,000.

SI.2.2. Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Sex: GC is more prevalent in males than females, with nearly two-thirds of all new GC cases occurring in males. The worldwide age-standardized incidence of GC in males is 15.8 per

100,000 compared with 7.0 per 100,000 among females. In the EU-27, incidence (ASR-World) of GC in males and females are 22.4 and 10.6 per 100,000 respectively.

Age: According to SEER 2014-2018 data, the median age at diagnosis in the US was 68 years, with 71.6% of patients diagnosed at 55 years to 84 years of age. A similar age distribution of patients with GC was found in the EU-27, with 73.9% of patients diagnosed at 55 years to 84 years of age.

Race and/or Ethnicity: According to SEER 2018 age-adjusted data, GC was most common in persons of Hispanic ethnicity (10.4 per 100,000), the Asian/Pacific Islander population (10.1 per 100,000), and the Black population (10.0 per 100,000). The incidence was significantly lower in the non-Hispanic White population (5.6 per 100,000).

***Helicobacter pylori* (H. pylori) infection:** *H. pylori* infection is the main risk factor of GC, with a 3-fold to 6-fold increased risk in persons with *H. pylori* infection compared to persons without *H. pylori* infection. Approximately 65% to 80% (660,000 new cases) of all GC cases are caused by *H. pylori*.

Obesity: Increased body mass index (BMI) is associated with an increased risk of cardia GC. Compared to individuals with a BMI of <25, individuals with a BMI of 30 to 35 have a 2-fold higher risk of GC and those with a BMI of >40 have a 3-fold risk.

Smoking: Smoking was found to be associated with higher risk of cardia GC, with male smokers having a higher risk of GC compared to female smokers. Approximately 11% of GC cases globally and 17% of GC cases in Europe were attributed to smoking.

Pernicious anaemia: A person with pernicious anaemia has a 6.9% chance of developing GC, particularly non-cardia cancer.

Diet: People who have a diet rich in salt and pickled foods exhibit higher rates of GC. Consuming preserved meats also increase the risk of GC. Higher intake of fruits and vegetables was associated with a 37% lower risk of GC.

Socioeconomic status: Socioeconomic status is inversely associated with GC risk, with higher status reported to be associated with lower GC risk.

Genetics: CDH1 germline mutations were found in 25% of families with hereditary diffuse GC. Mutation in the adenomatous polyposis coli (APC) gene was linked to familial adenomatous polyposis, which involves development of different tumours, including GC.

Gastroesophageal reflux disease (GERD): Several studies have reported a significant association between GERD and cardia GC. GERD also increases the risk of oesophageal adenocarcinoma by 5- to 7-fold.

SI.2.3. The Main Existing Treatment Options

Systemic chemotherapy has been shown to improve survival and quality of life compared to best supportive care alone in patients with locally advanced or metastatic disease with adequate performance status.

- For patients with locally advanced or metastatic HER2-positive GC, the current SoC in the first-line setting in the US, Europe, and Japan is a combination of chemotherapy with a fluoropyrimidine agent (fluorouracil or capecitabine or S-1 in Japan) and a platinum agent (oxaliplatin or cisplatin), plus the anti-HER2 trastuzumab. As an alternative to platinum-based therapy, irinotecan plus leucovorin and infusional 5-FU (FOLFIRI) was shown to be efficacious and well tolerated regardless of HER2 expression and may be

considered for selected patients. In the US, the combination of pembrolizumab in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy is approved in first-line setting. After progression in the first-line therapy, response rates and median survival are low.

- In the US and EU, T-DXd is approved as a second-line treatment option, and in Japan as a third-line treatment option, for HER2-positive gastric or gastroesophageal junction adenocarcinoma patients who had received prior trastuzumab based therapy.
- Other recommended treatment options for second and further-lines of chemotherapy include taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel dependent on Performance Status (PS).
- Regimens recommended for the third-line and later therapy regardless of HER2 expression include irinotecan, taxanes, pembrolizumab (if programmed cell death-ligand 1 expression by combined positive score ≥ 1), and the trifluridine/tipiracil- regimen. The programmed cell death protein-1-blocking antibody nivolumab is approved in Japan for use in the third-line- or later setting. Survival outcomes in the third-line metastatic setting and beyond are poor (approximately 6 months).

SI.2.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

- According to Globocan data, approximately 502,788 men and 266,005 women worldwide died from GC in 2020, with a 5-year age-adjusted mortality rate of 7.7 per 100,000.
- In the EU-27, an estimated 32,143 men and 19,942 women are expected to die from GC in 2020.
- Metastatic HER2-positive GC remains an incurable disease that is ultimately fatal. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive GC, the disease invariably progresses, with a 5-year relative survival rate of 32.4% in the US, while Stage IV GC has a 5-year survival rate of 5.5%, per the SEER 2011-2017 data.

Events that Occur Frequently in Subjects with Metastatic Gastric Cancer

Events that occur frequently in subjects with metastatic GC are described below. These include events associated with the disease or with therapies.

Bleeding: Approximately 2% to 8% of all upper gastrointestinal (GI) bleeding events are attributed to GI malignancies. The majority (58%) of cases of malignancy-related bleeding are caused by GC. In a population-based study in the UK, 62 (21%) of the 300 patients with previously undiagnosed GC presented with hematemesis/melena.

Malignant obstruction: Patients with advanced GC may develop malignant gastric outlet obstruction, which eventually leads to associated symptoms, including nausea, vomiting, abdominal pain, dehydration, malnutrition, and weight loss.

Nausea and vomiting: In a population-based study in the UK, 35% of the 300 patients with previously undiagnosed GC presented with vomiting. In advanced GC, pyloric stenosis may cause persistent vomiting.

Dumping syndrome: Approximately 68% of patients with GC experience early dumping syndrome after gastrectomy, which usually appears within 30 minutes after a meal. The most frequently experienced symptoms include abdominal pain or fullness (46.6%), diarrhoea

(37.5%), nausea or vomiting (20.3%), palpitations (16.3%), cold sweats (13.2%), and flushing (8.2%). In contrast, 38.4% of patients experienced late dumping syndrome that usually appears 2 hours to 3 hours after a meal, with hunger (20.7%) and faintness (20.7%), followed by dizziness (13.5%), cold sweats (10.2%), tremors (10.1%), and loss of consciousness (2.2%) as the most common symptoms.

SI.2.5. Important Comorbidities

Comorbidities play an important role in cancer treatment choice and patient survival. Multiple population-based studies in the Netherlands have found that 60% to 70% of patients with newly diagnosed GC also present with at least 1 comorbid condition. Hypertension (27.9%), cardiac disease (27.3%), digestive tract disease (18.2%), diabetes (16.6%), and previous malignancies (13.9%) are the most common comorbid conditions found in patients with stomach cancer.

Using the SEER-Medicare database, a US retrospective cohort study of 12,612 elderly patients with GC found that 61.3% of patients had at least 1 comorbidity. The prevalence at or before the index date and the 12-month incidence of most comorbid conditions were higher among the patients with GC compared to a cancer-free matched comparator group. The 12-month incidence of acute comorbid conditions (eg, anaemia, electrolyte disorder, and infection) was higher in patients with GC compared to the comparator group, which was thought likely to be related to treatment side effects and disease sequelae. Another retrospective cohort study using the Nationwide Inpatient Sample database from 2001 to 2011 identified all hospitalizations associated with GC. Hypertension (40.3%), anaemia (23.8%), and diabetes without complications (15.5%) were found to be the most common comorbidities associated with GC-related hospitalization. Obesity (odds ratio 2.0, 95% confidence interval [CI]: 1.6, 2.6) was significantly associated with increased risk of mortality in this patient population.

A population-based study in Japan found peptic ulcer (26%), diabetes without chronic complications (10%), other cancer (8%), and liver diseases (5%) to be the most common comorbidities in patients with GC. The adjusted hazard ratio for all-cause mortality for a single-point elevation in the Charlson Comorbidity Index score was 1.12 (95% CI: 1.02, 1.23) for GC.

SI.3. HER2-mutant Non-small Cell Lung Cancer

As there are limited epidemiological data in the literature for the HER2-mutant NSCLC population, data herein are presented on general lung cancer (LC) and NSCLC, with HER2-mutant NSCLC data included where available.

SI.3.1. Incidence and Prevalence

Lung cancer is the second most common cancer worldwide, accounting for 2.2 million new cases in 2020. Approximately 11.4% of all new cancers are LC, which has an annual incidence rate of 22.4 per 100,000 worldwide. Micronesia/Polynesia (36.7), Eastern Asia (34.4), Western Europe (32.7) and Northern America (32.6) have the highest incidence rate by region. In 2020, there were an estimated 2,604,791 men and women living with LC diagnosed in the last 5 years around the globe, with a 5-year prevalence proportion of 33.4 per 100,000.

Approximately 80% to 85% of LC patients have NSCLC according to the American Cancer Society. The HER2 mutation is reported to be found in 1.7% to 4.2% of NSCLC cases.

EU:

1.8.2 Risk Management Plan

Trastuzumab deruxtecan

In the 27 member states of the EU (ie, the EU-27), 318,327 new cases of LC were diagnosed in 2020, comprising approximately 11.9% of all cancers. The estimated annual age-standardised (worldwide) incidence rate of LC is 31.2 per 100,000 in the EU. In 2020, there were an estimated 394,704 people living with LC in the EU-27 who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 88.6 per 100,000.

US:

In the US, an estimated 236,740 new cases of LC cases were diagnosed in 2022, comprising approximately 12.3% of all new cancer cases. The lifetime risk of developing LC is approximately 6%. The age-standardised (worldwide) incidence rate of LC was estimated to be 33.1 per 100,000 in the US. In 2020, there were an estimated 295,263 people living with LC in the US who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 89.2 per 100,000.

Japan:

In Japan, 138,532 new cases of LC were diagnosed in 2020, comprising approximately 13.5% of all new cancer cases. The age-standardised (worldwide) incidence rate of LC was estimated to be 32.1 per 100,000 in Japan. In 2020, there were an estimated 216,629 people living with LC in Japan who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 171.28 per 100,000.

SI.3.2. Demographics of the Non-small Cell Lung Cancer Population and Risk Factors for the Disease

Sex: LC is more common in males than females. The worldwide age-standardised incidence of LC in males and females is 31.5 and 14.6 per 100,000, respectively. In the EU, the lifetime risk of developing LC is 1 in 19 for males and 1 in 37 for females. Nonsquamous NSCLCs with HER2 mutations are more associated with females than NSCLC without HER2 mutations.

Age: According to Globocan, only 2.4% of LCs in the world occur in people younger than 45 years. In the EU, 99% of LCs occur at or after 45 years of age. The median age at diagnosis of LC is 71 years in the US. Nonsquamous NSCLCs with HER2 mutations are more associated with younger age than NSCLC without HER2 mutations.

Race and/or ethnicity: According to SEER, the age-adjusted incidence of LC is highest in Black males, with 71.6 per 100,000 in the US. Among women, LC incidence is highest in White females, with 54.3 per 100,000.

Smoking: Smoking is, by far, the leading risk factor for LC. Each year, an estimated 80% of LC cases in men and 50% in women are caused by smoking.

Secondhand smoke (smoke from other people's cigarettes, pipes, or cigars) also can cause LC. According to the American Cancer Society, secondhand smoke is the cause of more than 7,000 LC deaths each year.

Nonsquamous NSCLCs with HER2 mutations are more associated with never-smokers than NSCLC without HER2 mutations.

Radon: Radon is the second most common cause of LC and the most common cause among never-smokers. In Europe, the risk of LC increases by 16% with exposure to each 100 Bq/m³ increase in indoor radon. In the US, the risk of LC increases by 11% with each 100 Bq/m³ increase in residential radon.

Occupational carcinogen exposure: Increased LC is associated with exposure to asbestos, arsenic, cadmium, chromium, beryllium, and nickel. Occupational exposure to asbestos (odds ratio: 1.76; 95% CI: 1.42, 2.18), crystalline silica (odds ratio: 1.31; 95% CI: 1.00, 1.71), and nickel–chromium (odds ratio: 1.18; 95% CI: 0.90, 1.53) is associated with increased risk of LC, even at a low exposure level.

Air pollution: The risk of LC is higher among urban people in comparison to rural people. Increase in the level of particulate matter 2.5 in the air increases the risk of LC. Indoor coal burning produces gas emissions that are carcinogenic to humans.

Familial: First-degree relatives of patients with LC have a 1.51-fold (95% CI: 1.39, 1.63) increased risk of developing LC.

Previous radiation therapy: According to the Centers for Disease Control, patients who had radiation therapy to the chest for prior cancers are at higher risk of LC.

SI.3.3. The Main Existing Treatment Options

Clinical guidelines from National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) for patients with metastatic NSCLC without an actionable oncogenic driver irrespective of programmed cell death ligand 1 (PD-L1) status are presented below.

In the first-line metastatic setting, the SoC is a combination of platinum-based chemotherapy and pembrolizumab (KEYTRUDA[®]) irrespective of PD-L1 expression. Other approved treatment options based on demonstrated OS improvement over other regimens are combination regimens that include atezolizumab or nivolumab.

In the second-line metastatic setting, the current SoC irrespective of PD-L1 expression for patients who have progressed on or after platinum-based chemotherapy and have not received prior PD-L1 therapy is anti-programmed cell death protein 1/PD-L1 agents. Other therapeutic options include docetaxel with or without ramucirumab. Clinical outcomes with currently approved treatment options for patients without an actionable oncogenic driver in the second-line metastatic setting are generally limited ([Table Part II: Module SI.3](#)).

Table Part II: Module SI.3: Disease Outcomes with Currently Approved Therapies in the First and Second-line Metastatic NSCLC Setting

Therapy	Objective Response Rate % (95% CI)	Median Duration of Response Months (Range)	Median Progression-free Survival Months (95% CI)	Median Overall Survival Months (95% CI)
Nivolumab	19 (15, 24)	17.2 (1.8, 22.6+)	2.3 (2.2, 3.3)	12.2 (9.7, 15.0)
Pembrolizumab [PD-L1 TPS ≥50% group]	33.1 (27.7, 38.8)	68.4 (2.0+, 71.7+)	5.3 (4.2, 6.5)	16.9 (12.3, 21.4)
Atezolizumab	13.7 (11.1, 16.7)	23.9 (12.8, NE)	2.7 (2.4, 2.9)	13.3 (11.3, 14.9)
Docetaxel	5.5 (1.1, 15.1)	Not reported	Not reported	7.5 (5.5, 12.8)

Therapy	Objective Response Rate % (95% CI)	Median Duration of Response Months (Range)	Median Progression-free Survival Months (95% CI)	Median Overall Survival Months (95% CI)
Ramucirumab plus docetaxel versus Placebo plus docetaxel	22.9 (19.7, 26.4) 13.6 (11.0, 16.5)	Not reported	4.5 (4.2, 5.4) 3.0 (2.8, 3.9)	10.5 (9.5, 11.2) 9.1 (8.4, 10.0)

CI = confidence interval; NE = not estimable; NSCLC = non-small cell lung cancer; TPS = tumor proportion score

Targeted Therapy (ADC) with Activity Against HER2 Mutations

T-DXd has been approved in the US on 11 Aug 2022 as a therapy for patients with previously treated HER2-mutant metastatic NSCLC. The use of T-DXd in metastatic HER2-mutant NSCLC is also recommended by NCCN. In addition, NCCN recommends the HER2-targeting ADC T-DM1 as a treatment option for patients with metastatic NSCLC and HER2 mutations based on a Phase 2 basket study.

SI.3.4. Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Patients with LC have a dismal prognosis with the highest mortality rate among all cancers. Surgical resection is an option in only one-third of patients with LC due to the late detection of the disease. The 5-year OS rate of treatment-naïve Stage IV NSCLC is only 6%.

According to Globocan data, LC caused approximately 1,796,144 deaths worldwide in 2020, with an age-adjusted mortality rate of 18.0 per 100,000.

LC is the most common cause of cancer death in the EU-27. The estimated number of deaths from LC in the EU was 257,293 in 2020. Overall, LC mortality rates in the EU declined in many countries. According to 2000 to 2007 data, 5-year survival of LC is highest in Austria, Germany, and Belgium and lowest in Bulgaria, Lithuania, and Denmark among EU countries.

Mutations in the gene-encoding HER2 (ERBB2) drive approximately 3% of nonsquamous NSCLCs and are associated with female sex, never-smoking history, and a poor prognosis, as well as with a slightly younger age and higher incidence of brain metastases than NSCLC without HER2 mutations or with other mutations.

Events That Occur Frequently in Patients with Lung Cancer

Events that occur frequently in patients with LC are described below. These include events associated with the disease or with therapies.

Dysgeusia with weight loss: Patients with LC commonly suffer from taste and smell alterations. Among patients with LC, 35% to 38% suffer from dysgeusia, and 53.4% of patients have significant weight loss.

Pneumonia: At baseline, 15.9% of patients with NSCLC present with pneumonia. During the course of LC, 50% to 70% of patients suffer from serious lung infections, including pneumonia.

Bone metastases: Bone is the most common site for metastasis in patients with LC. At diagnosis, 57.5% of patients with LC present with bone metastasis. Among patients with LC who had bone metastases, 57.7% developed skeletal related events, defined as bone pain requiring palliative

radiotherapy (71.4%), pathological fractures (16.3%), spinal cord compression (6%), and orthopaedic surgery (3.3%). Patients with LC have a median OS of 9.5 months after bone metastasis diagnosis.

Brain metastases (BM): An estimated 7.4% of patients with NSCLC present with BM at diagnosis, and 25% to 30% of patients develop BM during their illness. NSCLC patients with BM have a poor prognosis, with a median survival of 3.4 months.

Cough: Although cough is very common in LC, few robust data have been reported about its incidence in patients before treatment. In a single-institution cross-sectional study conducted in the UK, cough was reported by 57% of patients with LC.

Fatigue: In a study involving consecutive outpatients with Stage IV LC, fatigue was reported by 40% of patients. Fatigue can be caused by the disease, the treatment, or psychological distress. The prevalence of fatigue is 57% in surgically treated early-stage LC and 70% among LC survivors.

Hemoptysis: Hemoptysis is one of the most frequent clinical manifestations of LC. An estimated 10% to 30% of patients with LC in the US suffer from hemoptysis during their disease course. Massive hemoptysis can be found in 10% of these patients.

SI.3.5. Important Comorbidities

Most frequent comorbidities in patients with LC are usually smoking-related illnesses. This includes cardiovascular and respiratory diseases. Diabetes and its complications also share common risk factors with LC and frequently present in these patients.

A nationwide population-based cohort study of 10,378 patients with NSCLC of all ages in Denmark showed that 53% of patients have at least 1 comorbidity. NSCLC patients with comorbidities (hazard ratio: 1.12 for single disorder and 1.27 for multiple disorder) have overall higher mortality compared to patients without comorbidities. In Cox regression analysis, hazard ratio was significantly higher in patients with cardiovascular disorder (hazard ratio: 1.30, CI: 1.13, 1.49), chronic obstructive pulmonary disease (hazard ratio: 1.2, CI: 1.10, 1.31), diabetes (hazard ratio: 1.19, CI: 1.02, 1.39), and cerebrovascular disorders (hazard ratio 1.18, CI: 1.05, 1.33).

In a population-based cohort study from French cancer registries, 55% of the 1130 patients with NSCLC presented with at least 1 comorbidity. Chronic obstructive pulmonary disease, peripheral vascular disease, and congestive heart failure were the most frequent comorbidities. Even though observed and net survival rates decreased for Charlson Comorbidity Index Grade ≥ 3 for NSCLC, after adjustment for sex, age group, stage, and diagnostic mode, Charlson Comorbidity Index grades were no longer associated with lower survival rates.

In the US, a retrospective cohort study (N = 6662) in the LC population found 51% of patients had at least 1 comorbidity and 18% had at least 4 comorbidities at the time of cancer diagnosis. Chronic lung disease (43%), peripheral vascular disease (24%), renal disease (21%), diabetes with (15%) or without (9%) complications, prior cancer or metastatic carcinoma (15%), cerebrovascular disease (12%), myocardial infarction (11%), and heart failure (11%) were the most frequent comorbid conditions among the study population. Patients in comorbidity class 1 had significantly higher survival compared to the patients in other classes (2 to 5).

Some studies also suggest that the presence of comorbidity in patients with LC had led to a higher frequency of physician visits and was associated with early diagnosis of LC.

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety profile of T-DXd has been characterised using both in vitro and in vivo pharmacological, pharmacokinetic (PK), and toxicological studies in rats and monkeys.

Findings are discussed within the dose ranges specified in [Table Part II: Module SII.1](#).

Table Part II: Module SII.1: Human-Equivalent Doses of Trastuzumab Deruxtecan and Released Drug Studied in the Nonclinical Development Programme

Rats				Monkeys			
Trastuzumab Deruxtecan		Released Drug		Trastuzumab Deruxtecan		Released Drug	
Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)	Dose Studied (mg/kg)	HED (mg/kg)
20	3.2	3	0.48	3	0.96	1	0.32
60	9.7	10	1.6	10	3.2	3	0.97
197	31.8	30	4.8	30	9.7	12	3.9
-	-	-	-	78.8	25.4	-	-

FDA = Food and Drug Administration; HED = human equivalent dose

Conversion factors for rats and monkeys to estimate HED are per Appendix B Table 3 in the FDA Guidance for Industry

Information on key safety findings from the nonclinical studies with T-DXd and released drug (the drug component of T-DXd, a derivative of exatecan, a topoisomerase I inhibitor) and their relevance to human usage is presented in [Table Part II: Module SII.2](#).

**Table Part II: Module SII.2: Summary of Nonclinical Findings for
Trastuzumab Deruxtecan**

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
<u>Toxicity</u>	
Intestinal toxicity: <u>Trastuzumab deruxtecan:</u> In monkeys given 78.8 mg/kg of T-DXd (dosing once every 3 weeks [q3w] for 6 weeks), diarrhoea was noted. T-DXd -treated rats and monkeys had very slight single-cell necrosis of the crypt epithelium in the small and large intestines at low doses (rat: ≥ 20 mg/kg; monkey: ≥ 3 mg/kg). These changes showed reversibility after a recovery period in both rats and monkeys. <u>Released drug:</u> The intestinal toxicity caused by T-DXd also occurred in the 4-week intermittent dose study (once-weekly dosing) of the released drug in rats and monkeys (rat: ≥ 3 mg/kg; monkey: 12 mg/kg).	Nonclinical studies in rats and monkeys indicated a potential for GI effects, such as diarrhoea, with T-DXd and released drug. Several GI events are considered identified risks for T-DXd; however, these events can be adequately managed through labelling and are not considered important risks for inclusion in the RMP (Section SVII.3).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Lymphatic/haematopoietic toxicity: <u>Trastuzumab deruxtecan:</u> In the rat 6-week intermittent-dose (q3w dosing) toxicity study of T-DXd, a decrease in reticulocyte ratio at ≥ 20 mg/kg and decreases in white blood cell parameters (lymphocyte, eosinophil, basophil, and neutrophil counts) at ≥ 60 mg/kg were observed. The haematological changes in rats seemed to be associated with the following histopathological changes: decreased erythroblasts, single-cell necrosis of lymphocytes in the thymus, atrophy of follicles in the submandibular lymph nodes, and Peyer's patches at ≥ 60 mg/kg and decreased myelocytes in the bone marrow and atrophy in the thymus at 197 mg/kg. In the monkey 3-month intermittent dose (q3w dosing) toxicity study of T-DXd, a decrease in reticulocyte ratio associated with decreased erythroblasts in the bone marrow was observed at 30 mg/kg. At the higher dose of 78.8 mg/kg in the 6-week intermittent dose toxicity study, decreased peripheral erythroid parameters (erythrocytes, haemoglobin, haematocrit, and reticulocyte ratio) were also observed. <u>Released drug:</u> The lymphatic/hematopoietic organ toxicity observed with T-DXd also occurred in the 4-week intermittent dose (once-weekly dosing) study of the released drug in rats and monkeys (rat: ≥ 3 mg/kg; monkey: ≥ 1 mg/kg).	Haematological findings with T-DXd and released drug, including decreased haematopoietic cells (ie, red blood cells, white blood cells, and platelets) and reversible histopathological changes in lymphoid organs, were seen in nonclinical studies with rats and monkeys. Similarly, haematological laboratory abnormalities were observed in clinical studies. Anaemia, thrombocytopenia and neutropenia, including febrile neutropenia, are considered identified risks for T-DXd; however, they are not considered important risks for inclusion in the RMP as they can be managed through standard clinical practice (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Pulmonary toxicity: <u>Trastuzumab deruxtecan:</u> T-DXd caused pulmonary toxicity in monkeys at ≥ 30 mg/kg, and no pulmonary toxicity was observed in rats. In the 6-week monkey intermittent dose (q3w dosing, 3 animals/sex/group) toxicity study of T-DXd, 1 male given 78.8 mg/kg showed aggregation of foamy macrophages in the alveolus, focal interstitial inflammation, alveolar oedema, and anisokaryosis of the alveolar and bronchiolar epithelium at the end of the dosing period. Similar histopathological changes were found in 1 male and 2 females in the 78.8 mg/kg recovery group (2 animals/sex). In contrast, no changes in the lungs were noted in all monkeys in the 30 mg/kg group at the end of the dosing period (3 animals/sex), and very slight changes that were not accompanied by alveolar oedema were found in 1 of 4 monkeys at the end of the recovery period (2 animals/sex). The incidence and severity of the lesions were dose dependent. In the monkey 3-month study of T-DXd, similar lesions in the lungs were observed in the 30 mg/kg group (the highest dose) at the end of the dosing period. An extended dosing period did not increase the severity of lesions, and the pulmonary finding in monkeys observed at 30 mg/kg showed reversibility after the 3-month recovery period. <u>Released drug:</u> No pulmonary toxicity was observed in studies of the released drug in rats or monkeys.	Nonclinical studies in monkeys suggested T-DXd could potentially lead to pulmonary toxicity, with an associated dose dependency in incidence and severity. Events of dose-dependent ILD have been observed in clinical studies, with fatal outcomes reported. ILD/pneumonitis is considered an important identified risk for inclusion in this RMP (Section SVII.3).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Renal toxicity: <u>Trastuzumab deruxtecan:</u> In the rat 6-week study of T-DXd (q3w dosing), abnormalities in renal function were observed. Urinalysis revealed proteinuria at ≥ 60 mg/kg. Blood chemistry indicated increases in urea nitrogen, inorganic phosphorus, creatinine, and potassium and decreases in sodium and chloride at 197 mg/kg. Histopathological changes such as tubular basophilia and hyaline casts in the kidney were noted at ≥ 60 mg/kg. All findings in rats resolved after a 9-week recovery period. In the monkey 3-month study with T-DXd (q3w dosing), while anisokaryosis in the proximal tubules in the kidney was observed at 30 mg/kg at the end of dosing and the 3-month recovery periods, no findings suggestive of abnormalities in renal function were observed in urinalysis or blood chemistry. <u>Released drug:</u> No renal toxicity was observed in studies of the released drug in rats or monkeys.	Abnormal renal function was seen in rats but not in monkeys in nonclinical studies with T-DXd. Histopathological changes at only supratherapeutic doses of T-DXd were observed in both rats and monkeys. No renal toxicity was observed with the released drug. No safety concern with renal function from clinical studies with T-DXd has been identified. However, TEAEs of Blood creatinine increased were observed with a higher incidence (4.3% vs 1.1%) in the T-DXd arm than in the T-DM1 comparator arm in Study DS8201-A-U302 and, therefore, Blood creatinine increased is listed as an ADR in the SmPC. Based on the histopathological changes found in rats and monkeys as well as renal toxicity observed in rats, renal toxicity is a potential risk, but is not considered an important potential risk for inclusion in the RMP (Section SVII.1.1).
Skin toxicity: <u>Trastuzumab deruxtecan:</u> In the rat 6-week intermittent-dose (q3w dosing) toxicity study of T-DXd, trauma and/or crust at ≥ 20 mg/kg and sparse fur and/or loss of fur at 197 mg/kg were observed. In histopathological examinations, single-cell necrosis in the hair follicles, ulcer, crust, epidermal thickening, and/or fibrosis and inflammatory cell infiltration in the dermis were observed at ≥ 60 mg/kg. All the findings in the skin in rats resolved after a 9-week recovery period. In the monkey 3-month study with T-DXd (q3w dosing), single-cell necrosis in the hair follicles in the skin at ≥ 10 mg/kg and epidermal pigmentation at ≥ 30 mg/kg were noted. At the end of the 3-month recovery period, single-cell necrosis in the hair follicles resolved, whereas epidermal pigmentation persisted. <u>Released drug:</u> No skin toxicity was observed in studies of the released drug in rats or monkeys.	Nonclinical findings related to skin toxicity such as changes in the hair follicles and epidermis were seen in studies with rats and monkeys. The changes in the hair follicles seen in nonclinical studies may be associated with the alopecia observed in clinical studies. Rash (which includes rash, rash pustular and rash maculopapular) and hyperpigmentation are considered identified risks for T-DXd; however, they are not considered important risks for inclusion in the RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Hepatotoxicity: <u>Trastuzumab deruxtecan:</u> In the 6-week intermittent IV dose (q3w dosing) toxicity study of T-DXd in monkeys, transient increases in AST and ALT at ≥ 10 mg/kg were observed, while no histopathological findings were observed in the liver. In the 3-month monkey study (q3w dosing), elevations of enzymes (AST, lactate dehydrogenase, and creatine kinase) that did not accompany histopathological changes in the liver were observed in monkeys receiving 30 mg/kg T-DXd. These increases in the enzymes were not considered to be significant toxicological changes. <u>Released drug:</u> In the 4-week intermittent dose (once-weekly dosing) study of the released drug in monkeys, single-cell necrosis in hepatocytes accompanied by increases in AST and ALT were observed at the highest dose (12 mg/kg).	Nonclinical studies in monkeys suggested transient increases in ALT and AST without histopathological changes in the liver with T-DXd and released drug. Increases in ALT and AST have been observed in clinical studies, with no confirmed case of Hy's law. AST increased and ALT increased are considered identified risks for T-DXd but are not considered important for inclusion in this RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Cardiotoxicity: <u>Trastuzumab deruxtecan:</u> A 6-week or 3-month administration of T-DXd caused no histopathological changes in the heart in rats and monkeys. In the 6-week intermittent IV dose (q3w dosing; 3 animals/sex/group to 5 animals/sex/group) study of T-DXd in monkeys, ECG parameter changes (slight QTc prolongation; a change of approximately 14%) were found in 1 animal in the 78.8 mg/kg group (5 animals/sex). No abnormalities in ECG parameters, cardiac function tests (LVEF, etc), or cardiac troponin I levels were found in the 3-month intermittent dosing study in monkeys. In the safety pharmacology study, T-DXd had no effect on the cardiovascular parameters (blood pressure, heart rate, or ECG) at doses of up to 78.8 mg/kg when a single IV dose was administered to male monkeys. <u>Released drug:</u> In the 4-week intermittent-dose (once-weekly dosing) study of the released drug in rats and monkeys, myocardial cell degeneration/necrosis was observed in a moribund cynomolgus monkey at a dose level of 12 mg/kg. In hERG studies, the released drug did not show inhibition of the hERG channel current.	Nonclinical studies suggested a potential effect on QT interval with T-DXd and released drug. QT was routinely monitored through ECG in clinical studies with T-DXd. A study to evaluate the effect of T-DXd 6.4 mg/kg on QTc confirmed no clinically meaningful impact on the QTc interval. Therefore, QT prolongation is not considered a risk for inclusion in this RMP.
Ocular toxicity: <u>Trastuzumab deruxtecan:</u> In the intermittent IV dosing studies of T-DXd (q3w dosing for 6 weeks or 3 months), ocular toxicity was not found at doses up to the highest dose (78.8 mg/kg in cynomolgus monkeys, 197 mg/kg in rats). <u>Released drug:</u> In the 4-week intermittent-dose (once-weekly dosing) study of the released drug in rats and monkeys, single-cell necrosis in the corneal epithelium was seen at ≥ 3 mg/kg in rats and at 12 mg/kg in monkeys. The finding resolved after the 4-week recovery period.	Nonclinical studies suggested a potential for adverse corneal effects with only the released drug. Vision blurred is an identified risk for T-DXd but is not considered an important risk. Keratitis is a potential risk for T-DXd but is not considered an important risk for inclusion in this RMP (Section SVII.1.1).

Table Part II: Module SII.2: Summary of Nonclinical Findings for Trastuzumab Deruxtecan (Continued)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Reproductive/developmental toxicity and genotoxicity: Since embryo-foetal developmental toxicity studies are not warranted for drugs that are genotoxic and target rapidly dividing cells, embryo-foetal developmental toxicity studies were not conducted in accordance with the ICH S9. <u>Trastuzumab deruxtecan:</u> In the 6-week intermittent-dose study of T-DXd in rats, small-sized testes and epididymides that accompanied reduced organ weights were observed at 197 mg/kg. Histopathological findings in rats included spermatid retention at 20 mg/kg and 60 mg/kg, and tubular degeneration/atrophy in the testes accompanying secondary changes of luminal cell debris and reduced sperm in the epididymis at 197 mg/kg. The changes produced at 197 mg/kg did not recover by the end of the 9-week recovery period. In the 6-week and 3-month intermittent-dose studies of T-DXd in cynomolgus monkeys, decreased numbers of round spermatids in the Stage V to VI seminiferous tubule in the testes was observed at ≥ 30 mg/kg. These changes in the testes of monkeys showed reversibility. <u>Released drug:</u> There was no testicular toxicity in studies in rats and monkeys with the released drug. In vitro genotoxicity studies of the released drug indicated that this drug had no potential to induce gene mutation in bacteria but had the potential to induce structural chromosome aberrations in mammalian cultured cells. An in vivo micronucleus study in bone marrow of rats indicated that the released drug had the potential to induce micronuclei.	Reproductive studies in rats and monkeys indicate changes to the reproductive organs of males. Postmarketing AE reports for trastuzumab showed that treatment during pregnancy has resulted in oligohydramnios, manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. DXd, the released drug was genotoxic in an in vitro chromosome aberration study with mammalian cultured cells and an in vivo micronucleus study in rats. The characteristics of trastuzumab and released drug indicate that T-DXd can potentially cause foetal harm when administered to a pregnant woman. Embryo-foetal toxicity is considered an important potential risk for inclusion in this RMP (Section SVII.1.2). Testicular toxicity is a potential risk based on the findings in animal studies, however it is not considered an important potential risk for inclusion in the RMP (Section SVII.1.1).
Carcinogenicity: No carcinogenicity studies have been conducted in accordance with ICH S9.	T-DXd is being studied for the treatment of cancer.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GI = gastrointestinal; hERG = human ether-à-go-go-related gene; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; q3w = every 3 weeks; QTc = corrected QT interval; RMP = Risk Management Plan; T-DXd = trastuzumab deruxtecan

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The exposure data presented in this Risk Management Plan (RMP) focus exclusively on subjects in Daiichi Sankyo-sponsored studies and do not include subjects in investigator-sponsored studies.

Cumulatively, 2145 subjects were exposed to ≥ 5.4 mg/kg T-DXd in the following 9 pooled studies (Studies DS8201-A-J101, DS8201-A-U201, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303). An outline of these 9 studies in terms of design, exposure, and data cut-off dates is provided below (Module 5.3.5.3 SCS [SAP Version 2.0](#)):

- Study DS8201-A-J101, hereafter referred to as Study J101, was a Phase 1, 2-part, multicentre, nonrandomised, open-label, multiple-dose first-in-human study in subjects with advanced solid malignant tumours (280 treated subjects; data cut-off date: 01 Aug 2019).
- Study DS8201-A-U201, hereafter referred to as Study U201, was a Phase 2, multicentre, open-label study in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1 (253 subjects treated; data cut-off date: 08 Jun 2020).
- Study DS8201-A-J202, hereafter referred to as Study J202, was a Phase 2, multicentre, open-label study in subjects with HER2-expressing advanced gastric or GEJ adenocarcinoma (169 subjects treated; data cut-off date: 03 Jun 2020).
- Study DS8201-A-U204, hereafter referred to as Study U204, was a Phase 2, multicentre, open-label, 2-cohort study for HER2-overexpressing or HER2-mutated, unresectable and/or metastatic NSCLC (181 subjects treated; data cut-off date: 03 Dec 2021).
- Study DS8201-A-U205, hereafter referred to as Study U205, was a Phase 2, open-label, single-arm study in HER2-positive, unresectable or metastatic gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen (79 subjects treated; data cut-off date: 08 Nov 2021).
- Study DS8201-A-U206, hereafter referred to as Study U206, is a Phase 2, multicentre, randomised, 2-arm study in HER2-mutant NSCLC subjects who had disease recurrence or progression during/after at least 1 regimen of prior anticancer therapy (second-line or later) that must have contained a platinum-based chemotherapy drug in the metastatic/locally advanced setting (151 subjects, of whom 101 were treated with 5.4 mg/kg T-DXd and 50 were treated with 6.4 mg/kg T-DXd; interim analysis data cut-off date: 24 Mar 2022).
- Study DS8201-A-U301, hereafter referred to as Study U301, was a Phase 3, multicenter, open-label, active-controlled study for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1 (608 subjects, of whom 404 subjects were treated with 5.4 mg/kg T-DXd; data-cut-off date: 30 Jun 2022).

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- Study DS8201-A-U302, hereafter referred to as Study U302, was a Phase 3, multicentre, open-label, active-controlled study in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab and taxane (518 subjects, of whom 257 were treated with T-DXd; data cut-off date: 25 Jul 2022).
- Study DS8201-A-U303, hereafter referred to as Study U303, was a Phase 3, multicentre, open-label, active-controlled study for HER2-low, unresectable and/or metastatic breast cancer subjects (543 subjects, of whom 371 subjects were treated with T-DXd; data cut-off date: 11 Apr 2022).

The median duration of exposure among subjects within these 9 studies split into 5 pools (ie, 5.4 mg/kg [BC]; 5.4 mg/kg [NSCLC]; 5.4 mg/kg [ATT]; 6.4 mg/kg [GC]; 6.4 mg/kg [ATT]) is presented in [Table Part II: Module SIII.1](#).

For the purpose of this RMP, the overall pool of 2145 subjects treated with ≥ 5.4 mg/kg in the variety of tumour types (ie, the All Tumour Types [ATT] ≥ 5.4 mg/kg Pool) is referred to as “ATT ≥ 5.4 mg/kg Pool”. The number of subjects split by age group and sex across the 5 pools is presented in [Table Part II: Module SIII.2](#) and [Table Part II: Module SIII.3](#), while the number of subjects split by ethnic origin, race, and geographic distribution is presented in [Table Part II: Module SIII.4](#).

Table Part II: Module SIII.1: Duration of Exposure to Trastuzumab Deruxtecan (Safety Analysis Set)

Duration of Exposure (months) ^a	Number (%) of Subjects in Pool				
	BC 5.4 mg/kg (N = 1287)	HER2-mut NSCLC 5.4 mg/kg (N=101)	5.4 mg/kg All Tumour Types (N = 1449)	HER2-pos GC 6.4 mg/kg (N = 229)	6.4 mg/kg All Tumour Types (N = 669)
0 to ≤3	161 (12.5)	39 (38.6)	225 (15.5)	81 (35.4)	203 (30.3)
>3 to ≤6	196 (15.2)	43 (42.6)	252 (17.4)	64 (27.9)	165 (24.7)
>6 to ≤9	204 (15.9)	12 (11.9)	225 (15.5)	39 (17.0)	111 (16.6)
>9 to ≤12	149 (11.6)	7 (6.9)	162 (11.2)	16 (7.0)	50 (7.5)
>12 to ≤18	188 (14.6)	0	195 (13.5)	23 (10.0)	75 (11.2)
>18 to ≤24	192 (14.9)	0	192 (13.3)	3 (1.3)	32 (4.8)
>24	197 (15.3)	0	198 (13.7)	3 (1.3)	33 (4.9)
Median duration of exposure (months)	10.48	3.71	9.59	4.60	5.52
Total patient-years ^b	1426.0	35.24	1493.9	115.1	431.78

BC = breast cancer; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; mut = mutant; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer;.

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

BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, and DS8201-A-J101.

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206.

All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.

HER2-Positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, and DS8201-A-U206.

^a Duration of treatment (months) = (date of the last dose – date of the first dose + 21)/30.44.

^b Patient-years of exposure = sum (duration of exposure [months])/12.

Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205, 25 Jul 2022 for Study U302, 11 Jan 2022 for Study U303, and 30 Jun 2022 for U301.

Source: Module 5.3.5.3 SCS [Table 14.1.3.1 \(NSCLC\)](#), Module 5.3.5.3 SCS [Table 1.1.3 \(GC\)](#), Module 5.3.5.3 SCS [Table 1.1.3 \(U301\)](#).

Table Part II: Module SIII.2: Age Group and Sex of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Age Group ^a	All Tumour Types 5.4 mg/kg (N = 1449)				BC 5.4 mg/kg (N = 1287)				HER2 mut NSCLC 5.4 mg/kg (N = 101)			
	Number (%) of Subjects		Patient-Years of Exposure ^b		Number (%) of Subjects		Patient-years of Exposure ^b		Number (%) of Subjects		Patient-years of Exposure ^b	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<65 years	47 (3.2)	1052 (72.6)	19.6	1147.9	5 (0.4)	1000 (77.7)	4.1	1127.2	23 (22.8)	38 (37.6)	7.5	13.3
65-74 years	24 (1.7)	263 (18.2)	11.5	261.6	2 (0.2)	231 (17.9)	2.2	248.1	9 (8.9)	23 (22.8)	3.3	8.9
75-85 years	6 (0.4)	51 (3.5)	2.3	48.3	0	43 (3.3)	0	41.7	4 (4.0)	4 (4.0)	1.4	0.9
≥85 years	0	6 (0.4)	0	2.8	0	6 (0.5)	0	2.8	0	0	0.0	0.0

BC = breast cancer; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer..

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

BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, and DS8201-A-J101.

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206

All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.

^a Age in years was calculated by using the informed consent date and the birth date.

^b Patient-years = sum (duration of exposure [months])/12.

Data cut-off dates: 01 Aug 2019 for Study J101, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 25 Jul 2022 for Study U302, 11 Jan 2022 for U303, and 30 Jun 2022 for U301.

Source: Module 5.3.5.3 EU RMP [Table 2](#) and [Table 3 \(U301\)](#), Module 5.3.5.3 EU RMP [Table 3 \(NSCLC\)](#).

Table Part II: Module SIII.3: Age Group and Sex of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Age Group ^a	HER2-positive GC 6.4 mg/kg (N = 229)				All Tumour Types 6.4 mg/kg (N = 669)			
	Number (%) of Subjects		Patient-Years of Exposure ^b		Number (%) of Subjects		Patient-Years of Exposure ^b	
	Male	Female	Male	Female	Male	Female	Male	Female
<65 years	88 (38.4)	21 (9.2)	42.3	11.1	175 (26.2)	232 (34.7)	97.7	186.1
65-74 years	67 (29.3)	29 (12.7)	36.3	11.2	111 (16.6)	100 (14.9)	53.5	67.2
75-84 years	17 (7.4)	7 (3.1)	11.7	2.5	24 (3.6)	24 (3.6)	13.8	11.7
≥85 years	0	0	0	0	1 (0.1)	2 (0.3)	1.0	0.7

GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool;

T-DXd = trastuzumab deruxtecan.

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

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205

All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, and DS8201-A-U205.

^a Age in years was calculated by using the informed consent date and the birth date.

^b Patient-years = sum (duration of exposure [months])/12.

Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205.

Source : Module 5.3.5.3 EU RMP [Table 4 \(NSCLC\)](#), Module 5.3.5.3 EU RMP [Table 3 \(2L BC\)](#).

Table Part II: Module SIII.4: Ethnic Origin, Race, and Geographical Distribution of Subjects Receiving Trastuzumab Deruxtecan (Safety Analysis Set)

Parameter	Number (%) of Subjects				
	BC 5.4 mg/kg (N = 1287)	HER2-mut NSCLC T-DXd 5.4 mg/kg (N=101)	All Tumour Types 5.4 mg/kg (N = 1449)	HER2-positive GC 6.4 mg/kg (N = 229)	All Tumour Types 6.4 mg/kg (N = 669)
Ethnicity^a – n (%)					
Hispanic/Latino	107 (8.3)	1 (1.0)	109 (7.5)	5 (2.2)	19 (2.8)
Not Hispanic/Non-Latino	1023 (79.5)	88 (87.1)	1152 (79.5)	70 (30.6)	316 (47.2)
Unknown	21 (1.6)	12 (11.9)	33 (2.3)	4 (1.7)	306 (45.7)
Not applicable ^b	109 (8.5)	-	109 (7.5)	0	28 (4.2)
Not reported	0	-	4 (0.3)	0	-
Missing	27 (2.1)	-	42 (2.9)	150 (65.5)	-
Race					
White	633 (49.2)	23 (22.8)	692 (47.8)	69 (30.1)	212 (31.7)
Black or African American	34 (2.6)	-	36 (2.5)	1 (0.4)	-
Asian	525 (40.8)	64 (63.4)	607 (41.9)	154 (67.2)	401 (59.9)
American Indian or Alaska Native	4 (0.3)	-	5 (0.3)	0	-
Native Hawaiian or Other Pacific Islander	2 (0.2)	-	2 (0.1)	1 (0.4)	-
Multiple	2 (0.2)	-	2 (0.1)	0	0
Other	83 (6.4)	14 (13.9)	101 (7.0)	3 (1.3)	54 (8.1)
Missing	4 (0.3)	-	4 (0.3)	1 (0.4)	2 (0.3)
Region^c					
Asia	494 (38.4)	62 (61.4)	-	150 (65.5)	381 (57.0)
North America	214 (16.6)	4 (4.0)	-	34 (14.8)	162 (24.2)
Europe	425 (33.0)	33 (32.7)	299 (31.7) ^d	45 (19.7)	125 (18.7) ^d
Rest of World	154 (12.0)	2 (2.0)	-	0	1 (0.1)
Country of Origin					
US	-	-	186 (19.7)	34 (14.8)	-
Japan	193 (15.0)	37 (36.6)	166 (17.6)	124 (54.1)	324 (48.4)

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Parameter	Number (%) of Subjects				
	BC 5.4 mg/kg (N = 1287)	HER2-mut NSCLC T-DXd 5.4 mg/kg (N=101)	All Tumour Types 5.4 mg/kg (N = 1449)	HER2-positive GC 6.4 mg/kg (N = 229)	All Tumour Types 6.4 mg/kg (N = 669)
Not Japan	1094 (85.0)	64 (63.4)	-	-	345 (51.6)
Korea	-	-	107 (11.3)	26 (11.4)	-

BC = breast cancer; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool;

NSCLC = non-small cell lung cancer; US = United States

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

BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U201, and DS8201-A-J101.

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206

All Tumour Types 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-U302, DS8201-A-U301, DS8201-A-U201, DS8201-A-J101, DS8201-A-U204, and DS8201-A-U206.

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, and DS8201-A-U205.

All Tumour Types 6.4 mg/kg Pooled Data: Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J202, DS8201-A-U204, DS8201-A-U205, and DS8201-A-U206.

^a Ethnicity was not required to be collected in all countries.

^b Subjects of Japanese origin in Study DS8201-A-J101 were instructed to respond with “Not Applicable” upon enrolment. This option was removed for later studies.

^c Regional and country of origin information is collected differently for each data pool. Therefore, data are not available for all categories in each data pool.

^d Subjects were enrolled from Austria, Belgium, France, Greece, Hungary, Italy, Portugal, Russia, Spain, Sweden, Switzerland, the United Kingdom, and the Netherlands.

Data cut-off dates: 01 Aug 2019 for Study J101, 03 Jun 2020 for Study J202, 08 Jun 2020 for Study U201, 03 Dec 2021 for Study U204, 08 Nov 2021 for Study U205, 25 Jul 2022 for Study U302, and 11 Jan 2022 for Study U303.

Source : Module 5.3.5.3 EU RMP [Table 14.1.2.1 \(NSCLC\)](#), Module 5.3.5.3 EU RMP [Table 4 \(2L BC\)](#), Module 5.3.5.3 SCS [Table 1.1.2 \(U301\)](#).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The following were key exclusion criteria from the 9 pooled studies in the ATT ≥ 5.4 mg/kg Pool:

Age less than the years of maturity (eg, <18 years in the US and EU, <20 years in Japan and Korea)

Reason for exclusion:

Conditions under study are rare in paediatric patients and therefore not relevant to study.

Is it considered to be included as missing information?

No

Rationale:

These patients are not relevant for the current proposed indications.

Eastern Cooperative Oncology Group performance status ≥ 2

Reason for exclusion:

Cancer patients with poor performance status are excluded before safety and efficacy of a product are confirmed in patients with good PS. The inclusion criterion was limited to Eastern Cooperative Oncology Group PS 0 or 1 in order to monitor whether the drug has a negative effect on PS.

Is it considered to be included as missing information?

No

Rationale:

There is no evidence to suggest that the safety profile in these patients is different from that of the population intended for treatment.

Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection

Reason for exclusion:

To maximise subject safety during the conduct of these studies, subjects with known HIV or active Hepatitis B or C infection were excluded from participation in the clinical programme because of the potential for drug-drug interactions with concomitant medications.

Is it considered to be included as missing information?

No

Rationale:

There was no clinically meaningful drug-drug interaction with ritonavir or itraconazole in Study DS8201-A-A104 in subjects with HER2-expressing advanced solid malignant tumours (ie, minimal increase in exposure and no change in the safety profile). No differences are expected between subjects with HER2+ and HER2-low BC with respect to drug-drug interactions. No additional safety concerns are anticipated if the product is used in these patient populations. Therefore, the use of T-DXd in patients with pre-existing HIV or active Hepatitis B/C is not considered missing information.

Pre-existing severe renal impairment (creatinine clearance [CrCL] <30 mL/min)

Reason for exclusion:

Subjects with severe renal impairment were excluded from participation in the clinical programme before the safety profile was established in subjects without severe renal impairment. One subject in Study J101 and 1 subject in Study U204 met the CrCL criteria for severe renal impairment on the first day of the first cycle prior to dosing; however, the subject was enrolled meeting the CrCL criteria for moderate renal impairment at screening. Another subject in Study U204 was enrolled meeting the CrCL criteria for severe renal impairment at screening and CrCL values remained on the same level over the course of 20 cycles of treatment. In Study U303, 1 subject meeting the CrCL criteria for severe renal impairment was enrolled at screening and discontinued study drug after the first cycle because of worsening hepatic failure while severe renal impairment persisted.

Is it considered to be included as missing information?

No

Rationale:

The major excretion pathway of T-DXd, as observed in a rat study, was primarily through faeces via the biliary route with minimal renal excretion. In addition, based on the population PK analysis for mild and moderate renal impairment and data from nonclinical studies, a different safety profile is not expected in patients with severe renal impairment.

Pre-existing moderate hepatic impairment

Reason for exclusion:

A potential effect of impaired hepatic function on T-DXd elimination and exposure is possible. The inclusion criteria related to hepatic impairment were not identical among the 9 studies but allowed for inclusion of subjects with baseline moderate hepatic impairment.

Is it considered to be included as missing information?

No

Rationale:

Further data for PK and safety were collected in 12 subjects with moderate hepatic impairment at baseline from clinical studies across different indications including both doses of 5.4 and 6.4 mg/kg. Data in these 12 subjects did not reveal a significant difference in PK and safety in comparison to subjects with normal hepatic function at baseline.

Pre-existing severe hepatic impairment (defined as total bilirubin $>3.0 \times$ upper limit of normal [ULN] and any AST regardless of Gilbert Syndrome)

Reason for exclusion:

A potential effect of impaired hepatic function on T-DXd elimination and exposure is possible. This patient population was excluded before safety and efficacy data were established in patients without severe hepatic impairment.

Is it considered to be included as missing information?

Yes

History of myocardial infarction (MI), recent troponin levels consistent with MI, or recent unstable angina

Reason for exclusion:

Cardiotoxicity has been observed with anti-HER2 drugs, including trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys has shown myocardial cell degeneration/necrosis at supratherapeutic doses (not tested in humans) with the released drug of T-DXd.

Is it considered to be included as missing information?

No

Rationale:

Clinical data do not support an association between T-DXd and cardiotoxicity manifesting as ischemic cardiac events such as MI. This lack of cardiac liability suggests that the safety profile in this population would not be different from that of the indicated population and it is, therefore, not relevant for inclusion as missing information.

Left ventricular ejection fraction $<50\%$ or recent symptomatic congestive heart failure

Reason for exclusion:

Cardiotoxicity has been observed with anti-HER2 drugs, including trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys with T-DXd did not show an abnormality in cardiac function tests (including LVEF).

Is it considered to be included as missing information?

No

Rationale:

Left ventricular dysfunction is an important identified risk for T-DXd as described in SmPC Section 4.4 and 4.8. Additional information on this risk is included in Section [SVII.3](#).

QTcF >470 msec (female) or >450 msec (male) or recent serious cardiac arrhythmia requiring treatment

Reason for exclusion:

A nonclinical study in monkeys has shown a slight corrected QT interval using Fridericia's formula (QTcF) prolongation at supratherapeutic doses of T-DXd (not tested in humans).

Is it considered to be included as missing information?

No

Rationale:

No clinically meaningful association between QT prolongation and the use of T-DXd was observed in a study to evaluate QT effects (Study DS8201-A-J102). This result is consistent with the clinical data from the 9 completed studies. As there is no signal of QT liability with T-DXd, there is no evidence to suggest the safety profile in this population is different from that of the general target population.

History of Interstitial Lung Disease (ILD) requiring steroid treatment or active or suspected ILD

Reason for exclusion:

Nonclinical studies in monkeys have shown changes in the lung, such as focal interstitial inflammation and alveolar oedema, at supratherapeutic doses of T-DXd (not tested in humans). Patients with a history of ILD may be at an increased risk of recurrence and, therefore, may be associated with worse outcomes. In order to minimise the potential risk to patients in the clinical programme, these patients were excluded.

Is it considered to be included as missing information?

No

Rationale:

ILD/pneumonitis is an important identified risk for T-DXd and is described in SmPC Section 4.2, SmPC Section 4.4 and SmPC Section 4.8. Additional information on this risk is included in Section [SVII.3](#).

Use of OATP1B inhibitors or strong CYP3A4 inhibitors

Reason for exclusion:

In an in vitro study, cytochrome P450 (CYP)3A4 was identified as the primary CYP enzyme in the metabolism of the released drug of T-DXd. The released drug is also a substrate for organic anion transporting polypeptide (OATP)1B.

Is it considered to be included as missing information?

No

Rationale:

Based on a drug-drug interaction study (Study DS8201-A-A104), concomitant use of OATP1B inhibitors or strong CYP3A4 inhibitors with T-DXd resulted in a small increase in area under the curve that was not considered to be clinically meaningful.

Clinically significant corneal disease (Study U201 only)

Reason for exclusion:

In a nonclinical study of the released drug of T-DXd, single-cell necrosis in the corneal epithelium was observed in rats and monkeys at supratherapeutic doses (not tested in humans).

Is it considered to be included as missing information?

No

Rationale:

Corneal events observed in clinical studies with T-DXd were primarily keratitis. The majority of keratitis events in the All Tumour Types ≥ 5.4 mg/kg Pool were Grade 1 or Grade 2 in severity; 2 (0.1%) of the subjects experienced Grade 3 keratitis and 1 (0.1%) of the subjects experienced Grade 3 ulcerative keratitis. Dose reduction was required in 1 (0.1%) subject who had Grade 3 keratitis. None of the events was associated with drug discontinuation, and all events could be managed through standard clinical practice. Keratitis is classified as a potential risk for T-DXd; however, it is not considered important. There is no evidence to suggest that the safety profile in subjects with corneal disease would differ from that of the general indicated population and it is therefore not relevant for inclusion as missing information.

Pregnant or lactating women and women and men of reproductive/childbearing potential who do not use a highly effective form of contraception or abstinence

Reason for exclusion:

Trastuzumab, a HER2 receptor antagonist, has postmarketing case reports of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death during pregnancy. Additionally, based on nonclinical findings from reproductive/developmental and genotoxicity studies of T-DXd in rats and monkeys and its mechanism of action as a topoisomerase I inhibitor, the released drug of T-DXd may cause embryo-foetal harm when administered to a pregnant woman (SmPC Section 4.4 and SmPC Section 4.6).

Is it considered to be included as missing information?

No

Rationale:

Embryo-foetal toxicity is considered an important potential risk and testicular toxicity is considered a potential risk for T-DXd. Additional information on the risk of embryo-foetal toxicity is included in Section [SVII.3](#).

SmPC Section 4.6 advises that women of childbearing potential and men with female partners of childbearing potential should use effective contraception during and after treatment and that women should discontinue breastfeeding prior to initiating treatment. Exposure in these

populations is therefore not expected, and so they are not relevant for inclusion as missing information.

Clinically active brain metastases (symptomatic and untreated or requiring treatment)

Reason for exclusion:

This population was excluded from the T-DXd clinical development programme based on concerns of poor functional status and shortened life expectancy.

Is it considered to be included as missing information?

No

Rationale:

This population was excluded to avoid factors that may confound understanding of the safety profile and efficacy of T-DXd and to ensure appropriate interpretation of the safety data. There is no evidence to suggest that the safety profile in this population would be different from that of the general indicated population and it is therefore not relevant for inclusion as missing information.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme for T-DXd is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

With 2145 subjects in the ATT ≥ 5.4 mg/kg Pool, there is at least a 99.9% chance of observing Aes with a true incidence rate of 1% or higher.

SIV.3 Limitations in Respect to Populations Typically Under-represented in the Clinical Trial Development Programme

The number of subjects with a variety of tumour types that were exposed to T-DXd doses of 5.4 mg/kg and higher is presented in [Table Part II: Module SIV.3.1](#).

Table Part II: Module SIV.3.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programme (Safety Analysis Set)

Type of Special Population	Number of Subjects in Pool			
	BC 5.4 mg/kg Pool (N = 1287)	HER2-positive GC 6.4 mg/kg Pool (N = 229)	All Tumour Types ≥5.4 mg/kg Pool (N = 2145)	HER2 mut NSCLC 5.4 mg/kg Pool (N = 101)
Pregnant or breastfeeding women	Not included in the clinical development programme			
Paediatric	Not included in the clinical development programme ^a			
Elderly				
≥65 years	282 (21.9)	120 (52.4)	621 (29.0)	40 (39.6)
≥75 years	49 (3.8)	24 (10.5)	114 (5.3)	8 (7.9)
≥85 years	6 (0.5)	0	9 (0.4)	0
Subjects with relevant comorbidities (baseline)				
Subjects with renal impairment (all grades)				
Severe impairment (creatinine clearance ≥15, <30 mL/min)	2 (0.2)	0	4 (0.2) ^b	0
Moderate impairment (creatinine clearance ≥30, <60 mL/min)	136 (10.6)	56 (24.5)	306 (14.3)	22 (21.8)
Mild impairment (creatinine clearance ≥60, <90 mL/min)	448 (34.8)	91 (39.7)	795 (37.1)	40 (39.6)
Subjects with hepatic impairment (all grades) ^c				
Severe impairment	0	0	0	0
Moderate impairment	7 (0.5)	1 (0.4)	8 (0.4)	0
Mild impairment	561 (43.6)	57 (24.9)	788 (36.7)	25 (24.8)
Subjects with cardiovascular impairment	Subjects with LVEF <50% or recent symptomatic CHF were excluded from the clinical development programme			

AST = aspartate aminotransferase; BC = breast cancer; CHF = congestive heart failure; EMA = European Medicines Agency; GC = gastro/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; N = total number of subjects in the pool; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; TBL = total bilirubin; ULN = upper limit of normal

All Tumour Types ≥5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U301, and DS8201-A-U302

HER2-mut NSCLC 5.4 mg/kg Data: Study DS8201-A-U206

BC T-DXd 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-U201, and DS8201-A-U302

HER2-positive GC 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U205, and DS8201-A-U206.

^a EMA has waived the obligation to conduct clinical studies in the paediatric population for the intended indication.

^b For details on subjects with severe renal impairment please refer to Section [SIV.1](#).

^c Hepatic impairment: Severe impairment = TBL >3.0 × ULN and any AST regardless of Gilbert Syndrome; Moderate impairment = (TBL >1.5 × ULN and ≤3.0 × ULN) and any AST regardless of Gilbert Syndrome; Mild impairment = (TBL >ULN and ≤1.5 × ULN) and any AST except for subjects with Gilbert Syndrome; (TBL >ULN and ≤3.0 × ULN) and AST >ULN for subjects with Gilbert Syndrome; or (TBL ≤ULN and AST >ULN) regardless of Gilbert Syndrome.

Sources : Module 5.3.5.3 EU RMP [Table 4](#) (U301), Module 5.3.5.3 SCS [Table 14.1.2 .1](#) (NSCLC), Module 5.3.5.3 SCS [Table 1.1.2](#) (GC).

PART II: MODULE SV POSTAUTHORISATION EXPERIENCE

SV.1 Postauthorisation Exposure

T-DXd was approved for marketing in the US on 20 Dec 2019; it was first made available to patients on 31 Dec 2019. It was also approved by the Japan Ministry of Health, Labor, and Welfare (MHLW) on 25 Mar 2020 and since 18 Jan 2021 in the EU. Furthermore, T-DXd is also approved in over 40 countries.

SV.1.1 Method Used to Calculate Exposure

The postmarketing patient exposure in patient-years was estimated by (a) counting numbers of vials sold by MAH warehouses (b) further assuming average adult bodyweight in the approved country (eg. 4.3 vials are used in 1 infusion in US, 3.4 vials per infusion in Japan), and (c) multiplying the number of infusions by 21 days, divided by 365 days/year, to account for the administration of an infusion once every 3 weeks (21-day cycle).

SV.1.2 Exposure

Cumulatively, since the first approval of T-DXd on 20 Dec 2019 through 19 Dec 2022, there were [REDACTED] vials of T-DXd sold from MAH warehouses worldwide. Based on the average body weight of adults in the countries where the product is marketed, it is estimated that [REDACTED] infusions were administered. Considering that an infusion of T-DXd is administered once every 3 weeks (21-day cycle) and 17.3 cycles per year, the estimated cumulative patient exposure through 19 Dec 2022 was 17,108.3 patient-years.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for transmission of infectious agents

The risk of transmission of infectious agents by this product is considered negligible based on product design, manufacturing process, facility design and controls, and current testing programmes. European Pharmacopoeia standards have been met.

Potential for misuse for illegal purposes

T-DXd does not contain any substances that have the potential for misuse for illegal purposes.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

The safety concerns presented are supported by pooled data of the 9 completed studies.

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.1.1 Identified Risks

Adverse reactions with clinical consequences, even serious, but considered to be acceptable in relation to the severity of the treated indication include the following: gastrointestinal (GI) adverse drug reactions (ADRs), rash, alopecia, cough, dizziness, dry eye, dyspnoea, epistaxis, fatigue, headache, infusion-related reaction, upper respiratory tract infection, AST increased, ALT increased, hypokalaemia, anaemia, thrombocytopenia, leukopenia, lymphopenia, and neutropenia including febrile neutropenia (see individual descriptions below). All these events are recognized ADRs for T-DXd and are included in SmPC Section 4.8.

Identified Risk: Gastrointestinal ADRs

Preferred terms in the identified risk of gastrointestinal ADRs were reported at the following frequencies in the HER2-positive BC 5.4 mg/kg Pool: nausea (187 [79.9%] subjects), vomiting (114 [48.7%]), constipation (84 [35.9%]), decreased appetite (81 [34.6%]), diarrhoea (72 [30.8%]), abdominal pain (46 [19.7%]), stomatitis (35 [15.0%]), and dyspepsia (33 [14.1%]). The highest frequency of drug interruption and dose reduction due to a GI event was from nausea: 4 (1.7%) subjects and 8 (3.4%) subjects, respectively. Only 1 subject had a GI event (diarrhoea) that led to drug discontinuation. Although frequent, GI events were generally nonserious and generally Grade 1 to 2 in severity.

Identified Risk: Rash

Events of rash (grouped term that includes preferred terms [PTs] of rash, rash pustular, and rash maculo-papular) were reported in 30 (12.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of rash were all nonserious and generally Grade 1 in severity, leading to drug interruption in 1 subject and to no dose reduction or drug discontinuation.

Identified Risk: Alopecia

Events of alopecia were reported in 108 (46.2%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of alopecia were nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Cough

Events of cough were reported in 50 (21.4%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of cough were nonserious and generally Grade 1 in severity, leading to drug interruption in 1 (0.4%) subject and to discontinuation of study drug in 1 (0.4%) subject, with no dose reductions.

Identified Risk: Dizziness

Events of dizziness were reported in 25 (10.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dizziness were nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Dry Eye

Events of dry eye were reported in 27 (11.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dry eye were generally nonserious and Grade 1 in severity, except in 1 subject who had a Grade 4 event that improved to Grade 1 without requiring intervention and did not recur. No event of dry eye led to drug interruption, dose reduction, or drug discontinuation.

Identified Risk: Dyspnoea

Events of dyspnoea were reported in 34 (14.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of dyspnoea were generally nonserious (1 subject had dyspnoea reported as a serious AE (SAE) and generally Grade 1 to 2 in severity, leading to no dose reduction, to drug interruption in 2 (0.9%) subjects (both with dyspnoea) and to drug discontinuation in 1 subject who had drug discontinued due to concurrent dyspnoea and pneumonitis.

Identified Risk: Epistaxis

Events of epistaxis were reported in 33 (14.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of epistaxis were all nonserious and generally Grade 1 in severity, with no drug interruption, dose reduction or drug discontinuation.

Identified Risk: Fatigue

Events of fatigue (grouped term that includes PTs of fatigue and asthenia) were reported in 141 (60.3%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, all events of fatigue were nonserious and generally Grade 1 to 2 in severity. Dose was reduced in 9 (3.8%) subjects and drug was interrupted in 5 (2.1%) subjects. No events of fatigue led to drug discontinuation.

Identified Risk: Headache

Events of headache (grouped term that includes PTs of headache, sinus headache, and migraine) were reported in 47 (20.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of headache were all nonserious and Grade 1 or 2 in severity. No event led to drug interruption, dose reduction, or drug discontinuation in any subject.

Identified Risk: Infusion-related Reaction

Events of infusion-related reaction (a grouped term comprising 14 PTs, including infusion-related reaction [4 events], flushing [1 event], and hypersensitivity [1 event]) were reported in 6 (2.6%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of infusion-related reaction were generally nonserious (1 subject had hypersensitivity reported as an SAE), and all were Grade 2 in severity, leading to no dose reduction or drug discontinuation in any subject and to drug interruption in 1 subject (PT of infusion-related reaction).

Identified Risk: Upper Respiratory Tract Infection

Events of upper respiratory tract infection (grouped term that includes PTs of influenza, influenza-like illness, and upper respiratory tract infection) were reported in 43 (18.4%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, all events of upper respiratory

tract infection were nonserious, and generally Grade 1 to 2 in severity, leading to no dose reduction or drug discontinuation in any subject and to drug interruption in 7 (3.0%) subjects.

Identified Risk: Aspartate Aminotransferase Increased and Alanine Aminotransferase Increased

Events of AST increased were reported in 35 (15.0%) subjects and events of ALT increased were reported in 25 (10.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Although frequent, events of AST increased and ALT increased are consistent with laboratory-based increases in AST and ALT, all events were nonserious, and events were generally Grade 1 in severity, transient, and reversible, and did not lead to drug discontinuation. One (0.4%) subject had drug interruption due to ALT increase; 1 (0.4%) subject had dose reduction due to ALT increased and 1 (0.4%) due to AST increased. One subject had values that met the biochemical criteria for potential Hy's Law (ALT or AST $\geq 3 \times$ ULN and total bilirubin $>2 \times$ ULN). This case of potential Hy's Law was determined not to be causally associated with study drug due to alternative aetiology (acute hepatitis B ongoing from baseline) at the time of occurrence of the event.

Identified Risk: Hypokalaemia

Events of hypokalaemia were reported in 30 (12.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of hypokalaemia were consistent with laboratory-based decreases in potassium. Although frequent, events of hypokalaemia were reported as Grade 1 in 21 (9.0%) subjects, Grade 2 in 1 (0.4%) subject, and Grade 3 in 8 (3.4%) subjects; with 3 (1.3%) subjects having hypokalaemia reported as an SAE. Two (0.9%) subjects had drug interruption due to hypokalaemia, with no subjects having dose reduction or drug discontinuation.

Identified Risk: Anaemia

Events of anaemia (grouped term that includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased) were reported in 79 (33.8%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of anaemia were consistent with laboratory-based decreases in haemoglobin count. Although frequent, events in only 2 (0.9%) subjects were reported as SAEs. The majority of events were Grade 1 to 2 in severity, with 21 (9.0%) subjects reported as having anaemia events $\geq$ Grade 3. Events led to drug interruption in 8 (3.4%) subjects and dose reduction in 1 (0.4%) subject, with no drug discontinuation in any subject.

Identified Risk: Thrombocytopenia

Events of thrombocytopenia (grouped term that includes PTs of platelet count decreased and thrombocytopenia) were reported in 54 (23.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of thrombocytopenia were consistent with laboratory-based decreases in platelet count. Although frequent, events were generally Grade 1 to 2 in severity, with 10 (4.3%) subjects reported as having thrombocytopenia events of Grade 3. Events led to drug interruption in 6 (2.6%) subjects, dose reduction in 2 (0.9%) subjects, and drug discontinuation in 2 (0.9%)

subjects. One (0.4%) subject had an event reported as an SAE. No event was associated with major bleeding.

Identified Risk: Leukopenia

Events of leukopenia (grouped term that includes PTs of white blood cell (WBC) count decreased and leukopenia) were reported in 48 (20.5%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of white blood cell count decrease were consistent with laboratory-based decreases in WBC count. Although frequent, events were all nonserious and generally Grade 1 to 2 in severity, leading to drug interruption in 7 (0.3%) subjects and dose reduction in 1 (0.4%) subject, with no drug discontinuation in any subject.

Identified Risk: Lymphopenia

Events of lymphopenia (grouped term that includes PTs of lymphocyte count decreased and lymphopenia) were reported in 26 (11.1%) subjects in the HER2-positive BC 5.4 mg/kg Pool. Events of lymphopenia were consistent with laboratory-based decreases. Although frequent, events were all nonserious and generally Grade 1 to 2 in severity, leading to dose reduction in 1 (0.4%) subject, with no drug discontinuation or interruption in any subject.

Identified Risk: Neutropenia, Including Febrile Neutropenia

Events of neutropenia (grouped term) were reported in 76 (32.5%) subjects (observed in the HER2-positive BC 5.4 mg/kg Pool; however, these events were generally nonserious (1 [0.4%] subject had an SAE), did not require drug discontinuation, and were not associated with fatal outcomes. Laboratory data were consistent with the reported Aes of neutropenia (grouped term).

Febrile neutropenia was reported in 4 (1.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool, did not require drug discontinuation, and was not associated with fatal outcomes.

One subject had PTs of Grade 3 neutrophil count decrease and Grade 3 febrile neutropenia reported concurrently with a serious event of Grade 4 sepsis. The event of sepsis resolved following treatment with antibiotics. No other subjects with an event of Grade ≥ 3 neutropenia (grouped term) or Grade ≥ 3 febrile neutropenia had a concurrent serious infection.

Neutropenia, including febrile neutropenia, is generally manageable through standard clinical practice and following dose modification guidelines (SmPC Section 4.2).

SVII.1.1.2 Potential Risks

Risks With Minimal Clinical Impact on Patients: Keratitis

Corneal toxicity was observed in a nonclinical study of the released drug of T-DXd and has been seen in drugs in similar class. The mechanism for corneal toxicity with T-DXd remains unclear; however, it is known that HER2 is expressed in corneal epithelia. Keratitis was observed in clinical studies with T-DXd. In the HER2-positive BC 5.4 mg/kg Pool, keratitis was reported in 6 (2.6%) subjects, punctate keratitis in 2 (0.9%) subjects, and ulcerative keratitis in 1 (0.4%) subject. All events of keratitis were nonserious and either Grade 1 or 2 in severity, leading to drug interruption in 1 (0.4%) subject and to no dose reduction or drug discontinuation.

Risks With Minimal Clinical Impact on Patients: Testicular Toxicity

Reproductive studies in rats and monkeys indicate changes to the reproductive organs of males (eg, spermatid retention, small-sized testes and epididymides accompanying reduced organ weights; tubular degeneration/atrophy in the testes, luminal cell debris and reduced sperm in the epididymides) with T-DXd. It is not known whether T-DXd or its metabolites are found in seminal fluid. The potential risk for male patients is further minimized by statements in SmPC Section 4.6 advising male patients to seek counselling on sperm storage before starting treatment and male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of T-DXd.

Risks With Minimal Clinical Impact on Patients: Renal Toxicity

In nonclinical studies with T-DXd abnormal renal function was seen in rats but not in monkeys. In the rat 6-week study of T-DXd (q3w dosing), abnormalities in renal function were observed. At a supratherapeutic dose urinalysis revealed proteinuria and blood chemistry indicated increases in urea nitrogen, inorganic phosphorus, creatinine, and potassium and decreases in sodium and chloride. Supratherapeutic doses of T-DXd were observed in both rats and monkeys. At supratherapeutic doses, histopathological changes such as tubular basophilia and hyaline casts in the kidney were noted and all findings in rats resolved after a 9-week recovery period. In the monkey 3-month study while anisokaryosis in the proximal tubules in the kidney was observed at 30 mg/kg at the end of dosing and the 3-month recovery periods, no findings suggestive of abnormalities in renal function were observed in urinalysis or blood chemistry. No renal toxicity was observed in studies of the released drug in rats or monkeys.

In the HER2-positive BC 5.4 mg/kg Pool, no clinically meaningful shifts to worse creatinine values were observed. 2 (0.9%) subjects reported a TEAE of blood creatinine increase in the HER2-positive BC 5.4 mg/kg Pool. No subject in the pool had $\geq$ Grade 3 serum creatinine increase, except for 1 subject (██████████) who had fatal events of acute hepatic failure and acute renal injury 34 days after last study drug dose. Both events were assessed by the investigator as being due to disease progression (liver metastases). Overall, no safety concern with renal function from clinical studies or during postmarketing period with T-DXd has been identified.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important identified risks are: ILD/pneumonitis and left ventricular dysfunction. Important potential risks include embryo-foetal toxicity and product confusion-related medication errors.

SVII.1.2.1 Important Identified Risks

Important Identified Risk: Interstitial Lung Disease/Pneumonitis

Benefit-risk impact:

All data presented in this section are for “adjudicated drug-related ILD,” which is defined as events that were adjudicated as ILD and as related to trastuzumab deruxtecan (regardless of the determination made by the investigator) by an independent, multidisciplinary Adjudication Committee (AC).

The incidence of adjudicated ILD in the HER2-positive BC 5.4 mg/kg Pool was 32 (13.7%) subjects, with 12 (5.1%) subjects having events reported as serious.

Events of ILD were adjudicated to be Grade 1 in 6 (2.6%) subjects, Grade 2 in 19 (8.1%), Grade 3 in 1 (0.4%), Grade 4 in 0 (%), and Grade 5 in 6 (2.6%). These 6 Grade 5 events were adjudicated as ILD associated with a fatal outcome (including 4 subjects from the EU).

Drug was interrupted in 6 (2.6%) subjects, dose was reduced in 4 (1.7%), and drug was discontinued in 22 (9.4%) subjects. Among the 32 subjects with adjudicated drug-related ILD events, the reported outcome was resolved in 8 (25.0%) subjects, recovered with sequelae in 1 (3.1%), recovering in 2 (6.3%), not recovered in 13 (40.6%), fatal in 6 (18.8%), and missing/unknown in 2 (6.3%).

ILD/pneumonitis requires appropriate monitoring and management to mitigate the risk of Grade 4 or Grade 5 events, which have the potential to impact the benefit-risk for the patient. The risk of ILD/pneumonitis is further characterised in Section [SVII.3.1](#).

Important Identified Risk: Left Ventricular Dysfunction

Benefit-risk impact:

The incidence of the PT of Ejection fraction decreased in the HER2-positive BC 5.4 mg/kg Pool was 3 (1.3%) subjects, with no events reported as serious. The events were Grade 2 in 2 (0.9%) subjects and Grade 3 in 1 (0.4%) subject.

Study drug was interrupted in all 3 (1.3%) subjects, with no dose reductions or discontinuations of study drug due to ejection fraction decreased.

Left ventricular dysfunction is characterised in Section [SVII.3.1](#).

Because the lack of a control group in available clinical data does not allow to rule out completely a causal association with T-DXd, and cardiac failure has been reported for drugs in similar class, left ventricular dysfunction is considered an important identified risk. Appropriate monitoring and management is required to mitigate the risk of left ventricular dysfunction, which has the potential to impact the benefit-risk for the patient.

SVII.1.2.2 Important Potential Risks

Important Potential Risk: Embryo-Foetal Toxicity

Benefit-risk impact:

Nonclinical reproductive and developmental toxicity data for T-DXd are described in Section [Part II: Module SII](#).

No clinical data on the effect of T-DXd on embryo-foetal toxicity potential are available. However, in postmarketing reports, the use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the released drug of T-DXd can also cause embryo-foetal harm when administered to a pregnant woman (SmPC Section 4.4 and SmPC Section 4.6). Appropriate contraception as described in the SmPC is required to mitigate the risk of pregnancy, which could impact the benefit-risk of the drug.

Important Potential Risk: Product confusion-related medication errors

Benefit-risk impact:

With the availability of other trastuzumab-containing products and the HER2-targeted ADC trastuzumab emtansine (Kadcyla), prescribers could potentially mix up trastuzumab-containing products if they do not use the tradename. There is a potential for serious clinical consequences (eg, lack of efficacy) by inadvertently substituting one trastuzumab containing product for another.

For T-DXd there have been no reports of product confusion-related medication errors in clinical trials or since marketing of the product in the US and Japan.

Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment

No dedicated hepatic impairment study was conducted. While patients with moderate hepatic impairment were generally excluded from the clinical programme, up to a maximum of 10 patients with moderate hepatic impairment were eligible for enrolment into Study U201. However, only 1 patient meeting these criteria was enrolled. Patients with severe hepatic impairment were excluded from the clinical programme.

Based on the elimination of trastuzumab via hepatic metabolism, it is unknown whether moderate or severe hepatic impairment has an effect on trastuzumab deruxtecan elimination and exposure in humans, as well as whether patients with moderate or severe hepatic impairment have a safety profile different from that of the general indicated population. A warning statement is included in Section 4.4 of the SmPC that administration of trastuzumab deruxtecan should be undertaken with caution in patients with moderate to severe hepatic impairment.

Collection of PK and safety data from at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies with trastuzumab deruxtecan is planned.

Missing Information: Long-term Safety

The median treatment duration (defined as date of last dose – date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7 to 37.1). A total of 164/234 (70.1%) subjects had been treated for >6 months, 127/234 (54.3%) for >9 months, 69/234 (29.5%) for >12 months, and 5/234 (2.1%) for >24 months.

With continuation of currently ongoing Phase 3 studies (Studies DS8201-A-U301 and DS8201-A-U302), more long-term safety data will become available, which will be used to further characterise cumulative toxicity and the overall safety profile of trastuzumab deruxtecan.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Use in Patients with Moderate Hepatic Impairment was removed based on the analysis of further PK and safety data pertaining to moderate hepatic impairment in subjects administered T-DXd addressing the required post-authorization measure (Module 2.5 [Clinical Overview Addendum – Moderate Hepatic Impairment \[Sep 2023\]](#)).

This additional analysis included a total of 12 subjects with moderate hepatic impairment: 7 BC subjects treated with T-DXd 5.4 mg/kg and 1 GC and 4 colorectal cancer subjects treated

with T-DXd 6.4 mg/kg. Pharmacokinetic data reveal distinct exposure disparities between subjects with moderate hepatic impairment and those with normal hepatic function or mild hepatic impairment. However, it is important to note that these variations lack clinical significance in the approved indication for GC and BC and a definitive conclusion could not be drawn.

The safety data from the additional analysis align with the established safety profile, with no emergence of new safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Interstitial lung disease/Pneumonitis

Potential mechanisms:

The exact underlying mechanism of drug-induced ILD/pneumonitis with T-DXd is unknown. In drugs of similar class for which ILD/pneumonitis has been identified as a risk, 2 types of mechanisms have been proposed: chemotherapy that could lead to dose-dependent toxicity via an increase in the level of inflammatory cytokines, oxidative stress, and direct cytotoxic damage and monoclonal antibodies that could lead to an immune-mediated allergic lung injury.

Evidence source(s) and strength of evidence:

Dose-dependent changes in the lung were seen in nonclinical data. An independent AC adjudicated all potential events of ILD. Although T-DXd is associated with a risk of ILD/pneumonitis and cases with fatal outcomes have been reported, most events have been Grade 1 or 2 in severity and manageable following clinical treatment guidelines, which include close monitoring signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and proactive management with dose modification (dose reduction or interruption), and use of steroid treatment and (for moderate, severe or life-threatening ILD/pneumonitis) discontinuation of T-DXd.

Characterisation of the risk:

ILD data collected in the clinical programme are based on events that the independent ILD AC adjudicated as being ILD and as related to T-DXd (regardless of the determination made by the investigator).

ILD in the ATT $\geq$ 5.4 mg/kg Pool is summarized by event category and grade in [Table Part II: Module SVII.3.1](#), which includes 3 ILD events in Study J101 that occurred >28 days after the last dose (TEAE definition), per investigator-reported onset dates.

Among the 307 of 2145 (14.9%) subjects who had an adjudicated ILD event, 296 (13.8%) subjects had events that were adjudicated as drug-related ILD at the following grades: 78 (3.6%) Grade 1, 166 (7.7%) Grade 2, 22 (1.0%) Grade 3, 1 (0.0%) Grade 4, and 29 (1.4%) Grade 5 (Module 5.3.5.3 SCS [Table 1.2.5.1](#) [U301]).

Median time to onset date of the first adjudicated drug-related ILD event was 167.0 days (range: 0 to 960) (Module 5.3.5.3 SCS [Table 1.2.5.4](#) [U301]).

Table Part II: Module SVII.3.1: Number and Percentage of Adjudicated Drug-related ILD Events by Indication, Category, and Grade (Safety Analysis Set)

Pool	Outcome of Adjudication	Number (%) of Subjects by CTCAE Grade (as Graded by ILD Adjudication Committee)					
		1	2	3	4	5	Total
All Tumour Types ≥5.4 mg/kg [95% CI] (N = 2145)	Adjudicated as drug-related ILD	78 (3.6) (2.9, 4.5)	166 (7.7) (6.6, 9.0)	22 (1.0) (0.6, 1.5)	1 (0.05) (0.0, 0.3)	29 (1.4) (0.9, 1.9)	296 (13.8) (12.4, 15.3)
HER2-positive GC T-DXd 6.4 mg/kg Pool (N = 229)	Adjudicated as drug-related ILD	6 (2.6)	15 (6.6)	2 (0.9)	1 (0.4)	1 (0.4)	25 (10.9)
All BC 5.4 mg/kg (N = 1287)	Adjudicated as drug-related ILD	43 (3.3)	98 (7.6)	11 (0.9)	0	13 (1.0)	165 (12.8)
HER2-mut NSCLC 5.4 mg/kg (N=101)	Adjudicated as drug-related ILD	3 (3.0)	2 (2.0)	1 (1.0)	0	0	6 (5.9)

AC = Adjudication Committee; BC = breast cancer; 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 subjects in the pool; NSCLC = non-small cell lung cancer; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

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

The 95% confidence interval for the ILD rate is based on the exact (Clopper-Pearson) method for binomial distribution.

This table includes all events that were adjudicated and considered drug-related events by the AC.

If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade. If a subject has both missing and nonmissing CTCAE grades for an event, the worst CTCAE grade is based on the nonmissing grade.

The pooled analysis group is based on tumour type and first dose received for subjects in each study.

All Tumour Types T-DXd ≥5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, and DS8201-A-U302. HER2-positive GC T-DXd 6.4 mg/kg Pooled Data: Studies DS8201-A-J101, and DS8201-A-U205, DS8201-A-U206; BC 5.4 mg/kg Pooled Data: Studies DS8201-A-U303, DS8201-A-J101, DS8201-A-U201, and DS8201-A-U302.

Sources: Module 5.3.5.3 EU RMP [Table 10](#) (U301), Module 5.3.5.3 SCS [Table 1.2.5.1](#) (GC), Module 5.3.5.3 [Table 2.16](#) (NSCLC), Module 5.3.5.3 SCS [Table 1.2.5.1](#) (U301)

Table Part II: Module SVII.3.2: Summary of Adjudicated Drug-related ILD in the All Tumour Types ≥ 5.4 mg/kg Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects With Adjudicated Drug-related ILD
	All Tumour Types ≥ 5.4 mg/kg Pool (N = 2145)
Adjudicated Drug-related ILD	296 (13.8)
Worst CTCAE Grade ≥ 3	52 (2.4)
Serious AE	91 (4.2)
Associated with drug discontinuation	220 (10.3)
Associated with dose reduction	14 (0.7)
Associated with drug interruption	62 (2.9)
Associated with Grade 5 events	29 (1.4)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; N = total number of subjects in the pool

All Tumour Types ≥ 5.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303.

Sources: Module 5.3.5.3 SCS (U301) [Table 1.2.4.1](#), [Table 1.2.4.2](#), [Table 1.2.4.3](#), [Table 1.2.4.4](#), [Table 1.2.4.5](#), [Table 1.2.4.6](#), and [Table 1.2.5.1](#).

Among the 296 (13.8%) subjects with events adjudicated as drug-related ILD in the ATT ≥ 5.4 mg/kg Pool, per the investigator, 137 (46.3%) recovered, 13 (4.4%) recovered with sequelae, 22 (7.4%) were recovering, 95 (32.1%) were not recovered, 21 (7.1%) had a fatal outcome, 1 (0.3%) had an event that was ongoing, and 7 (2.4%) were missing outcome information (Module 5.3.5.3 SCS [Table 1.2.5.4](#) [U301]).

The median time to first onset of ILD event was 167 days, and the median duration of the first ILD event (as reported by the Investigator) was 47.5 days. In the ATT ≥ 5.4 mg/kg Pool, a higher incidence of adjudicated drug-related ILD was reported in subjects from Japan (121 [20.6%] subjects) compared with the subjects from other countries (175 [11.2%] subjects), and in subjects with mild/moderate renal impairment at baseline (172 [15.6%] subjects) compared with subject who had normal renal function (120 [11.8%] subjects). This difference was mainly driven by a higher number of subjects with Grade 1 and Grade 2 events in subjects with moderate renal impairment at baseline (Grade 1: 46 [4.2%] subjects and Grade 2: 96 [8.7%] subjects) (Module 5.3.5.3 SCS [Table 1.4.13](#) [U301]).

Spontaneous data from the global safety database up to data lock point (19 Dec 2022):

The following group of MedDRA PTs have been used to define T-DXd-related ILD in the postmarketing setting: Pneumonitis, Interstitial lung disease, Organising pneumonia, and Acute interstitial pneumonitis. By using this approach, a total of 945 cases were identified cumulatively. Of the 945 cases, 107 had a fatal outcome related to ILD, 427 met other seriousness criteria, and for 410 cases, ILD was classified as nonserious. Ages ranged from 27 years to 90 years (median: 64.0 years) with 68.1% female patients and 16.9% male patients (for remaining patients, sex was not reported). Indications for T-DXd were BC in 64.4% of cases,

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GC in 17.4% of cases, and the remaining cases derived from other cancer types (1.5%) and unknown indications (14.3%).

In the majority of cases (68.9%), T-DXd was withdrawn due to the ILD event. Outcomes primarily improved with appropriate ILD management (recovered 25.8%, recovering 20.1%, and recovered with sequelae 0.9%). Reporting rates are different between regions; in particular, the ILD reporting rate in Japan is higher because of more intensified reporting in ongoing ILD-directed surveys. Overall, evidence from post-marketing, spontaneous cases does not alter the risk of ILD/pneumonitis as observed in clinical studies.

Risk factors and risk groups:

A stepwise multivariate Cox regression model evaluating the association of baseline factors with the time to occurrence of any grade of adjudicated drug-related ILD was conducted among 1150 subjects who received at least 1 dose of T-DXd (5.4, 6.4, 7.4, or 8.0 mg/kg) in 9 phase 1 or 2 studies across multiple tumour types.

Seven baseline factors were potentially associated with increased ILD risk:

- Patients treated in Japan vs non-Japan
- Dose of >6.4 mg/kg vs ≤6.4 mg/kg
- Baseline oxygen saturation <95% vs ≥95%
- Moderate/severe renal impairment at baseline vs no impairment
- Presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis)
- Time since initial diagnosis of >4 years vs ≤4 years
- Age <65 years vs. ≥65 years

Given the limitations of this analysis (extensive prior treatment, differences in treatment durations, preselection of thresholds for Cox multivariate regression based on clinical judgement, and heterogeneity of the patient population), the potential clinical risk factors remain to be confirmed with future data in a larger, more homogenous patient population.

Preventability:

- While the occurrence of some events of ILD/pneumonitis is not completely preventable, steps can be taken to prevent events from progressing to a more serious outcome.
- Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms.
- Patients should be monitored for signs and symptoms of ILD/pneumonitis (SmPC Section 4.4).
- Evidence of ILD/pneumonitis should be promptly investigated and patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered.

- For asymptomatic (Grade 1) ILD/pneumonitis
 - Corticosteroid treatment (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent) should be considered.
 - T-DXd should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 of the SmPC Section 4.2.
- For symptomatic ILD/pneumonitis (Grade 2 or greater)
 - Corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent) should be promptly initiated and continued for at least 14 days and then gradually tapered for at least 4 weeks).
 - T-DXd should be permanently discontinued in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD/pneumonitis (SmPC Section 4.2).

Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis (SmPC Section 4.4). Patients with moderate or severe renal impairment should be monitored carefully because a higher incidence of Grade 1 and 2 ILD has been observed in these patients.

Additional risk minimisation measures that will be implemented will include a Health Care Professional (HCP) Guide and a Patient Card (PC) to reinforce early detection of and intervention for ILD/pneumonitis cases in clinical practice and thus minimise the occurrence of more serious ILD/pneumonitis cases.

Impact on the risk-benefit balance of the product:

Although T-DXd is associated with a risk of ILD/pneumonitis and cases with fatal outcomes have been reported, most events have been Grade 1 or 2 in severity and manageable following clinical treatment guidelines, which include close monitoring for signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and proactively managing events with dose modification (reduction or interruption), use of steroid treatment, and (for moderate, severe or life-threatening ILD/pneumonitis) discontinuing use of T-DXd. Appropriate monitoring and management is required to mitigate the risk of Grade 4 or Grade 5 ILD/pneumonitis, which has the potential to impact the benefit-risk for the patient.

Public health impact:

There is no potential public health impact beyond the treated population.

Important Identified Risk: Left Ventricular Dysfunction

Potential mechanisms:

The exact mechanism of potential cardiotoxicity manifesting as left ventricular dysfunction remains unknown for T-DXd. HER2 receptors expressed in the membranes of adult cardiomyocytes have an important role in transmitting growth and survival signals. Specifically, neuregulin (NRG)-HER2 signalling is involved in cardiac development and physiology, and it is suggested that blocking the NRG-1-mediated activation of HER2 reduces fundamental intracellular mechanisms that support cardiomyocyte contractility. This is a possible mechanism for anti-HER2 agent mediated cardiotoxicity; however, different mechanisms of action of HER2-

targeted therapies contribute to the variable risks of cardiotoxicity across these agents. Notably, the mAb trastuzumab is associated with mostly asymptomatic, reversible cardiac dysfunction, whereas the ADC T-DM1 allows intracellular drug delivery that is specific to HER2-overexpressing cells and is thereby associated with a lower rate of cardiac dysfunction.

Evidence source(s) and strength of evidence:

Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys with T-DXd did not show an abnormality in cardiac function tests (including LVEF).

Ejection fraction decreases have been reported with T-DXd. However, available clinical data show that the reported ejection fraction decreases are of low frequency and severity and are often asymptomatic in nature.

Characterisation of the risk:

Table Part II: Module SVII.3.3: Summary of LV Dysfunction in the All Tumour Types ≥ 5.4 mg/kg Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with LV Dysfunction ^a (N = 2145)
Treatment-emergent AE with any grade	69 (3.2)
CTCAE Grade ≥ 3	10 (0.5)
Serious AE	3 (0.1)
Associated with drug discontinuation	8 (0.4)
Associated with dose reduction	1 (0.0)
Associated with drug interruption	23 (1.1)
Associated with an outcome of death	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; LV = left ventricular;

PT = preferred term

All Tumour Types T-DXd ≥ 5.4 mg/kg Pooled Data: Studies DS8201-A-J101, DS8201-A-J202, DS8201-A-U201, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303.

^a LV dysfunction includes PTs of 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 failure, Right ventricular failure, Ventricular failure, and Left ventricular dysfunction.

Sources: Module 5.3.5.3 SCS (U301) [Table 1.2.6.1](#), [Table 1.2.6.2](#), [Table 1.2.6.3](#), [Table 1.2.6.4](#), [Table 1.2.6.5](#), and [Table 1.2.6.6](#)

LV dysfunction was reported infrequently. Specifically, 11 (0.5%) subjects experienced Grade 1 events, 48 (2.2%) subjects experienced Grade 2 events, and 10 (0.5%) subjects experienced Grade 3 events. Observed frequency of LVEF decreased on the basis of TEAEs and laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 318 (14.8%), the majority (290/2145 [13.5%]) being Grade 2 and 23 of 2145 (1.1%) being Grade 3 (Module 5.3.4.3 EU RMP Table 5 (U301)). Notably, in Study U302 similar proportions of subjects in the T-DXd and T-DM1 arms showed Grade 2 and Grade 3 LVEF measurements (see Module 5.3.4.3 SCS [Table 1.2.6.8](#) [HER2-low BC]). In addition, the maximum LVEF decrease and increase from baseline were similar in the T-DXd arm. The LVEF events were generally nonserious,

asymptomatic, and resolved. Dose reduction or drug discontinuation was only required in few subjects. Temporary LVEF decreases $<40\%$ was measured in 6 subjects in the ATT ≥ 5.4 mg/kg Pool (details below) (see Module 5.3.5.3 SCS [Table 1.2.6.8](#) [U301]).

The most frequent PT used for LV dysfunction was PT of Ejection fraction decreased (63/69). Seven additional subjects in the ATT ≥ 5.4 mg/kg Pool had events of PTs other than Ejection fraction decreased, including

- SAE of Grade 2 cardiac failure congestive that was associated with study drug discontinuation and resolved (LVEF value of 63% at baseline and 66% to 70% during the study).
- SAE of Grade 2 cardiac failure that was associated with study drug interruption and resolved (LVEF value of 52% at baseline and 39% to 64% during the study).
- Nonserious Grade 3 cardiac failure (LVEF value of 45%) that was associated with study drug discontinuation and resolved (LVEF value of 60% at baseline). Grade 2 ejection fraction decreased was also reported and was not resolved at the data cut-off date (LVEF value of 55%).
- Grade 1 cardiac failure on Day 1 after the first dose that was not resolved at the data cut-off date (LVEF value of 52% at baseline and 57% to 60% during the study).
- Grade 2 left ventricular dysfunction (LVEF value of 58% at baseline and 36% at Day 85) associated with study drug discontinuation; subject was recovering (LVEF value of 47%) 1 month later.
- Grade 1 left ventricular dysfunction that recovered without dose change.
- Grade 1 left ventricular dysfunction (LVEF value of 45%) at Cycle 9 that recovered within 35 days after drug interruption.

Spontaneous data from the global safety database up to data lock point (19 Dec 2022):

The SMQ Cardiac failure (Narrow Scope+PT left ventricular dysfunction) was used to define left ventricular dysfunction in the post-marketing setting. This approach yielded 49 cases cumulatively, 33 reporting ejection fraction (EF) decrease (4 of them accompanied by cardiac disorder, cardiomyopathy, cardiotoxicity, and acute myocardial infarction, respectively), 11 cardiac failure, 1 cardiopulmonary failure, 3 pulmonary edema, and 1 left ventricular dysfunction. Of the 49 cases, 24 cases were serious (mainly cases of cardiac failure, cardiomyopathy, cardiotoxicity, and EF decreased), and 25 cases were nonserious (mainly cases of EF decreased). Cases were often confounded by underlying cardiac/cardiovascular comorbidities and/or disease progression. For 4 cases (2 cardiac failure, 1 cardiopulmonary failure with pneumonitis, and 1 EF decrease with pneumonitis), a fatal outcome was reported; however, death was primarily associated with progression of the underlying disease.

The indication for T-DXd was breast cancer in 57.1% of the cases, gastric cancer in 18.4%, and lung cancer in 2%, with the remaining cases derived from other cancers (4.1%) and unknown indication (18.4%).

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When information was provided, EF decrease was reported to be mild, including isolated cases with EF decrease to 30%. Dose reduction in line with the scheme provided in T-DXd label led to improvement of EF decrease in most case, where information was available.

Risk factors and risk groups:

No risk factors or risk groups have been associated with LVEF decrease.

Anthracycline therapies are known to cause cardiotoxicity and have been shown to have a synergistic effect of cardiotoxicity with trastuzumab, a HER2 receptor antagonist. In the ATT T-DXd ≥ 5.4 mg/kg Pool, approximately 35% subjects received prior therapy of doxorubicin and epirubicin.

Preventability:

Standard cardiac function testing (echocardiogram or MUGA scanning) should be performed to assess LVEF prior to the initiation of T-DXd and at regular intervals during treatment, as clinically indicated (SmPC Section 4.4). LVEF decrease should be managed through treatment interruption or discontinuation (SmPC Section 4.2, 4.4). Treatment with T-DXd has not been studied in patients with LVEF $< 50\%$ prior to the initiation of treatment (SmPC Section 4.4).

Impact on the benefit-risk balance of the product:

If not identified and managed appropriately, left ventricular dysfunction has the potential to lead to serious consequences such as cardiac failure with a reduction in the benefit-risk for the patient.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Important Potential Risk: Embryo-Foetal Toxicity

Potential mechanisms:

Based on results from general animal toxicity studies, T-DXd and its topoisomerase I inhibitor component (DXd) were toxic to rapidly dividing cells (lymphatic/hematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity (SmPC Section 5.3).

Evidence source(s) and strength of evidence:

Findings from nonclinical data, the potential mechanism of action of the released drug of T-DXd, and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that T-DXd may potentially cause foetal harm.

Characterisation of the risk:

No pregnancy has occurred among women of childbearing potential who were subjects in or female partners of male subjects in clinical studies with T-DXd.

No clinical data on the effect of T-DXd on fertility are available.

Risk factors and risk groups:

No risk factors or risk groups have been associated with embryo-foetal toxicity.

Preventability:

Contraception guidelines for both women of childbearing potential and men with female partners of childbearing potential are provided in SmPC Section 4.4 and SmPC Section 4.6. The pregnancy status of females of childbearing potential should be verified prior to the initiation of T-DXd. Females of childbearing potential and male patients with female partners of childbearing potential should be advised to use highly effective contraception.

Impact on the benefit-risk balance of the product:

It is possible that exposure to T-DXd during pregnancy may cause foetal harm.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Important Potential Risk: Product confusion-related medication errors

Potential mechanisms:

With the availability of other trastuzumab-containing products and the HER2-targeted ADC trastuzumab emtansine (Kadcyla) prescribers could potentially mix up trastuzumab containing product if they would not use the tradename. Pharmacists reconstituting the infusion could potentially mix up trastuzumab-containing products if there are no specific distinguishing features regarding livery and cap colour of the vial to differentiate between trastuzumab-containing products.

Evidence source(s) and strength of evidence:

For trastuzumab emtansine (Kadcyla) 4 cases due to a confusion between trastuzumab emtansine and trastuzumab were reported in clinical trials and 2 spontaneous cases are evident for Kadcyla in the Eudravigilance database (data lock point 19 Dec 2022) reporting PT 'Wrong drug administered' or 'Product name confusion'. Both cases involve two trastuzumab-containing products and both cases were not associated with an adverse event.

As of 19 Dec 2022, there have been no case reports of product confusion-related medication errors associated with T-DXd.

Characterisation of the risk:

There is a potential for serious clinical consequences (eg, lack of efficacy) by inadvertently substituting one trastuzumab-containing product for another considering different dosing schedules apply for each product.

Risk factors and risk groups:

Not determinable.

Preventability:

To minimise the potential risk of product confusion-related medication errors with other trastuzumab-containing products, the vials and packages of T-DXd have distinctly different

designs. Additionally, the SmPC (SmPC Sections 4.2, 4.4, and 6.6) contains clear instructions for the health care professional regarding correct administration of T-DXd and differentiation from other trastuzumab-containing products, which is expected to further reduce the risk of medication errors with -DXd.

Furthermore, T-DXd will only be prescribed by a physician and administered under the supervision of a healthcare professional who is experienced in the treatment of cancer patients which will further reduce the risk of such medication error. The use of the trade name (ENHERTU), rather than the International Nonproprietary Name (trastuzumab deruxtecan) can also minimise this risk of product confusion-related medication errors.

Potential public health impact:

There is no potential public health impact beyond the treated population.

Missing Information: Use in Patients with Severe Hepatic Impairment

Evidence source:

Subjects with severe hepatic impairment were excluded from the clinical trial development programme. The safety profile of T-DXd may be different in subjects with severe hepatic impairment as the drug is primarily hepatically metabolised.

Population in need of further characterisation:

Patients with metastatic BC, GC, or NSCLC who have severe hepatic impairment. The safety profile in patients with severe hepatic impairment can further be characterised if such patients are exposed to T-DXd during postmarketing experience.

Missing Information: Long-term Safety

Evidence source:

T-DXd is intended for long-term treatment and to date, long-term safety is considered missing information

Population in need of further characterisation:

Patients with metastatic BC, GC, or NSCLC. Long-term safety will be further characterised through Phase 3 clinical studies.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of 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

Summary of safety concerns	
Missing information	• Use in patients with severe hepatic impairment • Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for ILD/Pneumonitis and LV dysfunction:

- **ILD/Pneumonitis:** Follow-up questionnaire for spontaneous ILD/pneumonitis events that captures additional details, including clinical course and presentation, relevant medical history, concomitant medications, laboratory data, and imaging data as available for enhanced safety surveillance and monitoring of this important identified risk in the postmarketing setting.
- **LV dysfunction:** Follow-up questionnaire for spontaneous LVEF decrease (including cardiac failure) events that captures additional details, including clinical presentation, relevant medical history, concomitant medications, and laboratory data as available for enhanced safety surveillance and monitoring of this important identified risk for any new safety signal in the postmarketing setting.

Batch related activities:

- T-DXd will be administered by a health care professional via IV infusion once every 3 weeks.
- The Marketing Authorisation Holder (MAH) will implement a process to systematically follow-up each postmarketing AE reported for T-DXd to obtain information on batch number(s) in the EU. If provided by the reporter, batch information for T-DXd will be included in the global safety database.
- Signal detection activities will include analysis for regional/batch-specific safety concerns.

III.2 Additional Pharmacovigilance Activities

A prescriber survey is implemented to measure effectiveness of an HCP Guide pertaining to the important identified risk of ILD/pneumonitis (details provided in [Annex 6](#)).

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.3.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study: Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation: 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

EU = European Union; ILD = interstitial lung disease

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

The MAH is currently conducting 2 Phase 3 clinical trials:

- Study DS8201-A-U306 is a confirmatory study expected to provide comprehensive evidence of the clinical benefit of T-DXd treatment in subjects with HER2-positive metastatic and/or unresectable gastric or gastro-esophageal junction (GEJ) adenocarcinoma.
- Study D967SC00001 (DESTINY-Lung04) is a confirmatory study expected to provide evidence of the clinical benefit of T-DXd as first-line treatment in subjects with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations.

Table Part IV.1: Efficacy Studies which are Conditions of the Marketing Authorisation

Study: Status	Summary of objectives	Efficacy uncertainty addressed	Milestones	Due dates
DS-8201-A-U306: A Phase 3, multicenter, 2-arm randomized, open-label study of trastuzumab deruxtecan in subjects with HER2-positive metastatic and/or unresectable gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen Ongoing	To examine the efficacy and safety of T-DXd, compared with subjects who received Ram + PTX for treatment of HER2-positive, gastric or gastro-esophageal junction adenocarcinoma	Overall efficacy and safety	Submission of results	Q4 2025
DESTINY-Lung04: An open-label, randomized, multicenter, Phase 3 study to assess the efficacy and safety of trastuzumab deruxtecan as first-line treatment of unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations Ongoing	To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations	Overall efficacy and safety	Submission of results	Q4 2025

BICR = blinded independent central review; HER2 = human epidermal growth factor receptor 2;
NSCLC = non-small cell lung cancer; PFS = progression-free survival; PTX = paclitaxel; Ram = ramucirumab;
T-DXd = trastuzumab deruxtecan

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

For the important identified risk of ILD/pneumonitis and for the important potential risk of product confusion-related medication errors, additional risk minimisation measures are proposed by the Applicant.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Interstitial lung disease/Pneumonitis	<u>Routine risk communication :</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. The use of corticosteroid treatment in ILD/pneumonitis is included in SmPC Section 4.2. Dose modification guidance for managing the risk of ILD/pneumonitis is included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: T-DXd is subject to medical prescription.

**Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern
(Continued)**

Safety Concern	Routine Risk Minimisation Activities
<u>Important Identified Risks</u>	
Left ventricular dysfunction	<u>Routine risk communication :</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendations for monitoring of LVEF decrease are included in SmPC Section 4.4. Dose modification guidance for managing the risk of LVEF decrease is included in SmPC Section 4.2. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: T-DXd is subject to medical prescription.
<u>Important Potential Risks</u>	
Embryo-foetal toxicity	<u>Routine risk communication :</u> SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: T-DXd is subject to medical prescription
Product confusion-related Medication error	<u>Routine risk communication :</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Not applicable <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: T-DXd is subject to medical prescription.

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern (Continued)

Safety Concern	Routine Risk Minimisation Activities
Missing Information	
Use in patients with severe hepatic impairment	<u>Routine risk communication:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None Legal status: T-DXd is subject to medical prescription
Long-term safety	<u>Routine risk communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: T-DXd is subject to medical prescription.

ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

V.2 Additional Risk Minimisation Measures

For the important identified risk of ILD/pneumonitis, an HCP Guide and a Patient Card are additional risk minimisation measures.

For the important potential risk of product confusion-related medication errors, an HCP Guide is an additional risk minimisation measure.

The proposed draft key messages of the additional risk minimisation activities are provided in [Annex 6](#).

Additional risk minimisation 1: Healthcare Professional Guide (ILD/Pneumonitis)

Objectives:

The objective of the HCP Guide is to ensure early recognition and diagnosis of ILD/pneumonitis, to allow prompt and appropriate treatment and minimise serious outcomes.

Rationale for the additional risk minimisation activity:

The HCP Guide improves HCP awareness of the risk of ILD/pneumonitis and management options, which may lead to early detection of and intervention for ILD/pneumonitis cases in clinical practice and thus potentially minimises the occurrence of more serious ILD/pneumonitis cases. The guide also improves the adherence to the key risk minimisation measures for ILD/pneumonitis defined in the T-DXd SmPC.

Target audience and planned distribution path:

Where T-DXd is supplied, all HCPs are provided with the HCP Guide to use as a reminder/quick reference material before the administration of T-DXd.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The Applicant verifies distribution of the HCP Guide and tests the understanding and knowledge of the key messages by the HCPs and evaluates the effectiveness using a survey.

The frequency of all ILD/pneumonitis including ILD/pneumonitis cases with a fatal outcome in the postmarketing setting will be evaluated periodically and are presented in each Periodic Safety Update Report.

Additional risk minimisation 2: Patient Card

Objectives:

The objective of the PC is to remind the patient of the risk of ILD/pneumonitis as well as its signs and symptoms and to encourage the patients to consult with the treating physician if they develop any relevant clinical signs/symptoms. The wallet-size Patient Card is intended as a convenient way to keep patients aware of the ILD/pneumonitis risk.

Rationale for the additional risk minimisation activity:

Being reminded about the signs and symptoms of ILD/pneumonitis increases the likelihood that patients will seek attention from an HCP for early detection and treatment of ILD/pneumonitis.

Target audience and planned distribution path:

The HCP provides the PC to the patient before initial administration of T-DXd. The PC has a compact design for portability.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The MAH verifies distribution of the PC in the prescriber survey.

The frequency of all ILD/pneumonitis including ILD/pneumonitis cases with a fatal outcome in the postmarketing setting are evaluated periodically and are presented in each Periodic Safety Update Report.

Additional risk minimisation 3: Healthcare Professional Guide for prevention of product confusion-related medication errors

Objectives:

The objective of the HCP Guide is to ensure that the medicinal product being prescribed, prepared and administered is T-DXd and not other trastuzumab-containing products or the HER2-targeted ADC trastuzumab emtansine (Kadcyla).

Rationale for the additional risk minimisation activity:

The HCP Guide improves HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine. The HCP Guide ensures the adherence to labelled language during the prescription, preparation and administration processes with T-DXd.

Target audience and planned distribution path:

Where T-DXd is supplied, all HCPs are provided with the HCP Guide for prevention of medication errors to use as a reminder/quick reference material before the administration of T-DXd.

Plans to evaluate the effectiveness of the interventions and criteria for success:

All cases representing potential product confusion-related medication errors in the postmarketing setting are evaluated periodically in terms of frequency, involved drugs, root causes (if available) as well as clinical outcomes and are presented in each Periodic Safety Update Report.

V.3 Summary of Risk Minimisation Measures

Table Part V.3.1: 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	<u>Routine risk minimisation measures:</u> 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. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. <u>Additional risk minimisation activities:</u> HCP Guide and Patient Card	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Targeted questionnaire <u>Additional pharmacovigilance activities:</u> Prescriber survey
Left ventricular dysfunction	<u>Routine risk minimisation measures:</u> 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. <u>Additional risk minimisation activities:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Targeted questionnaire <u>Additional pharmacovigilance activities:</u> None

Table Part V.3.1: 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	<u>Routine risk minimisation measures:</u> 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. <u>Additional risk minimisation activities:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Product confusion-related medication error	<u>Routine risk minimisation measures:</u> 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 <u>Additional risk minimisation activities:</u> HCP Guide	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Missing Information		
Use in patients with severe hepatic impairment	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 <u>Additional risk minimisation activities:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Long-term safety	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation activities:</u> None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None

HCP = healthcare professional; ILD = interstitial lung disease; PK = pharmacokinetic; SmPC = Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ENHERTU

This is a summary of the RMP for T-DXd. The RMP details important risks of T-DXd, how these risks can be minimised, and how more information will be obtained about T-DXd's risks and uncertainties (missing information).

The SmPC and package leaflet for T-DXd give essential information to HCPs and patients on how T-DXd should be used.

This summary of the RMP for T-DXd should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which will be part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of T-DXd's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Trastuzumab deruxtecan is indicated:

- 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.
- As monotherapy for the treatment of adult patients with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.
- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- As monotherapy for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum based chemotherapy with or without immunotherapy.

Further information about the evaluation of T-DXd's benefits be found in T-DXd's EPAR (<https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu>), including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of T-DXd, together with measures to minimise such risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be the following:
 - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
 - Important advice on the medicine's packaging.
 - The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
 - The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of T-DXd, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is continuously collected and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of is not yet available for T-DXd, it is listed under “missing information” below.

II.A List of Important Risks and Missing Information

Important risks of T-DXd are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of T-DXd. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI Module II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
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 severe hepatic impairment • Long-term safety

II.B Summary of Important Risks

Important identified risks with T-DXd include ILD/pneumonitis and left ventricular dysfunction as outlined below.

Important Identified Risk 1: Interstitial Lung Disease/Pneumonitis	
Evidence for linking the risk to the medicine	Dose-dependent changes in the lung were seen in nonclinical data (Section Part II: Module SII). ILD/pneumonitis was reported in clinical studies with T-DXd, including fatal outcomes. An independent Adjudication Committee adjudicated all potential events of ILD.
Risk factors and risk groups	Seven baseline factors of interest were identified: age <65 vs ≥65 years; patients treated in Japan vs non-Japan; dose of >6.4 vs ≤6.4 mg/kg; baseline oxygen saturation <95% vs ≥95%; moderate/severe renal impairment at baseline vs no impairment; presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis); and time since initial diagnosis of >4 vs ≤4 years.
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. The use of corticosteroid treatment in ILD/pneumonitis is included in SmPC Section 4.2. Dose modification guidance for managing the risk of ILD/pneumonitis is included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. <u>Additional risk minimisation measures:</u> Healthcare Professional Guide and Patient Card
Additional pharmacovigilance activities	Prescriber survey

ILD = interstitial lung disease; SmPC = Summary of Product Characteristics

1.8.2 Risk Management Plan

Trastuzumab deruxtecan

Important Identified Risk 2: Left Ventricular Dysfunction	
Evidence for linking the risk to the medicine	Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. LVEF decreases have been observed infrequently in clinical studies with T-DXd.
Risk factors and risk groups	None
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendations for monitoring of LVEF decrease are included in SmPC Section 4.4. Dose modification guidance for managing the risk of LVEF decrease is included in SmPC Section 4.2. <u>Additional risk minimisation measures:</u> None

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal toxicity and product confusion-related medication errors, as outlined below.

Important Potential Risk 1: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	Findings from nonclinical data, the potential mechanism of the released drug of T-DXd and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that T-DXd may potentially cause foetal harm.
Risk factors and risk groups	None
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Section 4.4 SmPC Section 4.6 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. <u>Additional risk minimisation measures:</u> None

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; SmPC = Summary of Product Characteristics

1.8.2 Risk Management Plan

Trastuzumab deruxtecan

Important Potential Risk 2: Product confusion-related medication errors	
Evidence for linking the risk to the medicine	Medication errors between trastuzumab (ie, Herceptin) and trastuzumab emtansine (ie, Kadcyla) have been reported. Potential for medication errors due to product confusion of T-DXd with trastuzumab and trastuzumab emtansine indicated for breast cancer treatment is considered.
Risk factors and risk groups	None
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Additional risk minimisation measures:</u> Healthcare Professional Guide

SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Missing information with T-DXd includes use in patients with severe hepatic impairment and long-term safety as outlined below.

Missing Information 1: Use in Patients With Severe Hepatic Impairment	
Evidence for linking the risk to the medicine	T-DXd has not been studied in subjects with severe hepatic impairment. Based on a population PK analysis, the clearance of the released drug of T-DXd decreases with increasing AST and increasing total bilirubin.
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Additional risk minimisation activities:</u> None

AST = aspartate aminotransaminase; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Missing Information 2: Long-term Safety	
Evidence for linking the risk to the medicine	The median treatment duration (defined as: date of last dose – date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7 to 37.1). A total of 164/234 (70.1%) subjects had been treated for >6 months, 127/234 (54.3%) for >9 months, 69/234 (29.5%) for >12 months, and 5/234 (2.1%) for >24 months.
Risk minimisation measures	<u>Routine risk minimisation communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Additional risk minimisation activities:</u> None

BC = breast cancer; HER2 = human epidermal growth factor receptor 2

II.C Postauthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The Phase 3 clinical trials DS8201-A-U306 and DESTINY-Lung04 serve as the confirmatory trials (see also RMP Part IV). Details are provided in the table below.

DS8201-A-U306	
Short title	A Phase 3, multicenter, 2-arm randomized, open-label study of trastuzumab deruxtecan in subjects with HER2-positive metastatic and/or unresectable gastric or gastro esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab containing regimen
Purpose of the study	<u>Primary objective:</u> To compare OS in HER2-positive (defined as IHC 3+ or IHC 2+/ISH+) gastric cancer (GC) and GEJ adenocarcinoma subjects treated with T-DXd vs. Ram + PTX. <u>Key secondary objective:</u> To compare PFS in HER2-positive GC and GEJ adenocarcinoma subjects treated with T DXd or Ram + PTX. <u>Other secondary Objectives:</u> • To evaluate the safety of T-DXd compared to Ram + PTX • To compare the clinical efficacy of T DXd and Ram + PTX by ORR based on investigator assessment • To compare the clinical efficacy of T-DXd and Ram + PTX by DoR. To compare the clinical efficacy of T-DXd and Ram + PTX by disease control rate (DCR) • To evaluate the PK of T-DXd • To evaluate immunogenicity of T DXd Safety concern addressed: overall safety

1.8.2 Risk Management Plan

Trastuzumab deruxtecan

DESTINY-Lung04	
Short title	Phase 3 study of the efficacy and safety of trastuzumab deruxtecan as first-line treatment for NSCLC with HER2 exon 19 or exon 20 mutations.
Purpose of the study	<u>Primary objective:</u> To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations. <u>Secondary objectives:</u> • To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of OS. • To further assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab in terms of PFS by investigator assessment, ORR, DoR, PFS2, and landmark analysis of PFS12 and OS24. • To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of CNS-PFS (per RECIST 1.1). • To assess the safety and tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab. • To assess the PK of T-DXd, total anti-HER2 antibody and DXd in serum. • To investigate the immunogenicity of T-DXd. • To assess the benefit of T-DXd relative to platinum with pemetrexed plus pembrolizumab with patient-reported pulmonary symptoms associated with NSCLC. • To describe patient-reported tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab. Safety concern addressed: overall safety

BICR = blinded independent central review; CNS-PFS = progression-free survival in central nervous system; DoR = duration of response; DXd = deruxtecan; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; OS24 = proportion of participants alive at 24 months; PFS = progression-free survival; PFS12 = proportion of participants alive and progression-free at 12 months; PFS2; time to second progression or death; PK = pharmacokinetics; PTX = paclitaxel; Ram = ramucirumab; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; T-DXd = trastuzumab deruxtecan

II.C.2 Other Studies in Postauthorisation Development Plan

Prescriber survey	
Short title	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis
Purpose of the study	The primary objective is to evaluate the effectiveness of proposed educational material as risk minimization measures by: Evaluating the level of knowledge of educational materials by HCPs of risks, early recognition, diagnosis and management of ILD/pneumonitis. Evaluating the extent to which HCPs receive the HCP guide and distribute the PC to patients. Safety concern addressed: risk minimization for ILD/pneumonitis.

EU = European Union; HCP = healthcare professional; ILD = interstitial lung disease; PC = Patient Card

PART VII ANNEXES

LIST OF ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

[ENHERTU® Potential Interstitial Lung Disease \(ILD\) Event Follow-up Questionnaire](#)

[ENHERTU® Potential Left Ventricular Ejection Fraction \(LVEF\) Follow-up Questionnaire](#)

ENHERTU® Potential Interstitial Lung Disease (ILD) Event Follow-up Questionnaire

Report Information			
Daiichi Sankyo ARGUS #:			
Patient Information			
Initials:		Date of birth (dd/mm/yyyy) or age:	
Gender:		Race/Ethnicity:	
Weight (units):		Height (units):	
BMI (units):		Occupation:	
ILD Adverse Event Details			
<i>Please provide start date and details of the ILD adverse event.</i>			
Start date (dd/mm/yyyy):			
ILD adverse event details			
Signs/Symptoms			
<i>Please provide start and stop date(s) and details of the following relevant signs/symptoms, if applicable.</i>			
Relevant Signs/Symptoms	Start and Stop Date(s) (dd/mm/yyyy)	Details	
☐ Fever			
☐ Dyspnea (shortness of breath)			
☐ Cough			
☐ Pleural effusion			
☐ Other(s)			

1.8.2 Risk Management Plan
Trastuzumab deruxtecan

Laboratory Tests				
<i>Please provide details of the following relevant lab tests, if applicable.</i>				
Relevant Lab Tests	Maximum Value (units)/ Reference Range	Date of Maximum Value (dd/mm/yyyy)	Most Recent Value (units)/ Reference Range	Date of Most Recent Value (dd/mm/yyyy)
Eosinophils				
Neutrophils				
Other:				
Other:				
Other:				

Diagnostic Tests		
<i>Please provide date(s) and results of the following relevant diagnostic tests, if applicable.</i>		
Relevant Diagnostic Tests	Date(s) (dd/mm/yyyy)	Results
☐ Chest X-ray		
☐ Computed tomography (CT)		
☐ High-resolution computed tomography (HRCT)		
☐ Bronchoscopy		
☐ Bronchoalveolar lavage (BAL)		
☐ Culture(s)		Type(s):
☐ Arterial blood gas (ABG) including PO2 (oxygen saturation)		
☐ ILD serum biomarkers (eg, KL-6, SP-D)		
☐ Pulmonary function tests		FEV1: FEV1/FVC: TLC: RV: FVC:
☐ Diffusing capacity of the lungs for carbon monoxide (DLCO)		
☐ Lung biopsy		Type:
☐ Other(s) (eg, rapid influenza diagnostic, CMV antigen, pneumococcal urinary antigen, beta D-glucan, BNP, NT-proBNP)		

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Pulmonary Consultation	
Was a pulmonary specialist consulted?	☐ Yes ☐ No If yes, consultation notes:
Primary Cancer History	
Date of initial diagnosis (dd/mm/yyyy):	
Did the patient have prior chest radiation?	☐ Yes ☐ No Details (eg, date [dd/mm/yyyy], dose, fraction, location):

Prior Cancer Therapy	
Number of prior cancer therapies:	
Did the patient receive prior cancer therapy known to cause ILD?	☐ Yes ☐ No Details (eg, drug/regimen name, indication, dose, frequency, start/stop dates [dd/mm/yyyy]):
Social History	
☐ Smoker	☐ Yes (☐ Current ☐ Past) ☐ No If yes, number of years: If yes, packs per year:
☐ Any e-cigarette/vaping (nicotine, THC) use in the past 30 days?	☐ Yes ☐ No If yes, what type of product?: ☐ Tobacco containing nicotine ☐ THC only ☐ Nicotine and THC ☐ Others Number of years: Frequency of use: ☐ Daily ☐ >3-5 times a week ☐ Occasionally ☐ Only for recreational purposes
☐ Occupational/environmental exposure	☐ Yes ☐ No If yes, details:
☐ Recreational exposure (other than THC products)	☐ Yes ☐ No If yes, details:

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Relevant Medical History		
<i>Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.</i>		
Relevant Medical History	Start Date/Diagnosis Date (dd/mm/yyyy)	Details
☐ Previous ILD		If yes, did patient receive steroid treatment? ☐ Yes ☐ No
☐ Lung metastases or pulmonary malignancy (eg, Lymphangitis Carcinomatosis)	☐ Past ☐ Present	
☐ Prior lung surgery		Location:
☐ Asthma		
☐ Chronic obstructive pulmonary disease (COPD)		
☐ Radiation pneumonitis		
☐ Respiratory infection (eg, pneumonia)		
☐ Renal impairment		
☐ Other(s) (eg, bronchiolitis obliterans organizing pneumonia, cryptogenic organizing pneumonia)		

Treatment(s)				
Did patient receive any treatment for ILD? ☐ Yes ☐ No				
Choose treatment(s) and specify details below:				
☐ Corticosteroid(s) ☐ Immunosuppressant(s) ☐ Antibiotic(s) ☐ Other(s)				
Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)
Action Taken				
ENHERTU discontinued due to ILD event?	☐ Yes ☐ No If yes, date of suspect drug discontinuation (dd/mm/yyyy):			
Event resolved after drug discontinued?	☐ Yes ☐ No ☐ N/A If yes, date (dd/mm/yyyy) of resolution:			
ENHERTU restarted?	☐ Yes ☐ No ☐ N/A If yes, date of suspect drug restarted (dd/mm/yyyy):			
ILD reoccurred after drug restarted?	☐ Yes ☐ No ☐ N/A If yes, date of suspect drug restarted (dd/mm/yyyy):			

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Is ILD event possibly related to ENHERTU?	☐ Yes ☐ No ☐ UNK	Explanation:
Event Outcome <i>Please select all that apply.</i>		
☐ Recovered without sequelae	☐ Recovered with sequelae Details:	☐ Recovered after treatment Treatment details:
☐ Recovering	☐ Not recovered	☐ Worsened Details:
☐ Unknown	☐ Fatal (please provide copy of post-mortem report)	

Suspect Drug <i>Please complete if reported ILD event was due to ENHERTU.</i>				
Suspect drug name:				
Lot number:		Indication:		
Dose:		Frequency:		
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):		
Suspect Drug <i>Please complete if reported ILD event was due to any other suspect drug besides ENHERTU.</i>				
Suspect drug name:				
Lot number:		Indication:		
Dose:		Frequency:		
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):		
Concomitant Medications (Prescription, illicit drug use, over the counter, nutritional supplements, herbals)				
Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

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Other	
Are there any other contributing factors to the adverse event?	☐ Yes ☐ No If yes, details:
Reporter Information	
Information provided by:	
Date of Report (dd/mm/yyyy):	Reporter Signature:

ENHERTU® Potential Left Ventricular Ejection Fraction (LVEF) Follow-up Questionnaire

Report Information			
Daiichi Sankyo ARGUS #: :			
Patient Information			
Initials:		Date of Birth (dd/mm/yyyy) or age:	
Gender:		Race/Ethnicity:	
Weight (units):		Height (units):	
LVEF Adverse Event Details			
Start date of event: (dd/mm/yyyy)		Stop date of event: (dd/mm/yyyy)	
Treatment with Enhertu discontinued due to LVEF event?	☐ Yes / ☐ No	Date of the drug discontinuation	
Event resolved after discontinuation?	☐ Yes / ☐ No	Treatment with Enhertu restarted?	☐ Yes / ☐ No If yes ☐ Dose unchanged ☐ Dose reduced to mg/kg
Date of treatment with Enhertu restarted		LVEF Event reoccurred?	☐ Yes / ☐ No
Causality between Enhertu and Event	☐ Yes ☐ No ☐ unknown	Further LVEF adverse event details:	
Event Outcome			
☐ Recovered	☐ Recovered with Sequelae If sequelae, please specify	☐ Recovering	
☐ Not Recovered	☐ Fatal (if conducted, please provide copy of post-mortem report)	☐ Unknown	
Signs/Symptoms <i>Please circle all that apply.</i>			
Dyspnea or orthopnea (shortness of breath)/Fatigue/Palpitations/Chest pain/Peripheral edema/Hepatomegaly (enlarged liver)/Other (s)			
Cardiac Consultation			

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Was a cardiac specialist consulted?		☐ Yes ☐ No If yes, consultation notes:	
New York Heart Association (NYHA) Classification <i>Please provide severity of heart failure (at the time of adverse event), if applicable.</i>			
Class	Definition	Yes or No	Date of Classification (dd/mm/yyyy)
NYHA I	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations	☐ Yes ☐ No	
NYHA II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea	☐ Yes ☐ No	
NYHA III	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms	☐ Yes ☐ No	
NYHA IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity	☐ Yes ☐ No	
Diagnostic/Laboratory Tests <i>Please provide date(s) and results of the following relevant diagnostic/laboratory tests, if applicable.</i>			
Relevant Diagnostic/Laboratory Tests		Date(s) (dd/mm/yyyy)	Results
☐ Echocardiography (ECHO) / Radionuclide ventriculography (MUGA)			% LVEF:
☐ Chest X-ray			
☐ Cardiac magnetic resonance imaging (MRI) / positron emission tomography (PET)			
☐ Electrocardiography (ECG)			
☐ Troponin test			
☐ Natriuretic peptides (eg, BNP, NT-proBNP)			
☐ Creatine kinase-muscle/brain (CK-MB)			
☐ Other(s)			
Primary Cancer History			
Specification of primary cancer:		Date of initial diagnosis (dd/mm/yyyy):	
Did the patient have prior chest radiation?		☐ Yes ☐ No Details (eg, date [dd/mm/yyyy], dose, fraction, location):	

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Prior Cancer Therapy			
Number of prior cancer therapies:			
Did the patient receive prior cancer therapy known to cause cardiotoxicity (eg, anthracycline [doxorubicin])?		☐ Yes ☐ No Details (eg, drug/regimen name, indication, dose, frequency, start/stop dates [dd/mm/yyyy]):	
Relevant Medical History			
<i>Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.</i>			
	Start Date/Diagnosis Date (dd/mm/yyyy)	Details	
☐ Previous heart failure		NYHA class:	
☐ Prior heart surgery		Location:	
☐ Acute coronary syndrome (eg, myocardial infarction [heart attack])			
☐ Arrhythmia (irregular heart beat)		If yes, on treatment?: ☐ Yes ☐ No	
☐ Hypertension (high blood pressure)		If yes, on treatment?: ☐ Yes ☐ No	
☐ Dyslipidemia (high cholesterol)		If yes, on treatment?: ☐ Yes ☐ No	
☐ Diabetes		If yes, on treatment?: ☐ Yes ☐ No	
☐ Pulmonary condition(s)		If yes, on treatment?: ☐ Yes ☐ No	
☐ Other(s) cardiac condition (eg, Ischemic heart disease, Valvular heart disease, Cardiomyopathy)		If yes, on treatment?: ☐ Yes ☐ No	
☐ Smoker			
☐ Alcohol use			
☐ Others (eg, Occupational/environmental exposure), please specify			
Other			
Are there any other contributing factors to the adverse event?		☐ Yes ☐ No If yes, details:	
Suspect Drug			
<i>Please complete if reported LVEF event was due to ENHERTU</i>			
Suspect drug name:			
Lot number:		Indication:	

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Dose:		Frequency:		
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):		
Concomitant Medications (Prescription, illicit drug use, over the counter, nutritional supplements, herbals)				
Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yy)	Stop Date (dd/mm/yyyy)
Treatment				
Did the patient receive any treatment for heart failure? ☐ Yes ☐ No Choose treatment(s) and specify details below: ☐ Beta-blocker ☐ Diuretic ☐ Angiotensin-converting enzyme (ACE) inhibitor ☐ Angiotensin II receptor blocker (ARB) ☐ Aldosterone receptor antagonist ☐ Cardiac glycoside (eg, digoxin) ☐ Other(s)				
Drug	Indication	Dose/Route/Frequency	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)
Reporter Information				
Information provided by:				
HCP ☐ Yes / ☐ No If no, please specify				
Date of Report (dd/mm/yyyy):		Reporter Signature:		

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Prior to the launch of trastuzumab deruxtecan in each member state, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme (Healthcare Professional [HCP] Guide, Patient Card for ILD/pneumonitis and HCP Guide for product confusion-related medication errors), including communication media, distribution modalities, and other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

- I) ensuring early recognition of interstitial lung disease (ILD)/pneumonitis, to allow prompt appropriate treatment and to mitigate worsening of the condition
- II) improving HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine

The MAH will ensure that each member state where trastuzumab deruxtecan is marketed, all HCPs and patients who are expected to administer/be administered trastuzumab deruxtecan are provided with the educational material.

I) Healthcare Professional (HCP) Guide for ILD/pneumonitis

The HCP Guide will contain the following key elements:

- Summary of important findings of trastuzumab deruxtecan-induced ILD/pneumonitis (eg, frequency, grade, time to onset) observed in the clinical trial setting
- Description of the appropriate monitoring and evaluation of ILD/pneumonitis in patients receiving trastuzumab deruxtecan
- Detailed description of management of ILD/pneumonitis in patients treated with trastuzumab deruxtecan including guidance on drug interruption, reduction and treatment discontinuation for ILD/pneumonitis
- Reminder to HCP that they should repeat the information about signs and symptoms of ILD/pneumonitis at each patient visit, including when the patient should seek attention from an HCP (eg, the symptoms to watch for; the importance to adhere to scheduled appointments)
- Reminder to HCP to provide the patient with the Patient Card (PC), including advice that the PC should be kept with the patient at all times

Patient Card

The Patient Card will contain the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan
- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber

- Cross-reference to Patient Information Leaflet

II) **Healthcare Professional Guide for prevention of medication errors**

The HCP Guide will contain the following key elements:

- Alert to HCPs about a potential risk of confusion between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla (trastuzumab emtansine)
- Mitigation measures for prescribing errors due to similarities in active ingredient names and measures to avoid errors during prescription phase by physicians
- Comparison of commercial appearance between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla (trastuzumab emtansine)
- Potential mitigation strategies to avoid errors during preparation phase by pharmacists
- Detailed Information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase by nurses
-