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 2024	RMP version number	10.0
Date of final sign off	16 Sep 2025		

Rationale for submitting an updated RMP:

Updated pooled safety data

Summary of significant changes in this RMP:

- Part II: Module SIII: Clinical trial exposure updated based on pooled data.
- Part II: Module SVII: Risk characterisation data updated based on pooled data.
- Condition of the Marketing Authorisation (EMEA/H/C/005124/II/0012): Study DS-8201-A-U306 is completed and removed from the RMP.
- Annex 5: Updated with the latest version of the DESTINY-Lung04 protocol synopsis.

QPPV name:

Dr. Stefan Freudenthaler

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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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:	1
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 humanised 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 is indicated 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 is indicated for the treatment of adult patients with unresectable or metastatic: • Hormone receptor (HR)-positive, HER2-low or HER2-ultralow BC who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (see sections 4.2 and 5.1). • 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 (see section 4.2). 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. Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.
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 lyophilised 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; 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. Breast Cancer

SI1.1. Incidence and Prevalence

Breast cancer (BC) is the most common cancer worldwide, with approximately 2.3 million new cases in 2020, which accounted for 11.7% of all new cancers in both males and females and 24.5% of all cancers in females. The global age-standardized incidence rate (ASIR) for females in 2020 was 47.8 per 100,000. Globally, there is some geographic variation in the incidence, with the highest ASIR (per 100,000) in 2020 observed in Australia and New Zealand (95.5), Western Europe (90.7), Northern America (89.4), Northern Europe (86.4), and Southern Europe (79.6).

In Europe, the estimated number of female BC cases in the 27 member states of the European Union (EU-27) in 2022 was 374,836, with an ASIR (using the world population for standardization) of 83.3 per 100,000 females.

In the United States (US), the 5-year age-adjusted incidence rate in females for the period 2016 to 2020 was 126.9 per 100,000.

In Japan, the estimated number of cases in 2020 was 92,024, with an estimated ASIR (per 100,000) of 76.3.

Globally, approximately 20% of patients with BC have human epidermal growth factor receptor 2 (HER2)-positive tumours. Breast cancer patients who test immunohistochemistry (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 HER2-low BC patients have hormone receptor-positive tumours. The rest of the HER2-low BC patients have hormone receptor-negative tumours.

Tumours that have HER2 IHC lower than 1+ but detectable HER2 staining, ie, faint and incomplete membrane staining that is seen in 10% or fewer tumour cells, are referred to as HER2-ultralow. Among studies of primary or metastatic HR-positive HER2-negative BC, approximately 65-70% of cases were HER2-low and approximately 30% were HER2-ultralow.

In the United Kingdom (UK), France, Germany, Spain, and Italy, among metastatic BC patients, HER2 overexpression varies from 22% (France) to 34% (Italy). For Germany, Spain, and the UK, the numbers were 32.4%, 26.3%, and 28.4%, respectively. Human epidermal growth factor receptor 2-positive/ hormone receptor-negative BC was the least prevalent in France (9%) and the most prevalent in Italy (13.5%). The proportion of HER2-positive/ hormone receptor-positive patients ranged from 13.1% in France to 20.7% in Italy.

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

Breast cancer is mainly a disease in females, with only approximately 1% occurring in males.

There is some variation in incidence rates of BC (all stages combined) by ethnicity in the US. In the US, incidence rates of BC (all stages combined) are slightly higher in non-Hispanic White

females compared to non-Hispanic Black, Asian/Pacific Islander, or Hispanic females. However, non-Hispanic Black females have the highest incident rates for advanced disease with distant metastases.

Overall, in the US, female BC is most common in middle-aged and older women.

Other risk factors for BC include family history of BC or ovarian cancer, genetic mutations, reproductive factors (early menarche, late menopause, nulliparity, age >30 years at first birth, not breastfeeding), obesity, previous benign disease, use of oral contraceptive pills, use of combined postmenopausal therapy, high breast density, exposure to the drug diethylstilbesterol, smoking, alcohol intake, and radiation exposure.

SI1.3. The Main Existing Treatment Options

HER2-positive Metastatic Breast Cancer

Although HER2-targeted therapies have been developed as molecularly targeted therapies, locally advanced and metastatic tumours invariably relapse with time. The current standard of care (SoC) for newly diagnosed HER2-positive metastatic BC, in general, is a combination of pertuzumab-trastuzumab and chemotherapy (if there are no contraindications for chemotherapy). For hormone receptor-positive disease, endocrine therapy may be added.

For subsequent-line anti-HER2 therapy, trastuzumab deruxtecan (T-DXd) has been established as the SoC. In patients with no, unknown, or stable bone metastases, options in the second-line setting include T-DXd or trastuzumab emtansine (T-DM1). In patients with active bone metastasis where no local intervention is indicated, tucatinib-capecitabine-trastuzumab or T-DXd are options.

Options in the third-line setting for patients include tucatinib-capecitabine-trastuzumab, T-DXd, or T-DM1, depending on what was administered in the second-line setting. For patients who progress, subsequent therapy options include lapatinib-trastuzumab, trastuzumab-chemotherapy, margetuximab-chemotherapy, or neratinib-chemotherapy.

HER2-low Metastatic Breast Cancer

In a 2023 published report of the European Society for Medical Oncology (ESMO) expert consensus statements on the definition, diagnosis, and management of HER2-low BC, patients with HER2-low (IHC 1+ or IHC 2+/in situ hybridization [ISH]-), hormone receptor-positive metastatic BC who have received prior cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy and at least 1 previous line of chemotherapy (or have experienced progression within 6 months of [neo]adjuvant chemotherapy) and are considered to have endocrine refractory disease are candidates for T-DXd if they do not have contraindications. In cases where both T-DXd and sacituzumab govitecan are available options, T-DXd should be prioritized.

HER2-negative 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-negative/hormone receptor-positive BC is endocrine therapy with or without a 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, endocrine therapy 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 BC gene (*BRCA*) mutations may be treated with poly adenosine diphosphate (ADP)-ribose polymerase inhibitors.

Once tumours are refractory to endocrine therapy, therapeutic guidelines recommend the use of sequential systemic single-agent chemotherapy not previously used in earlier lines. Preferred single-agent regimens in this setting include the anthracyclines doxorubicin and liposomal doxorubicin, the anti-metabolites 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-paclitaxel, the anthracycline epirubicin, and ixabepilone. Single-agent chemotherapy is preferred over combination therapy in this setting.

The approved treatment for patients with hormone receptor-positive tumours refractory to endocrine therapy who have received at least 1 prior line of chemotherapy is the CDK4/6 inhibitor abemaciclib and the antibody-drug conjugate (ADC) sacituzumab govitecan.

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

For patients with metastatic triple-negative BC (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-negative/hormone receptor-positive BCs that are refractory to endocrine therapy. 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 ADP-ribose polymerase inhibitors (olaparib or talazoparib) or platinum agents.

For patients with metastatic TNBC with programmed cell death ligand 1 (PD-L1)-positive disease, the preferred therapeutic option in the first-line setting is a programmed cell death protein 1 (PD-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 has been approved. Positive results from a small cohort of subjects with hormone receptor-negative BC suggest that T-DXd offers 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, there were an estimated 684,996 deaths due to BC among women in 2020, accounting for 15.5% of all cancer-related deaths in females. The global age-standardized mortality rate (ASMR) for BC in 2020 was 13.6 per 100,000 females. In Europe, the ASMR per 100,000 ranged from 13.3 in Southern Europe to 15.6 in Western Europe. In the US, based on 2016 to 2020 data from the Surveillance, Epidemiology, and End Results (SEER) program, the 5-year age-adjusted mortality rate for BC was 19.1 per 100,000 females. In Japan, the ASMR for BC in 2020 was 8.9 per 100,000 females.

The 5-year relative survival rate for BC (all stages) in the US for the 2016 to 2020 period was 90.8% for females. However, survival rates vary by stage, among other prognostic factors such as treatment options. For patients with regional and distant metastasis, the 5-year relative survival rates for the same period in the US were 86.3% and 31.0%, respectively. In Europe, the 5-year survival rate for metastatic disease was estimated to be 38% compared with 96% for early BC.

Metastatic BC was the leading cause of death among all cancers in women, accounting for 3.6% of all deaths in women in Europe in 2015. Metastatic BC after therapy for early BC tends to have a more aggressive tumour biology and a worse outcome compared with de novo metastatic BC.

Untreated BC patients with HER2-positive disease have been reported to have a more aggressive disease with a higher recurrence rate and increased mortality than patients with HER2-negative disease. Treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive BC. However, the disease invariably progresses, with median survival being 2 to 4 years.

SI1.5. Important Comorbidities

Patients with BC who have comorbidities have overall higher mortality compared to patients without comorbidities. In population-based cohort studies, 13% to 28% of patients have at least 1 comorbidity.

In a systematic review, the most common comorbidity reported in patients with BC was hypertension. Other common reported comorbidities were cardiovascular disease, diabetes, previous cancer, cerebrovascular disease, and pulmonary disease.

Events that occur frequently in patients with metastatic BC (both treated and untreated populations) include bone metastases, hepatotoxicity/liver metastases, pulmonary toxicity/metastases, lung metastases, brain metastases, and cardiotoxicity.

SI.2. HER2-positive Gastric Cancer

As there are limited epidemiological data in the literature for the HER2-positive gastric cancer (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

Gastric cancer is the fifth most common cancer worldwide, with approximately 1.1 million new cases in 2020, which accounted for 5.6% of all new cancers. The global ASIR in 2020 was 11.1 per 100,000 persons. Globally, there is some geographic variation in the incidence of GC, with the highest ASIR (per 100,000 persons) in 2020 observed in Eastern Asia (22.4).

In Europe, the ASIR (per 100,000 persons) ranged from 4.6 in Northern Europe to 11.3 in Central and Eastern Europe. In the EU-27, approximately 20,262 new cases of GC were diagnosed in 2022, with an ASIR (using the world population for standardization) of 6.5.

In the US, the 5-year age-adjusted incidence rate for the period 2017 to 2021 was 7.0 per 100,000 persons.

In Japan, the estimated number of GC cases in 2020 was 138,470, with an estimated ASIR (per 100,000 persons) of 31.6.

Overexpression of HER2 can be found in 8.2% to 29.5% of patients with GC. Human epidermal growth factor receptor 2 expression in GC varies based on the site of the primary tumour (gastric vs. gastroesophageal junction [GEJ]) and histological types.

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

Gastric cancer is more prevalent in males than in females and more common in older age groups.

There is some variation in the incidence rates of GC (all stages combined) by ethnicity in the US. In the US, for the period 2017 to 2021, age-adjusted incidence rates of GC (all stages combined) was highest in non-Hispanic American Indian/Alaska Native (11.0 per 100,000 persons) compared with other ethnicities. Non-Hispanic American Indian/Alaska Natives also have the highest incident rates for advanced disease with distant metastases.

Other risk factors for GC include *Helicobacter pylori* infection, obesity, smoking, pernicious anaemia, diet (rich in salt, pickled foods, and preserved meats and low in fruits and vegetables), low socioeconomic status, genetic mutations, and gastroesophageal reflux disease.

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, European Union (EU), 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-fluorouracil (FOLFIRI) was shown to be efficacious and well tolerated regardless of HER2 expression and may be considered for selected patients. In the US, pembrolizumab combined with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy is approved in the first-line setting.Also in the EU, pembrolizumab in combination with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy is approved in the first line for the treatment of locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score ≥1.

After progression in the first-line therapy, response rates and median survival are low. In the US, the EU, and Japan, T-DXd is approved for HER2-positive gastric or GEJ adenocarcinoma patients who had received prior trastuzumab-based therapy. Other recommended treatment options for second and further lines of chemotherapy include taxane (docetaxel and paclitaxel), irinotecan, or ramucirumab as single agents or in combination with paclitaxel, depending on performance status.

Regimens recommended for third- and later-line therapy include irinotecan, taxanes, pembrolizumab (if PD-L1 expression by combined positive score ≥1), and the trifluridine/tipiracil regimen. The PD-1 blocking antibody nivolumab is approved in Japan for use in the third- or later-line 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, there were an estimated 1.1 million deaths globally due to GC, accounting for 5.6% of all cancer deaths in males and females combined. The global ASMR for GC in 2020 was 7.7 per 100,000 persons. In Europe, the ASMR per 100,000 persons ranged from 2.9 in Northern Europe to 8.3 in Central and Eastern Europe. In the US, based on 2018 to 2022 data from the SEER program, the 5-year age-adjusted mortality rate for stomach cancer was 2.7 per 100,000 persons. In Japan, the ASMR for stomach cancer in 2020 was 8.2 per 100,000 persons.

The 5-year survival rate for GC (all stages) in the US for the 2014 to 2020 period was 36.4%. For patients with regional disease or distant metastasis, the rate was reduced to 35.8% and 7.0%, respectively.

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 overall survival (OS), while other studies did not demonstrate such an association.

SI.2.5. Important Comorbidities

Comorbidities play an important role in cancer treatment choice and patient survival. Multiple population-based studies estimate that 60% to 70% of patients with newly diagnosed GC also present with at least 1 comorbid condition. The most common comorbidities reported include hypertension, cardiac disease, digestive tract disease, diabetes, and previous malignant cancer.

Events that occur frequently in this population include bleeding, malignant gastric outlet obstruction, nausea and vomiting, and early dumping syndrome (which occurs after gastrectomy, usually within 30 minutes following a meal).

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

As there are limited epidemiological data in the literature for the HER2-mutant non-small cell lung cancer (NSCLC) population, data herein are presented on general lung cancer 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, with approximately 2.2 million new cases in 2020, which accounted for 11.4% of all new cancers. The global ASIR in 2020 was 22.4 per 100,000 persons. The highest ASIRs (per 100,000 persons) in 2020 were observed in Polynesia (37.3), Micronesia (36.4), Eastern Asia (34.4), Western Europe (32.7), and Northern America (32.6).

In Europe, the estimated number of lung cancer cases in 2022 in the EU-27 was 319,236, with an ASIR of 30.0 per 100,000 persons.

In the US, the 5-year age-adjusted incidence rate for the period 2016 to 2020 was 50.0 per 100,000 persons.

In Japan, the estimated number of cases in 2020 was 138,532, with an estimated ASIR (per 100,000 persons) of 32.1.

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

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

Lung cancer is more prevalent in males than in females and more common in older age groups. Non-squamous NSCLCs with HER2 mutations are more frequently associated with females and younger age groups than NSCLC without HER2 mutations.

There is some variation in the incidence rates of lung cancer (all stages combined) by ethnicity in the US. In the US, for the period 2016 to 2020, the age-adjusted incidence rate of lung cancer (all stages combined) was highest in non-Hispanic Whites (56.4 per 100,000) compared with

other ethnicities. However, non-Hispanic Blacks had the highest incidence rates for advanced disease with distant metastases.

Other risk factors for lung cancer include smoking (including second-hand smoking); exposure to radon; occupational exposure to asbestos, arsenic, cadmium, chromium, beryllium, and nickel; air pollution (including level of particulate matter 2.5 and indoor coal burning); family history of lung cancer; and previous radiation therapy.

Non-squamous NSCLCs with HER2 mutations are more frequently associated with never smokers than NSCLC without HER2 mutations.

Mutations in the gene encoding HER2 (ERBB2) 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.

SI.3.3. The Main Existing Treatment Options

Treatment options from current clinical guidelines from the National Comprehensive Cancer Network (NCCN) and ESMO for patients with metastatic NSCLC without an actionable oncogenic driver irrespective of PD-L1 status are presented below.

In the first-line metastatic setting, the SoC is a combination of platinum-based chemotherapy and pembrolizumab 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-PD-1/PD-L1 agents.

Targeted Therapy (ADC) with Activity Against HER2 Mutations

T-DXd is approved for patients with previously treated HER2-mutant metastatic NSCLC. The use of T-DXd in metastatic HER2-mutant NSCLC is also recommended by the NCCN. In addition, the NCCN recommends the HER2-targeting ADC T-DM1 as a treatment option for patients with metastatic NSCLC and HER2 mutations.

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

Patients with lung cancer have a dismal prognosis with the highest mortality rate among all cancers. Surgical resection is an option in only one-third of lung cancer patients due to the late detection of the disease.

According to GLOBOCAN, there were an estimated 796,144 deaths due to lung cancer in 2020, accounting for 18% of all cancer deaths. The global ASMR in 2020 was 18.0 per 100,000 persons. Lung cancer is the most common cause of cancer death in the EU-27, with an estimated ASMR of 22.5 per 100,000 persons. In Europe, the ASMR (per 100,000 persons) ranged from 20.1 in Northern Europe to 23.8 in Western Europe. In the US, based on 2016 to 2020 data from the SEER program, the 5-year age-adjusted mortality rate for lung and bronchus cancer was 35.0 per 100,000 persons. In Japan, the ASMR for lung cancer in 2020 was 14.7 per 100,000 persons.

The 5-year relative survival rate for lung and bronchus cancer (all stages) in the US for the 2013 to 2019 period was 25.4%. This was reduced to 34.8% and 8.2% for regional and advanced disease with distant metastases, respectively.

SI.3.5. Important Comorbidities

The most frequent comorbidities in lung cancer patients are smoking-related illnesses including cardiovascular and respiratory diseases. Diabetes and its complications also share risk factors with lung cancer and frequently present in these patients. Population-based cohort studies of NSCLC and lung cancer patients in Europe and North America have shown that more than 50% of patients have at least 1 comorbidity. Prevalent comorbidities in NSCLC patients include chronic lung disease, peripheral vascular disease, renal disease, diabetes with or without complications, prior cancer or metastatic carcinoma, cerebrovascular disease, myocardial infarction, and heart failure. NSCLC patients with comorbidities have overall higher mortality compared to patients without comorbidities.

Events that occur frequently in patients with lung cancer include dysgeusia with weight loss, pneumonia, bone metastases, brain metastases, cough, fatigue, and haemoptysis.

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
Toxicity	
Intestinal toxicity: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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. Released drug: The lymphatic/haematopoietic 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: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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. Released drug: 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: Trastuzumab deruxtecan: 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). Released drug: 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. Trastuzumab deruxtecan: 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. Released drug: 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.

ADR = adverse drug reaction; 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; SmPC = Summary of Product Characteristics; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

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

Cumulatively, 2335 subjects were exposed to 5.4 mg/kg T-DXd and 1133 subjects were exposed to 6.4 mg/kg T-DXd in 16 pooled studies. An outline of these 16 studies in terms of design, exposure, and data cut-off (DCO) dates is provided below (Module 5.3.5.3 Summary of Clinical Safety [SCS] SAP Version 2.0):

- Breast cancer
  - Study DS8201-A-U201, DESTINY-Breast01, hereafter referred to as Study DB-01, was a Phase 2, multicentre, open-label study in subjects with HER2-positive, unresectable and/or metastatic BC previously treated with T-DM1 (184 subjects treated with 5.4 mg/kg T-DXd and 48 subjects treated with 6.4 mg/kg T-DXd; DCO date: 08 Jun 2020).
  - Study DS8201-A-U301, DESTINY-Breast02, hereafter referred to as Study DB-02, was a Phase 3, multicentre, open-label, active-controlled study for HER2-positive, unresectable and/or metastatic BC subjects previously treated with T-DM1 (608 subjects, of whom 404 subjects were treated with 5.4 mg/kg T-DXd; DCO date: 30 Jun 2022).
  - Study DS8201-A-U302, DESTINY-Breast03, hereafter referred to as Study DB-03, was a Phase 3, multicentre, open-label, active-controlled study in subjects with HER2-positive, unresectable and/or metastatic BC subjects previously treated with trastuzumab and taxane (518 subjects, of whom 257 were treated with 5.4 mg/kg T-DXd; DCO date: 25 Jul 2022).
  - Study DS8201-A-U303, DESTINY-Breast04, hereafter referred to as Study DB-04, was a Phase 3, multicentre, open-label, active-controlled study for HER2-low, unresectable and/or metastatic BC subjects (543 subjects, of whom 371 subjects were treated with 5.4 mg/kg T-DXd; DCO date: 11 Apr 2022).
  - Study D9670C00001, DESTINY-Breast06, hereafter referred to as Study DB-06, was a Phase 3, multicentre, open-label, active-controlled study for hormone receptor-positive, HER2-low (IHC 1+ and IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining), unresectable and metastatic BC subjects (851 subjects, of whom 434 subjects were treated with 5.4 mg/kg T-DXd; DCO date: 18 Mar 2024).
  - Study DS8201-A-J101, hereafter referred to as Study J101, and Study D967MC00001 (DESTINY-PanTumor01), hereafter referred to as Study DP-01, included 71 and 20 BC subjects, respectively. Further details on these studies can be found below under Pan Tumours.

- Gastric cancer
  - Study DS8201-A-J202, DESTINY-Gastric01, hereafter referred to as Study DG-01, was a Phase 2, multicentre, open-label study in subjects with HER2-expressing advanced gastric or GEJ adenocarcinoma (169 subjects treated with 6.4 mg/kg T-DXd; DCO date: 03 Jun 2020).
  - Study DS8201-A-U205, DESTINY-Gastric02, hereafter referred to as Study DG-02, 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 with 6.4 mg/kg T-DXd; DCO date: 08 Nov 2021).
  - Study DS8201-A-U306, DESTINY-Gastric04, hereafter referred to as Study DG-04, was a Phase 3, multicentre, 2-arm randomised, open-label study of T-DXd in subjects with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen (244 subjects treated with 6.4 mg/kg T-DXd; DCO date: 24 Oct 2024).
  - Study D9676C00002, DESTINY-Gastric06, hereafter referred to as Study DG-06, was a Phase 2, open-label, single-arm, multicentre study conducted in mainland China (95 subjects treated with 6.4 mg/kg T-DXd; DCO date: 28 Feb 2024).
- Non-small cell lung cancer
  - Study DS8201-A-U204, DESTINY-Lung01, hereafter referred to as Study DL-01, was a Phase 2, multicentre, open-label, 2-cohort study for HER2-overexpressing or HER2-mutated, unresectable and/or metastatic NSCLC (181 subjects, of whom 41 were treated with 5.4 mg/kg T-DXd and 140 were treated with 6.4 mg/kg T-DXd; DCO date: 03 Dec 2021).
  - Study DS8201-A-U206, DESTINY-Lung02, hereafter referred to as Study DL-02, was 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; DCO date: 23 Dec 2022).
- Colorectal cancer
  - Study DS8201-A-J203, DESTINY-CRC01, hereafter referred to as Study DC-01, was a multicentre, open-label, 3-cohort, Phase 2 study of the safety and efficacy of T-DXd 6.4 mg/kg in subjects with advanced HER2-expressing colorectal cancer (CRC) who had received at least 2 prior regimens of standard treatment that had to include fluoropyrimidine, irinotecan and oxaliplatin, and an anti-epidermal growth factor receptor (EGFR) antibody in subjects with RAS-wild type (86 subjects were treated with 6.4 mg/kg T-DXd; DCO date: 28 Dec 2020).

  - Study DS8201-A-U207, DESTINY-CRC02, hereafter referred to as Study DC-02, is an ongoing, global, multicentre, randomised, 2-arm, parallel, Phase 2 study to evaluate T-DXd 5.4 mg/kg and 6.4 mg/kg in subjects with locally advanced, unresectable, or metastatic HER2-overexpressing (IHC 3+ or IHC 2+/ISH-positive) CRC (83 subjects were treated with 5.4 mg/kg T-DXd and 39 subjects were treated with 6.4 mg/kg T-DXd; DCO date: 01 Nov 2022).

- Pan Tumours
  - Study J101 was a Phase 1, 2-part, multicentre, non-randomised, open-label, multiple-dose, first-in-human study in subjects with advanced solid malignant tumours (91 subjects treated with 5.4 mg/kg T-DXd and 183 subjects treated with 6.4 mg/kg T-DXd; DCO date: 01 Aug 2019).
  - Study DP-01 was a Phase 2, multicentre, open-label study of T-DXd for the treatment of unresectable and/or metastatic solid tumours harbouring HER2-activating mutations regardless of tumour histology in subjects who had progressed following prior treatment or had no satisfactory alternative treatment options including approved second-line therapies in the specific tumour type (102 subjects were treated with 5.4 mg/kg T-DXd; DCO date: 25 Jan 2023).
  - Study D967VC00001, DESTINY-PanTumor02, hereafter referred to as Study DP-02, is an open-label, multicentre, single-arm, Phase 2 study to evaluate the antitumour activity and safety of T-DXd for the treatment of selected HER2-expressing solid tumours. Eligible subjects had locally advanced unresectable or metastatic disease and had progressed following prior treatment or have no satisfactory alternative treatment options (267 subjects were treated with 5.4 mg/kg T-DXd; DCO date for the primary analysis: 08 Jun 2023).

For the purpose of this RMP, the data of treated subjects are split into 2 pools: All Tumour Types 5.4 mg/kg (N = 2335) and All Tumour Types 6.4 mg/kg (N = 1133). The median duration of exposure among subjects within these 2 pools is presented in Table Part II: Module SIII.1.

The number of subjects split by age group and sex across the 2 pools is presented in Table Part II: Module SIII.2, while the number of subjects split by ethnic origin, race, and geographic distribution is presented in Table Part II: Module SIII.3.

Notably, in 2 of the 16 aforementioned studies, a total of 36 subjects were exposed to T-DXd doses other than 5.4 mg/kg or 6.4 mg/kg; specifically:

- In the dose escalation part of Study J101, 3 subjects were exposed to 0.8 mg/kg, 3 subjects to 1.6 mg/kg, 3 subjects to 3.2 mg/kg, and 6 subjects to 8.0 mg/kg (Module 5.3.3.2, Study J101 clinical study report [CSR] Table 14.1.1.1.1).
- In the dose finding part of Study DB-01, 21 subjects were exposed to 7.4 mg/kg (Module 5.3.5.2, Study DB-01 CSR Table 14.1.1.1).

Based on the limited sample sizes, these additional dose levels do not meaningfully contribute to the T-DXd risk assessment and they are not further discussed in the RMP. Of note, none of these additional doses are going to be further investigated in future studies.

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

	All Tumour Types 5.4 mg/kg Pool (N = 2335)	**All Tumour Types 6.4 mg/kg Pool (N = 1133)**
Duration of exposure, n (%)[a]		
0 to ≤3 months	406 (17.4)	372 (32.8)
>3 to ≤6 months	391 (16.7)	265 (23.4)
>6 to ≤9 months	375 (16.1)	188 (16.6)
>9 to ≤12 months	273 (11.7)	107 (9.4)
>12 to ≤18 months	370 (15.8)	118 (10.4)
>18 to ≤24 months	273 (11.7)	46 (4.1)
>24 months	247 (10.6)	37 (3.3)
Median duration of exposure (months), range	8.97 (0.2, 45.1)	5.06 (0.4, 41.0)
Total patient-years of exposure[b]	2235.2	674.4

N = total number of subjects in the pool; SCS = Summary of Clinical Safety
[a] Duration of treatment (months) = (date of the last dose - date of the first dose + 21)/30.44.
[b] Total patient-years of exposure = sum of duration of treatment (months)/12.
All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).
All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).
Source: DB-06 Module 5.3.5.3 SCS Table 2.7.4.1.3 and DG-04 Module 5.3.5.3 SCS Table 1.1.3

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

Age Group[a]	Number (%) of Subjects		Patient-years of Exposure[b]	
	Male	Female	Male	Female
All Tumour Types 5.4 mg/kg Pool (N = 2335)[c]				
<65 years	138 (5.9)	1523 (65.2)	80.6	1572.0
65-74 years	82 (3.5)	445 (19.1)	40.4	425.8
75-84 years	31 (1.3)	106 (4.5)	17.0	95.1
≥85 years	0	10 (0.4)	0	4.3
All Tumour Types 6.4 mg/kg Pool (N = 1133)[d]				
<65 years	359 (31.7)	325 (28.7)	193.7	237.7
65-74 years	220 (19.4)	139 (12.3)	109.5	188.4
75-84 years	55 (4.9)	32 (2.8)	28.3	15.2
≥85 years	1 (0.1)	2 (0.2)	1.0	0.7

N = total number of subjects in the pool; RMP = Risk Management Plan

[a] Age in years was calculated using the informed consent date and the birth date.

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

[c] All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).

[d] All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).

Percentages are calculated using the number (n) of subjects in each age group as the denominator.

Source: Module 5.3.5.3 RMP Table 1 (All Tumour Types 5.4 mg/kg Pool) and Table 1 (All Tumour Types 6.4 mg/kg Pool)

Table Part II: Module SIII.3: Ethnic Origin, Race, and Geographical Distribution of Subjects Receiving Trastuzumab Deruxtecan by Pool (Safety Analysis Set)

Parameter	Number (%) of Subjects	
	All Tumour Types 5.4 mg/kg Pool (N = 2335)	**All Tumour Types 6.4 mg/kg Pool (N = 1133)**
Ethnic origin[a]		
Hispanic or Latino	149 (6.4)	27 (2.4)
Not Hispanic or Latino	1972 (84.5)	736 (65.0)
Unknown[b]	38 (1.6)	44 (3.9)
Not applicable[c]	109 (4.7)	6 (0.5)
Not reported	4 (0.2)	22 (1.9)
Missing	63 (2.7)	298 (26.3)
Race		
White	1172 (50.2)	395 (34.9)
Black or African American	48 (2.1)	12 (1.1)
Asian	928 (39.7)	647 (57.1)
American Indian or Alaska Native	6 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	2 (0.1)	2 (0.2)
Multiple	2 (0.1)	1 (0.1)
Other	118 (5.1)	69 (6.1)
Not reported	55 (2.4)	0
Missing	4 (0.2)	6 (0.5)

Table Part II: Module SIII.3: Ethnic Origin, Race, and Geographical Distribution of Subjects Receiving Trastuzumab Deruxtecan by Pool (Safety Analysis Set) (Continued)

Parameter	Number (%) of Subjects	
	All Tumour Types 5.4 mg/kg Pool (N = 2335)	**All Tumour Types 6.4 mg/kg Pool (N = 1133)**
Region of origin		
Asia	877 (37.6)	622 (54.9)
North America	368 (15.8)	178 (15.7)
Europe	908 (38.9)	307 (27.1)
Rest of the World	182 (7.8)	26 (2.3)

N = total number of subjects in the pool; SCS = Summary of Clinical Safety
[a] Ethnicity was not required to be collected in all countries.
[b] Case report forms for the different studies included different options, and ethnic origins are reported according to the specific study.
[c] Subjects of Japanese origin in Study J101 were instructed to respond with "Not Applicable" upon enrolment. This option was removed for later studies.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
The pooled analysis group is based on tumour type and first dose received for subjects in each study.
All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).
All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).
Source: DB-06 Module 5.3.5.3 SCS Table 2.7.4.1.2 and DG-04 Module 5.3.5.3 SCS Table 1.1.2

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 all pooled studies in the All Tumour Types 5.4 mg/kg Pool and the All Tumour Types 6.4 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.

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 16 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 × 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 (LVEF) <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.

Clinically significant corneal disease (Study DB-01 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 2335 subjects in the All Tumour Types 5.4 mg/kg Pool and 1133 subjects in the All Tumour Types 6.4 mg/kg Pool, there is at least a 99.9% chance of observing adverse events (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 6.4 mg/kg in the clinical development programme 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 by Pool (Safety Analysis Set)

Type of Special Population	Number of Subjects in Pool	
	All Tumour Types 5.4 mg/kg Pool (N = 2335)	**All Tumour Types 6.4 mg/kg Pool (N = 1133)**
Pregnant or breastfeeding women	Not included in the clinical development programme	
Paediatric	Not included in the clinical development programme[a]	
Elderly		
≥65 years	674 (28.9)	449 (39.6)
≥75 years	147 (6.3)	90 (7.9)
≥85 years	10 (0.4)	3 (0.3)
Subjects with relevant comorbidities (baseline)		
Subjects with renal impairment (all grades)[b]	1224 (52.4)	645 (56.9)
Severe impairment (creatinine clearance ≥15, <30 mL/min)	5 (0.2)	2 (0.2)
Moderate impairment (creatinine clearance ≥30, <60 mL/min)	317 (13.6)	196 (17.3)
Mild impairment (creatinine clearance ≥60, <90 mL/min)	902 (38.6)	447 (39.5)
Subjects with hepatic impairment (all grades)[c]	956 (40.9)	329 (29.0)
Severe impairment	1 (0.0)	0
Moderate impairment	18 (0.8)	9 (0.8)
Mild impairment	937 (40.1)	320 (28.2)
Subjects with cardiovascular impairment	Subjects with LVEF <50% or recent symptomatic CHF were excluded from the clinical development programme	

AST = aspartate aminotransferase; CHF = congestive heart failure; EMA = European Medicines Agency; LVEF = left ventricular ejection fraction; N = total number of subjects in the pool; RMP = Risk Management Plan; TBL = total bilirubin; ULN = upper limit of normal

[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.

All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).

All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).

Source: Module 5.3.5.3 RMP Table 3 (All Tumour Types 5.4 mg/kg Pool) and RMP Table 3 (All Tumour Types 6.4 mg/kg Pool).

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 50 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 Marketing Authorisation Holder (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 2024, there were 5,579,274 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 1,403,834 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 2024 was 80,768.5 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 16 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 ≥3 x ULN and total bilirubin >2 x 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 ≥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 minimised 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 ≥Grade 3 serum creatinine increase, except for 1 subject ([redacted]) 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 T-DXd (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 (EF) 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 EF 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 DB-01. 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 T-DXd 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 T-DXd 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 T-DXd 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 DB-02 and DB-03), more long-term safety data will become available, which will be used to further characterise cumulative toxicity and the overall safety profile of T-DXd.

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

There were no new safety concerns identified for T-DXd and no safety concern reclassification proposed.

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).

In the All Tumour Types 5.4 mg/kg Pool, among the 379/2335 (16.2%) subjects who had an adjudicated ILD event, 276 (11.8%) subjects had events that were adjudicated as drug-related ILD (DB-06 Module 5.3.5.3 SCS Tables 2.7.4.2.4.1 and 2.7.4.2.5.1).

In the All Tumour Types 6.4 mg/kg Pool, among the 212/1133 (18.7%) subjects who had an adjudicated ILD event, 170 (15.0%) subjects had events that were adjudicated as drug-related ILD (DG-04 Module 5.3.5.3 SCS Table 1.2.5.1).

ILD in the All Tumour Types 5.4 and 6.4 mg/kg Pools is summarised by event category and grade in Table Part II: Module SVII.3.1.

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

Pool	Number (%) of Subjects with Any Event of Adjudicated Drug-related ILD by CTCAE Grade (as Graded by ILD Adjudication Committee)					
	1	2	3	4	5	Total
All Tumour Types T-DXd 5.4 mg/kg Pool (N = 2335)	65 (2.8)	171 (7.3)	17 (0.7)	0	23 (1.0)	276 (11.8)
All Tumour Types T-DXd 6.4 mg/kg Pool (N = 1133)	44 (3.9)	96 (8.5)	11 (1.0)	1 (0.1)	18 (1.6)	170 (15.0)

CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; N = total number of subjects in the pool; T-DXd = trastuzumab deruxtecan

Percentages were calculated using the number of subjects with non-missing ILD grade as the denominator.

If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade.

The pooled analysis groups were based on tumour type and assigned first dose received for subjects in each study.

All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).

All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).

Source: DB-06 Module 5.3.5.3 SCS Table 2.7.4.2.4.1 and DG-04 Module 5.3.5.3 SCS Table 1.2.4.1

Table Part II: Module SVII.3.2: Summary of Adjudicated Drug-related ILD by Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with Adjudicated Drug-related ILD	
	All Tumour Types 5.4 mg/kg Pool (N = 2335)	All Tumour Types 6.4 mg/kg Pool (N = 1133)
Subjects with any event adjudicated as drug-related ILD	276 (11.8)	170 (15.0)
Worst CTCAE Grade ≥3[a]	40 (1.7)	30 (2.6)
Grade 5[a]	23 (1.0)	18 (1.6)
Serious AE	77 (3.3)	50 (4.4)
Associated with drug discontinuation	190 (8.1)	111 (9.8)
Associated with dose reduction	24 (1.0)	8 (0.7)
Associated with drug interruption	57 (2.4)	52 (4.6)

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

[a] As graded by ILD Adjudication Committee

All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).

All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95), DL-01 (N = 140), and DL-02 (N = 50).

Source: DB-06 Module 5.3.5.3 SCS Tables 2.7.4.2.4.1, 2.7.4.2.4.2, 2.7.4.2.4.3, 2.7.4.2.4.4, and 2.7.4.2.4.5 and DG-04 Module 5.3.5.3 SCS Tables 1.4.2.4.1, 1.4.2.4.2, 1.4.2.4.3, 1.4.2.4.4, and 1.4.2.4.5

Among the 276 (11.8%) subjects with events adjudicated as drug-related ILD in the All Tumour Types 5.4 mg/kg Pool, per investigator, 146 (52.9%) recovered, 10 (3.6%) recovered with sequelae, 14 (5.1%) were recovering, 83 (30.1%) were not recovered, 16 (5.8%) had a fatal outcome, 1 (0.4%) was ongoing, and 6 (2.2%) were missing outcome information (DB-06 Module 5.3.5.3 SCS Table 2.7.4.2.5.4). The median time to first onset of ILD event was 204.0 days, and the median duration of the first ILD event (as reported by the investigator) was 76.0 days.

Among the 170 (15.0%) subjects with events adjudicated as drug-related ILD in the All Tumour Types 6.4 mg/kg Pool, per the investigator, 72 (42.4%) recovered, 5 (2.9%) recovered with sequelae, 12 (7.1%) were recovering, 63 (37.1%) were not recovered, 14 (8.2%) had a fatal outcome, none had an event that was ongoing, and 4 (2.4%) were missing outcome information (DG-04 Module 5.3.5.3 SCS Table 1.2.5.4). The median time to first onset of ILD event was 176.6 days, and the median duration of the first ILD event (as reported by the investigator) was 78.0 days.

In the All Tumour Types 5.4 mg/kg Pool, a higher incidence of adjudicated drug-related ILD was reported in subjects from Japan (63 [19.8%] subjects) compared with the subjects from other

countries (213 [10.6%] subjects) and in subjects with moderate renal impairment at baseline (58 [18.3%] subjects) compared with subjects who had mild renal impairment at baseline (93 [10.3%] subjects) or normal renal function (123 [11.1%] subjects) (DB-06 Module 5.3.5.3 SCS Table 2.7.4.4.13). 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 (DB-06 Module 5.3.5.3 SCS Table 2.7.4.4.13).

Similarly, in the All Tumour Types 6.4 mg/kg Pool, a higher incidence of adjudicated drug-related ILD was reported in subjects from Japan (86 [21.9%] subjects) compared with the subjects from other countries (84 [11.4%] subjects) and in subjects with moderate renal impairment at baseline (40 [20.4%] subjects) compared with subjects who have mild renal impairment at baseline (66 [14.8%] subjects) or normal renal function (62 [13.1%] subjects) (DG-04 Module 5.3.5.3 SCS Table 1.4.13).

Spontaneous data from the global safety database up to data lock point (19 Dec 2024):

The following group of Medical Dictionary for Regulatory Activities (MedDRA) PTs have been used to define ILD for T-DXd in the postmarketing setting: Pneumonitis, Interstitial lung disease, Organising pneumonia, and Acute interstitial pneumonitis. By using this approach, a total of 2501 cases were identified cumulatively. Reporting rates are different between regions; in particular, the ILD reporting rate in Japan is higher. It is unknown whether this is due to biological factors or differences in monitoring and management practices; however, this trend of higher incidence of ILD in Japan has continuously been observed in T-DXd clinical trials, and prior studies in other anticancer drugs have also observed a higher incidence of drug-induced ILD in Japan compared to other countries.

The proportion between fatal cases and total ILD cases remains stable over time.

Time to onset ranged from 1 to 1240 days with a median of 127 days. Age spanned from 24 years to 93 years (median 63). Indication for T-DXd was BC in 67.5% of the cases, GC in 10.5%, lung cancer in 4.4%, and the remaining cases derived from other cancers or unknown indication in 17.7%.

In the majority of cases (60.9%), T-DXd was withdrawn due to the ILD event. Outcome data suggest that ILD might be managed appropriately in clinical practice (recovered 24.3%, recovered with sequelae 1.1%, recovering 21.6%, not recovered 7.9%, fatal 13.6%, and unknown 31.4%).

A review of drug-related ILD in patients where renal impairment was reported in their medical history prior to treatment with T-DXd (cumulative data until 19 Dec 2024) revealed that renal impairment at baseline was reported in less than 1% (13/2501 [0.5%]) of patients with drug-related ILD. Patients with moderate renal impairment should be monitored carefully.

Overall, evidence from postmarketing, 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.

The following 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
- 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.

Although the multivariate analysis showed baseline peripheral oxygen saturation (SpO2) to be associated with an increased hazard of drug-related ILD/pneumonitis for the data pool including multiple tumours, this finding is not confirmed across pools per indication (ie, BC and GC). Further analysis revealed that most subjects with SpO2 <95% at baseline showed fluctuation of SpO2 values to ≥95% in the following treatment cycles, regardless of later occurrence of ILD/pneumonitis. In addition, no literature suggesting the value of SpO2 as a predictable marker for occurrence of pulmonary disease was identified. Therefore, baseline SpO2 is excluded as a risk factor.

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).

EF decreases have been reported with T-DXd. However, available clinical data show that the reported EF 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 by Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with LV Dysfunction[a]	
	All Tumour Types 5.4 mg/kg Pool (N = 2335)	All Tumour Types 6.4 mg/kg Pool (N = 1133)
Treatment-emergent AE with any grade	108 (4.6)	23 (2.0)
CTCAE Grade ≥3	14 (0.6)	6 (0.5)
Serious AE	5 (0.2)	1 (0.1)
Associated with drug discontinuation	9 (0.4)	3 (0.3)
Associated with dose reduction	1 (0.0)	0
Associated with drug interruption	27 (1.2)	6 (0.5)
Associated with an outcome of death	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; LV = left ventricular; N = total number of subjects in the pool; PT = preferred term; SCS = Summary of Clinical Safety

[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.

All Tumour Types 5.4 mg/kg Pool: Studies J101 (N = 91), DB-01 (N = 184), DB-02 (N = 404), DB-03 (N = 257), DB-04 (N = 371), DB-06 (N = 434), DC-02 (N = 83), DL-01 (N = 41), DL-02 (N = 101), DP-01 (N = 102), and DP-02 (N = 267).

All Tumour Types 6.4 mg/kg Pool: Studies J101 (N = 183), DB-01 (N = 48), DC-01 (N = 86), DC-02 (N = 39), DG-01 (N = 169), DG-02 (N = 79), DG-04 (N = 244), DG-06 (N = 95); DL-01 (N = 140), and DL-02 (N = 50).

Source: DB-06 Module 5.3.5.3 SCS Tables 2.7.4.2.6.1, 2.7.4.2.6.2, 2.7.4.2.6.3, 2.7.4.2.6.4, and 2.7.4.2.6.5 and DG-04 Module 5.3.5.3 SCS Tables 1.2.6.1, 1.2.6.2, 1.2.6.3, 1.2.6.4, 1.2.6.5, and 1.2.6.6

LV dysfunction was reported infrequently. Specifically, 14 (0.6%) subjects in the All Tumour Types 5.4 mg/kg Pool and 1 (0.1%) subject in the All Tumour Types 6.4 mg/kg Pool experienced Grade 1 events, 80 (3.4%) and 16 (1.4%) subjects, respectively, experienced Grade 2 events, 13 (0.6%) and 6 (0.5%) subjects, respectively, experienced Grade 3 events, and 1 (0.0%) and no subjects, respectively, experienced Grade 4 events (DB-06 Module 5.3.5.3 SCS

Table 2.7.4.2.6.1 and DG-04 Module 5.3.5.3 SCS Table 1.2.6.1). The observed frequency of LVEF decreased on the basis of TEAEs and laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 325 (13.9%) in the All Tumour Types 5.4 mg/kg Pool (the majority being Grade 2 [295 (12.6%)] and 23 [1.0%] being Grade 3) and 128 (11.3%) in the All Tumour Types 6.4 mg/kg Pool (the majority being Grade 2 [114 (10.1%)] and 13 [1.1%] being Grade 3 (Module 5.3.5.3 RMP Table 4 [All Tumour Types 5.4 mg/kg Pool] and DG-04 Module 5.3.5.3 SCS Table 1.2.6.9). Notably, in Study DB-03, similar proportions of subjects in the T-DXd and T-DM1 arms experienced Grade 2 and Grade 3 LVEF decrease. 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 decrease <40% was measured in 3 (0.1%) subjects in the All Tumour Types 5.4 mg/kg Pool and in 5 (0.4%) subjects in the All Tumour Types 6.4 mg/kg Pool (see DB-06 Module 5.3.5.3 SCS Table 2.7.4.2.6.8 and DG-04 Module 5.3.5.3 SCS Table 1.2.6.8).

The most frequent PT used for LV dysfunction was PT of EF decreased (99/108 subjects in the All Tumour Types 5.4 mg/kg Pool and 20/23 subjects in the All Tumour Types 6.4 mg/kg Pool; DB-06 Module 5.3.5.3 SCS Table 2.7.4.2.6.1 and DG-04 Module 5.3.5.3 SCS Table 1.2.6.1). Other than EF decreased, PTs reported included cardiac failure (5 subjects), cardiac failure acute (1 subject), cardiac failure chronic (1 subject), cardiac failure congestive (1 subject), and left ventricular dysfunction (3 subjects) in the All Tumour Types 5.4 mg/kg Pool and cardiac failure (2 subjects), cardiac failure acute (1 subject), cardiac failure congestive (1 subject), and left ventricular dysfunction (1 subject) in the All Tumour Types 6.4 mg/kg Pool.

Spontaneous data from the global safety database up to data lock point (19 Dec 2024):

The standardised MedDRA query (SMQ) Cardiac failure (Narrow Scope) and PT left ventricular dysfunction was used to define left ventricular dysfunction in the postmarketing setting. This approach yielded 188 cases cumulatively, with 119 reporting EF decrease (14 of them accompanied by other cardiac events, including cardiac failure congestive, cardiac failure, cardiac disorder, cardiac dysfunction, ventricular dysfunction, cardiac ventricular thrombosis, cardiomyopathy, cardiotoxicity, ventricular hypokinesia, bundle branch block, and echocardiogram abnormal. The remaining 69 cases included PTs of cardiac failure, pulmonary oedema, left or right ventricular dysfunction/failure, cardiopulmonary failure, cardiac arrest, and cardiogenic shock. In total, 102 cases were serious (mainly cases of EF decreased, cardiac failure, and pulmonary oedema) and 86 cases were nonserious (mainly cases of EF decreased). Cases were often confounded by underlying cardiac/cardiovascular comorbidities and/or disease progression. For 12 cases, a fatal outcome was reported (3 cardiac failure, 2 cardiac failure acute, 1 cardiac failure congestive, 2 cardiogenic shock, 2 cardiopulmonary failure, and 2 EF decreased with ILD); however, death was mostly associated with progression of the underlying disease or ILD/pneumonitis.

Indication for T-DXd was BC in 72.9% of the cases, GC in 9.6%, lung cancer in 4.8%, and the remaining cases derived from other cancers or unknown indication in 12.8%.

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.

Overall, evidence from postmarketing cases does not alter the risk of left ventricular dysfunction as observed in clinical trials.

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 All Tumour Types 5.4 mg/kg and All Tumour Types 6.4 mg/kg Pool, 40% and 8.6% of subjects, respectively, received prior therapy of anthracyclines.

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/haematopoietic 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:

As of 19 Dec 2024, no cases of pregnancy have been reported in clinical studies of T-DXd and 3 cases of pregnancy were reported in the postmarketing setting for T-DXd.

One case of pregnancy was reported in Greece. A 55-year-old female with HER2-positive metastatic BC was pregnant with twins during exposure to T-DXd. Action taken with T-DXd and outcome were reported as unknown, and no further follow-up information could be obtained.

Another case of pregnancy was reported in the US. A 40-year-old female with HER2-positive metastatic BC became pregnant while taking T-DXd. The pregnancy was terminated, and an intrauterine device was placed. No further information is expected for this case.

One case of drug exposure before pregnancy in a 36-year-old female with HER2-positive BC was received in France; the subject elected voluntary premature termination of pregnancy.

In all cases, no AE was reported.

No pregnancy in a female partner of a male receiving T-DXd has occurred in clinical studies or postmarketing reports for T-DXd.

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 reporting PT ‘wrong drug administered’ or ‘product name confusion’. Both cases involve two trastuzumab-containing products and both cases were not associated with an AE.

As of 19 Dec 2024, 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 HCP 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 T-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
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.
  - MedDRA search criteria for the identification of cases of ILD/pneumonitis for which the follow-up questionnaire is sent includes ILD SMQ Narrow PTs and select Broad PTs.
- **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.
  - MedDRA search criteria for the identification of cases of left ventricular dysfunction for which the follow-up questionnaire is sent includes Cardiac Failure SMQ Narrow PTs and Select Broad PTs.

Batch related activities:

- T-DXd will be administered by an HCP via IV infusion once every 3 weeks.
- The 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

Not applicable.

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 : None				

PART IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

The MAH is currently conducting 1 Phase 3 clinical trial:

- 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 harbouring 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
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 harbouring HER2 exon 19 or 20 mutations	Overall efficacy and safety	Submission of results	Q4 2026

BICR = blinded independent central review; HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; PFS = progression-free survival; 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	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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. Other routine risk minimisation measures beyond the Product Information: 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
Important Identified Risks	
Left ventricular dysfunction	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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. Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription.
Important Potential Risks	
Embryo-foetal toxicity	Routine risk communication : SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal status: T-DXd is subject to medical prescription
Product confusion-related Medication error	Routine risk communication : SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: 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	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Legal status: T-DXd is subject to medical prescription
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: 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	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Recommendations for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. Dose modification guidance and recommendation for corticosteroid treatment for managing the risk of ILD/pneumonitis are included in SmPC Section 4.2. Recommendation for careful monitoring of patients with moderate or severe renal impairment is included in SmPC Section 4.2. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

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	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for ENHERTU on the packaging and specific colours for vial cap and bottle to distinguish from other trastuzumab-containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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

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:
  - HR-positive, HER2-low or HER2-ultralow BC who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment (see sections 4.2 and 5.1).
  - 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 (see section 4.2).
- 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 CHARACTERISE 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	The following 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; 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	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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. Additional risk minimisation measures: Healthcare Professional Guide and Patient Card
Additional pharmacovigilance activities	None

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

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	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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. Additional risk minimisation measures: 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	Routine risk communication: SmPC Section 4.4 SmPC Section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation measures: None

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

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	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation measures: 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	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation activities: 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, as defined in the All Tumour Types 5.4 mg/kg Pool (N = 2335), was 8.97 months (range: 0.2 to 45.1). A total of 375 (16.1%) subjects had been treated for >6 to ≤9 months, 273 (11.7%) for >9 to ≤12 months, 370 (15.8%) for >12 to ≤18 months, 273 (11.7%) for >18 to ≤24 months, and 247 (10.6%) for >24 months. The median treatment duration, as defined in the All Tumour Types 6.4 mg/kg Pool (N = 1133), was 5.06 months (range: 0.4 to 41.0). A total of 188 (16.6%) subjects had been treated for >6 to ≤9 months, 107 (9.4%) for >9 to ≤12 months, 118 (10.4%) for >12 to ≤18 months, 46 (4.1%) for >18 to ≤24 months, and 37 (3.3%) for >24 months.
Risk minimisation measures	Routine risk minimisation communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation activities: 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 trial DESTINY-Lung04 serves as a confirmatory trial (see also RMP Part IV). Details are provided in the table below.

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	Primary objective: 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. Secondary objectives: • 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; 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; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; T-DXd = trastuzumab deruxtecan

II.C.2 Other Studies in Postauthorisation Development Plan

Not applicable.

PART VII ANNEXES

LIST OF ANNEXES

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 *Please provide start date and details of the ILD adverse event.*			
Start date (dd/mm/yyyy):			
ILD adverse event details			
Signs/Symptoms *Please provide start and stop date(s) and details of the following relevant signs/symptoms, if applicable.*			
Relevant Signs/Symptoms	**Start and Stop Date(s) (dd/mm/yyyy)**	**Details**	
☐ Fever			
☐ Dyspnea (shortness of breath)			
☐ Cough			
☐ Pleural effusion			
☐ Other(s)			

Laboratory Tests *Please provide details of the following relevant lab tests, if applicable.*				
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 *Please provide date(s) and results of the following relevant diagnostic tests, if applicable.*		
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)		

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:

Relevant Medical History *Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.*		
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):

Is ILD event possibly related to ENHERTU?	☐Yes ☐No ☐UNK	Explanation:
Event Outcome *Please select all that apply.*		
☐ 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 *Please complete if reported ILD event was due to* ENHERTU.			
Suspect drug name:			
Lot number:		Indication:	
Dose:		Frequency:	
Start dates (dd/mm/yyyy):		Stop dates (dd/mm/yyyy):	
Suspect Drug *Please complete if reported ILD event was due to any other suspect drug besides* ENHERTU.			
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)

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 *Please circle all that apply.*			
Dyspnea or orthopnea (shortness of breath)/Fatigue/Palpitations/Chest pain/Peripheral edema/Hepatomegaly (enlarged liver)/Other (s)			
Cardiac Consultation			

Was a cardiac specialist consulted?	☐ Yes ☐ No If yes, consultation notes:

New York Heart Association (NYHA) Classification

Please provide severity of heart failure (at the time of adverse event), if applicable.

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

Please provide date(s) and results of the following relevant diagnostic/laboratory tests, if applicable.

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):

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

Please provide date(s)/diagnosis date and details of the following relevant past medical history, if applicable.

	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

Please complete if reported LVEF event was due to ENHERTU

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)

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 shall ensure that in 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 following educational materials:

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

The HCP Guide contains 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

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

The HCP Guide contains 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

III) **Patient Card**

The Patient Card contains 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