EU Risk Management Plan for Enhertu (Trastuzumab Deruxtecan)

RMP version to be assessed as part of this application:

Data lock point for this RMP	1 Aug 2019	RMP Version number	1.0
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Rationale for submitting an updated RMP:

Not applicable

Summary of significant changes in this RMP:

Not applicable

QPPV name:

[redacted]

QPPV signature: [redacted]

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PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	Trastuzumab deruxtecan (DS-8201a)
Pharmacotherapeutic group(s) (ATC Code):	ATC code not yet assigned
Name of Marketing Authorisation Applicant:	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers:	Trastuzumab deruxtecan
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 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 trastuzumab deruxtecan is a humanized IgG1 mAb produced by mammalian (Chinese hamster ovary) cell culture.
Hyperlink to the Product Information:	Summary of Product Characteristics (SmPC)

Indication(s) in the EEA:	Current: Not applicable
	Proposed: Trastuzumab deruxtecan is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens.

Table Part I.1: Product Overview (Continued)

Dosage in the EEA	Current: Not applicable
	Proposed: The recommended dose of trastuzumab deruxtecan is 5.4 mg/kg given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. . The initial dose should be administered as a 90-minute IV infusion. If the prior infusion was well tolerated, subsequent doses of trastuzumab deruxtecan may be administered as 30-minute infusions. The infusion rate of trastuzumab deruxtecan should be slowed or interrupted if the patient develops infusion-related symptoms. Trastuzumab deruxtecan should be permanently discontinued in case of severe infusion reactions. See SmPC Section 4.2 for detailed dose modification information.
Pharmaceutical form(s) and strengths	Current: Not aplicable
	Proposed: 100 mg of trastuzumab deruxtecan as a white to yellowish-white lyophilized powder in a single-dose vial. Must be reconstituted and diluted by a healthcare professional and administered as an IV infusion. Trastuzumab deruxtecan must not be administered as an IV push or bolus.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

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

As there are limited epidemiological data in the literature for the HER2-positive breast cancer (BC) population, data herein are generally presented on general BC, with HER2-positive BC data included where available.

Indication: Trastuzumab deruxtecan is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens.

Incidence and Prevalence:

Approximately 11.6% of all new cancers are female BC, which has an annual incidence rate of 46.3 per 100,000 worldwide.[1] Australia/New Zealand, Europe, and North America have the highest incidence by region.

Crude and world- and Europe-standardised incidence rates for HER2-positive BC are compared to overall BC incidence rates in Table Part II: Module SI.1.[2]

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

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

Source: Cortet 2018[2]

Breast cancer is the most common cancer in women, accounting for 2.1 million new cases worldwide in 2018. In 2018, there were an estimated 6,875,099 women living with BC diagnosed in the last 5 years worldwide, with a 5-year prevalence rate of 181.8 per 100,000.[1]

Approximately 20% of patients with BC globally have HER2-positive tumors.[3] HER2 positivity is associated with more aggressive disease. HER2-positive BC is also associated with negative hormone receptor (HR) status and a younger patient population.[4,5] Among all BC cases in the Cortet study cited above, 6.3% were HR-positive/HER2-positive and 3.7% were HR-negative/HER2-positive.[2]

European Union (EU):

In the EU-27, 349,481 new cases of female BC were diagnosed in 2018, comprising approximately 12.3% of all cancers. The estimated annual age-standardised (worldwide) incidence rate of BC is 82.4 per 100,000 in the EU. In 2018, there were an estimated 1,410,831 women living with BC in the EU who were diagnosed in the last 5 years, providing a 5-year prevalence rate of 623.6 per 100,000.[1]

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. The study population comprised a total of 152,311 metastatic BC patients in the EU-5 countries. HER2-positive/HR-negative BC was the least prevalent in France (9%) and most prevalent in Italy (13.5%). The proportion of with HER2-positive/HR-positive patients ranged from 13.1% in France to 20.7% in Italy.[6]

Demographics of the population in the proposed indication and risk factors for the disease:

Gender:

Breast cancer is mainly a disease in females, with 1% of cases occurring in males.[7]

Age:

Approximately10.5% of BCs occur in women younger than 45.[4] Worldwide, 48% of the newly diagnosed BC patients are 45 years to 64 years of age. In Europe (47%), BC is most frequently diagnosed among older women (55 years to 75 years of age).[1] Breast cancer incidence is much higher among adults and increases with age, with the highest incidence rate among those 65 years and older.[1,8]

Among patients with metastatic BC, those with HER2-positive tumors are younger than those with HER2-negative. The youngest among a metastatic BC EU-5 population seemed to be those with HER2-positive HR-negative tumors, where 28% were younger than 50 years of age.[6]

Race and/or Ethnicity

According to the SEER cancer query system, age-adjusted incidence of BC is highest in White females (103 per 100,000). Incidence of BC in Black and Asian/Pacific Islander females is 98.6 and 81.3 per 100,000, respectively. Breast cancer risk is lower in Hispanic females, with an age-adjusted incidence rate of 77.7 per 100,000.[9]

Family history:

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

Reproductive factors:

Women who have early menarche (before age 12) or late menopause (after age 55) have a higher risk of developing BC.[10,11] Nulliparous women and women who are over age 30 at their first birth may have a greater chance of developing BC.[11]

Obesity:

Obesity increases the risk of BC (possibly through an increase in estrogen levels) in postmenopausal women. In premenopausal women, obesity is associated with a reduced incidence of BC.[12]

Previous benign breast disease:

Women with atypical epithelial hyperplasia have a higher risk (4 to 5 times) of developing BC.[13]

Birth control pills:

Oral contraceptive use may slightly increase the risk of developing BC. The risk decreases once the pills are stopped. Ten years after cessation of the oral contraceptive agent, there is no significantly increased risk of having BC.[14]

Combined postmenopausal hormone therapy:

Women who use combined hormone therapy after menopause have an increased risk of developing BC. There is a dose-response relationship, with larger risks corresponding with longer durations of combined hormonal therapy use.[15]

Radiation exposure:

Children or young adults exposed to radiation therapy to the chest area have a significantly increased risk of developing BC later in life.[16]

The main existing treatment options:

Although HER2-targeted drugs have been developed as molecularly targeted therapies, locally advanced and metastatic tumors invariably relapse with time.[3]

The first targeted agent for HER2 therapy, trastuzumab (HERCEPTIN®), is a humanized mAb directed against the extracellular domain of HER2. Other HER2-targeting agents have subsequently been approved, including the ADC KADCYLA® (T-DM1); the tyrosine kinase inhibitor NERLYNX® (neratinib) as monotherapy in early-stage BC and in combination with capecitabine in metastatic BC; and the mAb PERJETA® (pertuzumab), and the tyrosine kinase inhibitor TYKERB® (lapatinib) each in combination with other chemotherapeutic agents. Although anti-HER2 targeted therapies have improved outcomes, they are not curative in the metastatic setting. The ADC fam-trastuzumab deruxtecan-nxki (Enhertu) monotherapy was approved by the United States (US) Food and Drug Administration (FDA) on 20 Dec 2019 as a new treatment option for HER2-positive unresectable or metastatic BC after 2 or more prior anti-

HER2 BC treatments, in the metastatic setting. Trastuzumab deruxtecan was approved in Japan on 25 Mar 2020 for patients with HER2-positive unresectable or recurrent BC that has progressed after chemotherapy, limiting the use to patients who are refractory or intolerant to standard treatments.

The current standard of care for newly diagnosed HER2-positive metastatic BC in Europe is a combination of pertuzumab, trastuzumab, and taxane, per the European Society for Medical Oncology (ESMO),[17] based on results from the CLEOPATRA[18] study, followed by treatment with T-DM1, as established by the EMILIA[19] study. T-DM1 has been established as the standard of care for subsequent line anti-HER2 therapy.[20]

T-DM1 (a HER2-targeted ADC) was approved by the European Medicines Agency (EMA) and the US FDA in 2013 as a single agent for the treatment of patients with HER2-positive, metastatic BC (in the US) or patients with HER2-positive, unresectable locally advanced or metastatic BC (in the EU) who previously received trastuzumab and a taxane, separately or in combination.

There is no single, clearly defined standard of care approved for patients with metastatic disease after failure of trastuzumab/pertuzumab and T-DM1-containing regimens. ESMO/National Comprehensive Cancer Network (NCCN) guidelines recommend continued anti-HER2 therapy in this setting but offer no specific recommendation for the choice of regimen.[17,20]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

- Metastatic HER2-positive BC remains an incurable disease that is ultimately fatal. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic HER2-positive BC, the disease invariably progresses with median survival being 2 to 4 years.
- Metastatic BC is the third most common cause of death in Europeans after lung and colorectal cancer. According to Globocan data, approximately 626,679 women died from BC worldwide in 2018, with a 5-year age-adjusted mortality rate of 13.0 per 100,000.[1] Data from 279 population-based cancer registries from 67 countries showed that the 5-year survival from BC is increasing in most developed countries.[21]
- The estimated number of deaths from BC in the EU was 98,755 in 2018.[1] Overall, BC mortality rates in the EU declined by 15%, from 17.9% in 2002 to 15.2% per 100,000 in 2012. The mortality rate increased with increasing age and was highest among the oldest age group (70 years to 79 years).[22]
- The 5-year relative survival rate for BC patients in the US is 89.7%. Survival is higher among White patients than African American patients in all age groups. Survival also differs by cancer stage at diagnosis, with localised disease having a survival rate up to 98.7% and metastatic disease having a survival rate up to 27.0%. Overall, the 5-year relative survival for BC has been increasing from 74.8% in 1975 to 91.1% in 2014. In 2018, there were an estimated 40,920 deaths among BC patients in the US. The mortality rate has been estimated to be 20.9 deaths per 100,000 persons per year based on the 2013 to 2015 data. The median age at death was 68 years, and most deaths occurred among those aged 65 to 74 years.[8]

- In 2018, Japan had an estimated 15,452 BC deaths, with a 5-year mortality rate of 9.3 per 100,000.[1]

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

Bone pain: Among BC patients with distant metastases, bone is the most common site for metastasis.[23] The risk of developing bone metastases within 10 years after diagnosis was 7% to 9% according to a Canadian study.[24] A retrospective study on 35,912 Danish BC patients found that 4.2% of BC patients develop bone metastasis within 5 years of diagnosis. Among BC patients with bone metastases, 47.7% developed skeletal-related events (SREs) defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopedic surgery.[25]

Brain metastases: Brain metastasis (BM) was found in 5.1% of BC patients.[26,27] The symptoms most commonly associated with BM were headache (35%), vomiting (26%), nausea (23%), hemiparesis (22%), visual changes (13%), seizures (12%) and altered mental status (7%).[28] In a retrospective study of clinical data of German BC patients with BM, median overall survival (OS) time after BM development was reported as 7.4 months, with a one-year survival rate of 37.7%. Patients with HER2-positive tumours had the longest median OS of 11.6 months (95% confidence interval: 10.0, 13.4) and those who received anti-HER2 therapy had a longer median OS (17.1 months).[29]

Cardiotoxicity: Anthracyclines (eg, doxorubicin and epirubicin) used in the treatment of BC cause a dose-dependent, cumulative, progressive cardiac dysfunction that may ultimately lead to symptomatic congestive heart failure (CHF).[30] Cardinale et al reported that in 1344 BC patients receiving anthracycline-based therapy, the incidence of cardiac toxicity was 9.7% at a median follow-up of 5.2 years.[31]

Trastuzumab treatment in HER2-positive BC patients was associated with cardiac toxicity with heart failure incidence up to 4.7%[32] and asymptomatic decline in left ventricular ejection fraction (LVEF) up to 20.6%.[33]

Radiation exposure in BC patients is associated with increased risk of ischemic heart disease with a magnitude of the risk of 7.4% per gray. There was no apparent threshold below which there was no risk. The risk was dose-dependent with a lag time of up to 20 years.[34]

Hepatoxicity/Liver metastases: Liver metastases develop in approximately half of the women with metastatic BC and represent a frequent cause of mortality among these patients.[23] According to a UK study, the risk of developing liver metastasis in 6 years after BC diagnosis is 5.2%.[35] Liver metastases were present in only 1.4% of overall BC patients and 3.3% of HER2-positive BC patients at the time of the initial BC diagnosis and are typically associated with metastases at other sites.[36] In 78.6% of cases, the liver metastases were asymptomatic at the time of metastatic diagnosis. The remainder were symptomatic, presenting with epigastric pain or fullness (21.4%), palpable hepatomegaly (27.3%) and ascites (6.2%).[37]

Patients with HER2-positive BC receiving anti-HER2 therapy may develop hepatotoxicity. In an analysis of T-DM1 trials, increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of ≥Grade 3 were reported in 4.3% and 3.1% of T-DM1-exposed BC patients, respectively.[38]

Pulmonary toxicity/Pulmonary metastases: In a systematic literature review of pneumonitis associated with BC therapy, the authors reported that most of the currently used BC treatments may induce pneumonitis with an incidence of 1% to 3%.[39]

Approximately 31% of metastatic BC patients suffer lung metastasis.[23] Metastasis to the lung is associated with poor prognosis, with patients presenting with clinical symptoms such as pain, cough, hemoptysis, pleural effusion, and pulmonary dysfunction.[40]

Important co-morbidities:

Breast cancer patients with comorbidities have overall higher mortality compared to patients without comorbidities.

Multiple registry studies have shown a correlation between the presence of comorbidities and higher mortality. A nationwide population-based cohort study of 9329 BC patients of all ages in Denmark, a nationally representative cancer registry in Sweden including 42,646 BC patients from 1992 to 2008, and a Dutch registry-based study of 9123 BC patients all included similar proportions of patients with at least 1 comorbidity (22%, 13%, and 28%, respectively). In each of these studies, patients with at least 1 comorbid condition had a higher mortality rate than patients with no comorbidities.[41,42,43]

In the US, a retrospective cohort study (N = 5186) in an elderly BC population found 22% of patients had at least 1 comorbidity at the time of BC diagnosis. Patients with comorbidities had a significantly higher mortality rate (risk ratio [RR] = 1.4 for patients with a single comorbidity and RR = 2.0 for patients with 2 or more comorbidities) compared to patients without any comorbidities.[44]

A systematic review of 18 studies on BC survival and comorbid conditions demonstrated that the presence of comorbidities at baseline was an important independent prognostic factor and was associated with poorer BC survival. In this review population, hypertension was the most common comorbidity. Other reported common comorbid conditions were cardiovascular disease, diabetes, previous cancer, cerebrovascular disease, and pulmonary disease.[45, 46, 47, 48, 49, 50, 51]

Among patients in a study of 5 European countries, the majority of patients with HER2-positive BC had no comorbidities (Table Part II: Module SI.2).[6]

Table Part II: Module SI.2: Summary of Safety Concerns

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

BC = breast cancer; COPD = chronic obstructive pulmonary disease; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor
Includes patients from UK, Germany, France, Spain and Italy
Source: DeKoven 2012[6]

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety profile of trastuzumab deruxtecan 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	-	-

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[52]

Information on key safety findings from the nonclinical studies with trastuzumab deruxtecan and released drug (the drug component of trastuzumab deruxtecan, 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 trastuzumab deruxtecan (dosing once every 3 weeks [q3w] for 6 weeks), diarrhoea was noted. Trastuzumab deruxtecan-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 trastuzumab deruxtecan 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 trastuzumab deruxtecan and released drug. Several GI events are considered identified risks for trastuzumab deruxtecan; however, these events can be adequately managed through labelling and are not considered important risks for inclusion in the RMP (Section Part II: Module SVIISVII.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/hematopoietic toxicity: Trastuzumab deruxtecan: In the rat 6-week intermittent-dose (q3w dosing) toxicity study of trastuzumab deruxtecan, 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 hematological 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 trastuzumab deruxtecan, 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, hemoglobin, hematocrit, and reticulocyte ratio) were also observed. Released drug: The lymphatic/hematopoietic organ toxicity observed with trastuzumab deruxtecan 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 trastuzumab deruxtecan and released drug, including decreased hematopoietic 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 trastuzumab deruxtecan; however, they are not considered important risks for inclusion in the RMP as they can be managed through standard clinical practice (Section Part II: Module SVIISVII.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: Trastuzumab deruxtecan 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 trastuzumab deruxtecan, 1 male given 78.8 mg/kg showed aggregation of foamy macrophages in the alveolus, focal interstitial inflammation, alveolar edema, 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 edema 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 trastuzumab deruxtecan, 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 trastuzumab deruxtecan 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 Part II: Module SVIISVII.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 trastuzumab deruxtecan (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 trastuzumab deruxtecan (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 trastuzumab deruxtecan. Histopathological changes at only supratherapeutic doses of trastuzumab deruxtecan 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 trastuzumab deruxtecan has been identified. 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 Part II: Module SVIISVII.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
Skin toxicity: Trastuzumab deruxtecan: In the rat 6-week intermittent-dose (q3w dosing) toxicity study of trastuzumab deruxtecan, 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 trastuzumab deruxtecan (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 maculo-papular) is considered an identified risk for trastuzumab deruxtecan; however, it is not considered an important risk for inclusion in the RMP (Section Part II: Module SVIISVII.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 trastuzumab deruxtecan 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 trastuzumab deruxtecan. 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 trastuzumab deruxtecan 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 trastuzumab deruxtecan but are not considered important for inclusion in this RMP (Section Part II: Module SVIISVII.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 trastuzumab deruxtecan 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 trastuzumab deruxtecan 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, trastuzumab deruxtecan 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 trastuzumab deruxtecan and released drug. QT was routinely monitored through ECG in clinical studies with trastuzumab deruxtecan. A study to evaluate the effect of trastuzumab deruxtecan 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.

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

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Ocular toxicity: Trastuzumab deruxtecan: In the intermittent IV dosing studies of trastuzumab deruxtecan (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. Dry eye is an identified risk for trastuzumab deruxtecan but is not considered an important risk. Keratitis is a potential risk for trastuzumab deruxtecan but is not considered an important risk for inclusion in this RMP. (Section Part II: Module SVIISVII.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.[53] Trastuzumab deruxtecan: In the 6-week intermittent-dose study of trastuzumab deruxtecan 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 trastuzumab deruxtecan 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 with trastuzumab deruxtecan. Post-marketing AE reports for trastuzumab showed that treatment during pregnancy has resulted in oligohydramnios, manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. 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 trastuzumab deruxtecan 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 Part II: Module SVIISVII.7SVII.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 Part II: Module SVIISVII.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
Carcinogenicity: No carcinogenicity studies have been conducted in accordance with ICH S9.	Trastuzumab deruxtecan is being studied for the treatment of cancer.

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

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

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

Cumulatively through 01 Aug 2019, 645 subjects had been exposed to trastuzumab deruxtecan in the 5 completed studies (Studies DS8201-A-U201, DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104). The pivotal results are based on the pooling of data from Study DS-8201-A-J101 and Study DS-8201-A-U201 (described below), which comprise a majority of patients in the target indication treated at the target dose.

- Study DS8201-A-J101 was a Phase 1, 2-part, multicentre, non-randomised, open-label, multiple-dose first-in-human study in subjects with advanced solid malignant tumors (289 treated subjects; data cut-off date: 01 Feb 2019)
- Study DS8201-A-U201 was a Phase 2, multicentre, open-label study in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1 (253 subjects treated; data cut-off date: 21 Mar 2019)

The median duration of exposure among subjects with HER2-positive BC who received 5.4 mg/kg in these 2 pivotal studies is presented in Table Part II: Module SIII.1.

Table Part II: Module SIII.1: Duration of Exposure to Trastuzumab Deruxtecan in Study DS8201-A-J101 and Study DS8201-A-U201 (Safety Analysis Set)

	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg (N = 234)	**HER2-positive BC ≥6.4 mg/kg (N = 137)**	**All Tumor Types 5.4 mg/kg (N = 275)**	**All Tumor Types ≥6.4 mg/kg (N = 258)**
Duration of Exposure (months) [a]				
0 to ≤3	35 (15.0)	14 (10.2)	48 (17.5)	52 (20.2)
>3 to ≤6	35 (15.0)	24 (17.5)	46 (16.7)	47 (18.2)
>6 to ≤9	37 (15.8)	32 (23.4)	40 (14.5)	48 (18.6)
>9 to ≤12	58 (24.8)	17 (12.4)	64 (23.3)	30 (11.6)
>12 to ≤24	64 (27.4)	43 (31.4)	70 (25.5)	70 (27.1)
>24	5 (2.1)	7 (5.1)	7 (2.5)	11 (4.3)
Median duration of exposure (months)	9.82	8.97	9.43	7.84
Total patient-years [b]	188.9	124.0	215.6	205.7

BC = breast cancer; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool
Note: The pooled analysis groups for HER2-positive BC and all tumor types at their respective dose levels were based on data for subjects in Studies DS8201-A-J101 and DS8201-A-U201. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] Duration of exposure (months) = (date of the last dose - date of the first dose + 21)/30.44.
[b] Patient-years of exposure = sum (duration of exposure [months])/12.
Source: Safety Update Table 1.1.3.

The number of subjects in the HER2-positive BC 5.4 mg/kg Pool is presented by age group and gender in REF _Ref34659930 \h * MERGEFORMAT Table Part II: Module SIII.2. The median age was 56.0 years in the HER2-positive BC 5.4 mg/kg Pool and 57.0 years in the All Tumor Types 5.4 mg/kg Pool (ISS Table 1.1.2).

Table Part II: Module SIII.2: Age Group and Gender of Subjects Receiving Trastuzumab Deruxtecan 5.4 mg/kg in Study DS8201-A-J101 and Study DS8201-A-U201 (Safety Analysis Set)

Age group	HER2-positive BC 5.4 mg/kg Pool (N = 234) [a]				All Tumor Types 5.4 mg/kg Pool (N = 275) [b]			
	Number (%) of subjects		Patient years of exposure c		Number (%) of subjects		Patient years of exposure c	
	Male	Female	Male	Female	Male	Female	Male	Female
<65 years	0	173 (73.9)		137.3	5 (1.8)	189 (68.7)	1.5	147.8
65-74 years	1 (0.4)	49 (20.9)	0.7	42.7	7 (2.5)	59 (21.5)	3.0	50.0
75-84 years	0	8 (3.4)		7.0	1 (0.4)	11 (4.0)	0.2	11.8
≥85 years	0	3 (1.3)		1.3	0	3 (1.1)		1.3

BC = breast cancer; HER2 = human epidermal growth factor receptor 2
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] HER2-positive BC subjects assigned to receive 5.4 mg/kg in DS8201-A-J101 or DS8201-A-U201.
[b] All treated subjects assigned to receive 5.4 mg/kg in DS8201-A-J101 or DS8201-A-U201.
[c] Patient years = sum (duration of exposure [months])/12
Source: Summary of Clinical Safety Appendix 1 Table 30

Table Part II: Module SIII.3: Ethnic Origin of Subjects Receiving Trastuzumab Deruxtecan in Study DS8201-A-J101 and Study DS8201-A-U201 (Safety Analysis Set)

Parameter	Number (%) of Subjects			
	HER2-positive BC 5.4 mg/kg (N = 234)	HER2-positive BC ≥6.4 mg/kg (N = 137)	All Tumor Types 5.4 mg/kg (N = 275)	All Tumor Types ≥6.4 mg/kg (N = 258)
Ethnic origin [a]				
Hispanic or Latino	13 (5.6)	8 (5.8)	17 (6.2)	10 (3.9)
Not Hispanic or Latino	167 (71.4)	80 (58.4)	184 (66.9)	114 (44.2)
Not applicable [b]	32 (13.7)	6 (4.4)	32 (11.6)	6 (2.3)
Missing	22 (9.4)	42 (15.3)	21 (42.0)	1 (0.5)

Table Part II: Module SIII.3: Ethnic Origin of Subjects Receiving Trastuzumab Deruxtecan in Study DS8201-A-J101 and Study DS8201-A-U201 (Safety Analysis Set) (Continued)

Parameter	Number (%) of Subjects			
	HER2-positive BC 5.4 mg/kg (N = 234)	HER2-positive BC ≥6.4 mg/kg (N = 137)	All Tumor Types 5.4 mg/kg (N = 275)	All Tumor Types ≥6.4 mg/kg (N = 258)
Race				
White	119 (50.9)	50 (36.5)	136 (49.5)	78 (30.2)
Black or African American	7 (3.0)	3 (2.2)	8 (2.9)	5 (1.9)
Asian	97 (41.5)	80 (58.4)	118 (42.9)	168 (65.1)
American Indian or Alaska Native	2 (0.9)	1 (0.7)	2 (0.7)	1 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.7)	1 (0.4)	1 (0.4)
Other	4 (1.7)	1 (0.7)	6 (2.2)	4 (1.6)
Missing	4 (1.7)	1 (0.7)	4 (1.5)	1 (0.4)
Region/country of origin				
US	82 (35.0)	49 (35.8)	103 (37.5)	85 (32.9)
EU [c]	68 (29.1)	12 (8.8)	68 (24.7)	12 (4.7)
Japan	51 (21.8)	69 (50.4)	71 (25.8)	154 (59.7)
Korea	33 (14.1)	7 (5.1)	33 (12.0)	7 (2.7)

BC = breast cancer; EU = European Union; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool; US = United States
Note: The pooled analysis groups for HER2-positive BC and all tumor types at their respective dose levels were based on data for subjects in Studies DS8201-A-J101 and DS8201-A-U201. Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
[a] Ethnicity was not required to be collected in all countries.
[b] Subjects of Japanese origin in Study DS8201-A-J101 were instructed to respond with "Not Applicable" upon enrollment. This option was removed for later studies.
[c] Subjects were enrolled from Belgium, France, Italy, Spain, and the United Kingdom.
Source: ISS 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 Study DS8201-A-J101 and Study DS8201-A-U201:

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

Reason for exclusion:

The patient population consisting of children and adolescents was excluded from the clinical development programme to allow for analysis of benefit-risk in adult patients with BC. In addition, BC in paediatric patients is rare.

Is it considered to be included as missing information?

No

Rationale:

These patients are not relevant for the current proposed indication of treatment of adults with HER2-positive BC.

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 tumors (ie, minimal increase in exposure and no change in the safety profile). No additional safety concerns are anticipated if the product is used in these patient populations. Therefore, the use of trastuzumab deruxtecan 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 because the safety profile had not been established in subjects with normal function or mild or moderate renal impairment.

Is it considered to be included as missing information?

No

Rationale:

The major excretion pathway of trastuzumab deruxtecan, 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 (defined as a total bilirubin >1.5 × ULN, ≤3 × ULN, and any AST regardless of Gilbert Syndrome)

Reason for exclusion:

To maximise subject safety during the conduct of these studies, subjects with moderate hepatic impairment were excluded from participation in the clinical programme until the safety profile was established in subjects with normal function or mild hepatic impairment.

Is it considered to be included as missing information?

Yes

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 trastuzumab deruxtecan 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 trastuzumab deruxtecan.

Is it considered to be included as missing information?

No

Rationale:

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

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

Reason for exclusion:

Cardiotoxicity has been observed with anti-HER2 drugs, including trastuzumab, which has a warning for cardiomyopathy. A nonclinical study in monkeys with trastuzumab deruxtecan 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 trastuzumab deruxtecan as described in SmPC Section 4.4 and 4.8. Additional information on this risk is included in Section Part II: Module SVIISVII.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 trastuzumab deruxtecan (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 trastuzumab deruxtecan was observed in a study to evaluate QT effects (Study DS8201-A-J102). This result is consistent with the clinical data from DS8201-A-U201 and DS8201-A-J101. As there is no

signal of QT liability with trastuzumab deruxtecan, 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 edema, at supratherapeutic doses of trastuzumab deruxtecan (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 trastuzumab deruxtecan 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 Part II: Module SVIISVII.3.

Use of OATP1B inhibitors or strong CYP3A4 inhibitors

Reason for exclusion:

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

Is it considered to be included as missing information?

No

Rationale:

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

Clinically significant corneal disease (Study DS8201-A-U201 only)

Reason for exclusion:

In a nonclinical study of the released drug of trastuzumab deruxtecan, 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 trastuzumab deruxtecan were primarily keratitis. Events of keratitis in HER2-positive BC subjects were either Grade 1 or Grade 2 in severity, none led to dose reduction or drug discontinuation, and all events could be managed through standard clinical practice. Keratitis is classified as a potential risk for trastuzumab deruxtecan; 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 post-marketing 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 trastuzumab deruxtecan in rats and monkeys and its mechanism of action as a topoisomerase I inhibitor, the released drug of trastuzumab deruxtecan 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 trastuzumab deruxtecan. Additional information on the risk of embryo-foetal toxicity is included in Section Part II: Module SVIISVII.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 trastuzumab deruxtecan 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 trastuzumab deruxtecan 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 trastuzumab deruxtecan 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 234 subjects in the pooled safety database for HER2-positive BC, there is at least a 90% 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 HER2-positive BC from under-represented populations that were exposed to trastuzumab deruxtecan 5.4 mg/kg is presented in Table Part II: Module SIV.3.1.

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

Type of Special Population	**Number of Subjects in Pool**	
	HER2-Positive BC 5.4 mg/kg (N = 234)	**All Tumor Types 5.4 mg/kg (N = 275)**
Pregnant or breastfeeding women	Not included in the clinical development programme	
Paediatric	Not included in the clinical development programme [a]	
Elderly		
≥65 years	61 (26.1)	81 (29.5)
≥75 years	11 (4.7)	15 (5.5)
Subjects with relevant comorbidities		
Subjects with renal impairment (all)	[redacted]	[redacted]
Severe impairment (CrCL <30 mL/min)	[redacted]	[redacted]
Moderate impairment (CrCL ≥30 to <60 mL/min)	[redacted]	[redacted]
Mild impairment (CrCL ≥60 to <90 mL/min)	[redacted]	[redacted]
Subjects with hepatic impairment (all)	[redacted]	[redacted]
Severe impairment (TBL >3.0 × ULN and any AST regardless of Gilbert Syndrome)	[redacted]	

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

Type of Special Population	Number of Subjects in Pool	
	HER2-Positive BC 5.4 mg/kg (N = 234)	All Tumor Types 5.4 mg/kg (N = 275)
Moderate impairment (TBL >1.5 × ULN, ≤3 × ULN and any AST regardless of Gilbert Syndrome)	[redacted]	[redacted]
Mild impairment (TBL > ULN, ≤1.5 × ULN, and any AST except for subjects with Gilbert Syndrome; TBL > ULN, ≤3.0 × ULN and AST > ULN for subjects with Gilbert Syndrome; or TBL ≤ ULN and AST > ULN regardless of Gilbert Syndrome)	[redacted]	[redacted]
Subjects with cardiovascular impairment	Subjects with LVEF <50% or recent symptomatic CHF were excluded from the clinical development programme	

AST = aspartate aminotransferase; BC = breast cancer; CHF = congestive heart failure; CrCL = creatinine clearance; EMA = European Medicines Agency; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; 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] One subject in Study DS8201-A-J101 met the CrCL criteria for severe renal impairment on the first day of the first cycle prior to dosing; however, the subject was enrolled meeting the CrCL criteria for moderate renal impairment at screening.

Source: ISS Table 1.1.2.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Since the data lock point for this RMP (01 Aug 2019), trastuzumab deruxtecan 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.

SV.1.1 Method Used to Calculate Exposure

The post-marketing patient exposure in patient-years was estimated by (a) assuming that 2/3 of the distributed vials are in actual use and the remaining 1/3 of vials are put into inventory for future use, (b) further assuming that, on average, 4.3 vials are used in 1 infusion, 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

Since the first approval of trastuzumab deruxtecan in the US on 20 Dec 2019, the estimated cumulative global post-marketing patient exposure through 19 Jun 2020 was [redacted] patient-years ([redacted] infusions x 21 / 365).

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

Trastuzumab deruxtecan 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 primarily by Study DS8201-A-J101 and Study DS8201-A-U201. Data are presented from the pooled HER2-positive BC 5.4 mg/kg population, unless otherwise specified.

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) 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 trastuzumab deruxtecan 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 TBL >2 x ULN). This case of potential Hy's Law was determined not to be causally associated with study drug due to alternative etiology (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 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 trastuzumab deruxtecan and has been seen in drugs in similar class. The mechanism for corneal toxicity with trastuzumab deruxtecan remains unclear; however, it is known that HER2 is expressed in corneal epithelia.[54] Keratitis was observed in clinical studies with trastuzumab deruxtecan. 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 (e.g. 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 trastuzumab deruxtecan. It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. The potential risk for male patients is further minimized by statements in SmPC Section 4.6 advising male patients to seek counselling on sperm storage before starting treatment and male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

Risks with Minimal Clinical Impact on Patients: Renal toxicity

In nonclinical studies with trastuzumab deruxtecan abnormal renal function was seen in rats but not in monkeys. In the rat 6-week study of trastuzumab deruxtecan (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 trastuzumab deruxtecan 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. [redacted] 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 post-marketing period with trastuzumab deruxtecan has been identified.

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

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

SVII.1.2.1 Important Identified Risks

Important Identified Risk: Interstitial Lung Disease/Pneumonitis

Benefit-risk impact:

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

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

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

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

ILD/pneumonitis requires appropriate monitoring and management to mitigate the risk of Grade 4 or Grade 5 events, which has the potential to impact the benefit-risk for the patient.

The risk of ILD/pneumonitis is further characterised in Section Part II: Module SVIISVII.3.

Important Identified Risk: Left Ventricular Dysfunction

Benefit-risk impact:

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

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

Left ventricular dysfunction is characterised in Section Part II: Module SVIISVII.3.

Because the lack of a control group in available clinical data does not allow to rule out completely a causal association with trastuzumab deruxtecan, and cardiac failure have 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 trastuzumab deruxtecan are described in Section Part II: Module SII.

No clinical data on the effect of trastuzumab deruxtecan on embryo-foetal toxicity potential is available. However, in post-marketing 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 trastuzumab deruxtecan 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 antibody-drug conjugate trastuzumab emtansine (Kadcyla) prescribers could potentially mix-up trastuzumab-containing product if they do not use the tradename. There is a potential for serious clinical consequences (e.g. lack of efficacy) by inadvertently substituting one trastuzumab containing product for another.

For trastuzumab deruxtecan there have been no reports of product confusion-related medication errors in clinical trials or since marketing of the product in U.S 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 DS8201-A-U201. However, only 1 patient meeting these criteria was enrolled. Patients with severe hepatic impairment were excluded from the clinical programme.

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

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

Missing Information: Long-term safety

The median treatment duration (defined as: date of last dose − date of first dose + 21) in the HER2-positive BC 5.4 mg/kg Pool (N = 234) was 9.82 months (range: 0.7-37.1). 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 (DS8201-A-U301 and DS8201-A-U302) more long-term safety data will become available, which would be used to further characterize cumulative toxicity and overall safety profile of trastuzumab deruxtecan.

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

Not applicable, as this is the initial EU RMP for trastuzumab deruxtecan.

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 trastuzumab deruxtecan 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.[55]

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 trastuzumab deruxtecan 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 closely monitoring signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and proactively managing events with dose modification (dose reduction or interruption), and use of steroid treatment and (for moderate, severe or life-threatening ILD/pneumonitis) discontinuation of trastuzumab deruxtecan.

Characterisation of the risk:

An independent ILD AC was established for trastuzumab deruxtecan and has been adjudicating all events of potential ILD reported in the clinical development programme. Potential ILD events that are adjudicated comprise 44 PTs, including 42 PTs from the ILD Standard Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) as well as 2 additional PTs (respiratory failure and acute respiratory failure) as listed in the ILD AC Charter. The ILD AC has been adjudicating whether an event of potential ILD was an ILD and whether it was related to trastuzumab deruxtecan (regardless of the determination made by the investigator), as well as grades and onset dates for events that the ILD AC considers to be ILD and, where applicable, whether death (on-study death as defined in the study protocol) was due to ILD.

Herein, “adjudicated drug-related ILD” is defined as events that the ILD AC adjudicated as being ILD and as related to trastuzumab deruxtecan (regardless of the determination made by the investigator). The following PTs have been adjudicated as drug-related ILD (note that some subjects had more than 1 PT reported): pneumonitis (14 subjects), ILD (13), respiratory failure (3), organising pneumonia (2), lung infiltration (1), alveolitis (1), acute respiratory failure (1), and lymphangitis (1).

ILD in the HER2-positive BC 5.4 mg/kg Pool is summarized by event category and grade in Table Part II: Module SVII.3.1, which includes 3 ILD events in Study DS8201-A-J101 that occurred >28 days after the last dose (TEAE definition), per investigator-reported onset dates.

Among the 41/234 (17.5%) subjects who had potential ILD, 32/234 (13.7%) subjects had events that were adjudicated as drug-related ILD at the following grades: 6 (2.6%) Grade 1, 19 (8.1%) Grade 2, 1 (0.4%) Grade 3, 0 Grade 4, and 6 (2.6%) Grade 5 [redacted].

Table Part II: Module SVII.3.1: Number and Percentage of ILD Events by Category and Grade (Safety Analysis Set)

Pool	Outcome of Adjudication	Number (%) of Subjects by CTCAE Grade [a] (as Graded by ILD Adjudication Committee)					
		1	2	3	4	5	Total
HER2-positive BC 5.4 mg/kg (N = 234)	Adjudicated as ILD	6 (2.6)	21 (9.0) [b]	1 (0.4)	0	7 (3.0)	35 (15.0)
	Adjudicated as drug-related ILD	6 (2.6)	19 (8.1) [b]	1 (0.4)	0 [c]	6 (2.6) [c]	32 (13.7)
	Adjudicated as not drug-related ILD	0	2 (0.9)	0	0	1 (0.4) [d]	3 (1.3)
All Tumor Types 5.4 mg/kg (N = 275)	Adjudicated as ILD	7 (2.5)	24 (8.7) [b]	2 (0.7)	0	7 (2.5)	40 (14.5)
	Adjudicated as drug-related ILD	7 (2.5)	22 (8.0) [b]	2 (0.7)	0	6 (2.2)	37 (13.5)
	Adjudicated as not drug-related ILD	0	2 (0.7)	0	0	1 (0.4) [d]	3 (1.1)

AC = Adjudication Committee; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; GC = gastric/gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of subjects in the pool
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 2 pooled analysis groups were based on tumor type and assigned dose for subjects in DS8201-A-J101 and DS8201-A-U201.

[a] The ILD AC assigned grades to those events that were determined to be ILD.

[b] Includes 2 events in DS8201-A-J101 that occurred >28 days after the last dose, per investigator-reported onset date: 1 in the HER2-positive BC 5.4 mg/kg Pool and 1 in the All Tumor Types 5.4 mg/kg Pool (HER2-low GC).

[c] One subject in DS8201-A-U201 had a TEAE of respiratory failure and subsequently died; the death was adjudicated as being due to ILD (after the database lock, the severity was updated from Grade 4 to Grade 5, following ILD AC re-adjudication of the event).

[d] One subject in DS8201-A-U201 had an event adjudicated as not related to trastuzumab deruxtecan, with death not due to ILD. The ILD AC commented that "This is ARDS [acute respiratory distress syndrome] related to pneumococcal sepsis."

Source: Safety Update Table 1.2.2.19

The following results were seen in the HER2-positive BC 5.4 mg/kg Pool:

- 32 (13.7%) subjects had an adjudicated drug-related ILD
- Median time to adjudicated onset date of the first event was 134.0 days (range: 35-338).
- Median duration of the first event of ILD (grouped term) (as reported by the investigator) was 31.5 days (range: 3-261).
- Study treatment was discontinued due to a TEAE of adjudicated drug-related ILD in 22 (9.4%) subjects.
- Dose was reduced in 4 (1.7%) subjects and dosing was interrupted in 6 (2.6%) subjects due to adjudicated drug-related ILD.

Table Part II: Module SVII.3.2: Summary of Adjudicated Drug-related ILD in the HER2-Positive BC 5.4 mg/kg Pool (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with Adjudicated Drug-related ILD, by Pool	
	HER2-positive BC 5.4 mg/kg (N = 234)	All Tumor Types 5.4 mg/kg (N = 275)
Treatment-emergent AE	32 (13.7) [a]	37 (13.5)
Worst CTCAE Grade ≥3 [b]	7 (3.0)	8 (2.9)
Serious AE	12 (5.1)	13 (4.7)
Associated with drug discontinuation	22 (9.4)	24 (8.7)
Associated with dose reduction	4 (1.7)	4 (1.5)
Associated with drug interruption	6 (2.6)	7 (2.5)
Associated with an outcome of death	6 (2.6)[c,d]	6 (2.2)

AC = Adjudication Committee; AE = adverse event; BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of subjects in the pool

[a] Includes 1 subject in Study DS8201-A-J101 who had an event of potential ILD that occurred >28 days after the last dose, per investigator-reported onset date.

[b] A subject was counted once at the maximum severity, if he/she reported at least 1 AE.

[c] One subject in DS8201-A-U201 had a TEAE of respiratory failure and subsequently died; the death was adjudicated as being due to ILD (after the database lock, the severity was updated from Grade 4 to Grade 5, following ILD AC re-adjudication of the event).

[d] One subject in Study DS8201-A-U201 had an event of potential ILD adjudicated as not related to trastuzumab deruxtecan, with death not due to ILD; the ILD AC commented that "This is ARDS [acute respiratory distress syndrome] related to pneumococcal sepsis."

Source: Summary of Clinical Safety Appendix 1 Table 21

Among the 32 subjects with events adjudicated as drug-related ILD in the HER2-positive BC 5.4 mg/kg Pool, 11 (34.4%) recovered or were recovering, 13 (40.6%) were not recovered (partly due to no requirement, as of the study data cut-off dates (DCOs), to follow up the non-serious AEs after discontinuation of study treatment due to any reason), 6 (18.8%) had a fatal outcome, and 2 were missing outcome information. Of the 15 subjects who had not recovered or had an unknown outcome, 13 had non-serious events.

[redacted]

[redacted]

Clinical Summary of Safety Appendix 1

Table 22

[redacted]

[redacted]

Risk factors and risk groups:

An exploratory analysis was conducted among all subjects from the 5 completed clinical studies (Studies DS8201-A-J101, DS8201-A-U201, DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104) to evaluate the correlation between ILD (adjudicated drug-related ILD of any grade) and potential risk factors. Results are included in the ILD Assessment Summary, based on results observed at the DCOs for the individual studies. The following noteworthy differences were observed:

- A higher proportion of Asian subjects than non-Asian subjects had events adjudicated as drug-related ILD.
- A higher proportion of subjects from Japan than subjects from other countries had events adjudicated as drug-related ILD (12/51 [23.5%] vs. 20/183 [10.9%] subjects), while a lower proportion of subjects from Japan had ILD events of ≥Grade 3.
- A higher proportion of subjects with ≥10 prior chemotherapy/targeted therapies had adjudicated drug-related ILD compared to subjects with <10.

In the HER2-positive BC 5.4 mg/kg Pool, a higher proportion of subjects with moderate renal impairment at baseline had events of adjudicated drug-related ILD (9/29 [31.0%] subjects) compared to subjects with normal renal function (12/113 [10.6%]) or mild renal impairment (10/91 [11.0%]) at baseline (Safety Update Table 1.4.13.13).

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 prednisolone or equivalent) should be considered.
    - Trastuzumab deruxtecan 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 prednisolone or equivalent) should be promptly initiated, with gradual tapering (eg, over the course of 4 weeks) after improvement is observed.
    - Trastuzumab deruxtecan 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)

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 trastuzumab deruxtecan 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 closely monitoring 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 trastuzumab deruxtecan. 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 trastuzumab deruxtecan. 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.[56,57,58]

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 trastuzumab deruxtecan did not show an abnormality in cardiac function tests (including LVEF).
Ejection fraction decreases have been reported with trastuzumab deruxtecan. However, available clinical data show that the reported ejection fraction decreases are of low frequency and severity, and are often asymptomatic in nature.

Characterisation of the risk:

Table Part II: Module SVII.3.3: Summary of PT Ejection Fraction Decreased in the HER2-Positive BC 5.4 mg/kg Pool (N = 234) (Safety Analysis Set)

Adverse Event Category	Number (%) of Subjects with PT Ejection Fraction Decreased
Treatment-emergent AE	3 (1.3)
Worst CTCAE Grade ≥3a	1 (0.4)
Serious AE	0
Associated with drug discontinuation	0
Associated with dose reduction	0
Associated with drug interruption	3 (1.3)
Associated with an outcome of death	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; N = total number of subjects in the pool; PT = preferred term
Note: In the HER2-positive BC pool, the 5.4 mg/kg dose was based on the first dose received for subjects in Studies DS8201-A-J101 and DS8201-A-U201.
[a] A subject was counted once at the maximum severity if he or she reported at least 1 AE.
Sources: Safety Update Tables 1.2.1.2; 1.2.1.3; 1.2.1.5; 1.2.1.7; 1.2.1.9; 1.2.1.11; 1.2.1.11.1

The PT of ejection fraction decreased was reported infrequently, with 2 Grade 2 events and 1 Grade 3 event. Observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 37 (16.9%); all were Grade 2. These events were nonserious, asymptomatic, and resolved. Events of ejection fraction decreased did not require dose reduction or drug discontinuation, and were not associated with fatal outcomes.

No LVEF decreases <40% were observed in the HER2-positive BC 5.4 mg/kg Pool. Two additional subjects in the HER2-positive BC 5.4 mg/kg Pool had events of PTs other than

ejection fraction decreased: an SAE of Grade 2 cardiac failure congestive that led to the withdrawal of the study drug and resolved (LVEF value of 63% at baseline and 66% to 70% during the study) and a Grade 1 cardiac failure on Day 1 that was not resolved at the data cutoff date (LVEF value of 52% at baseline and 57% to 60% during the study).

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 HER2-positive BC 5.4 mg/kg Pool, 67 (28.6%) and 47 (20.1%) subjects received prior therapy of doxorubicin and epirubicin, respectively.

Preventability:

Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed to assess LVEF prior to the initiation of trastuzumab deruxtecan 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 trastuzumab deruxtecan 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, trastuzumab deruxtecan and its topoisomerase I inhibitor component (DXd) were toxic to rapidly dividing cells (lymphatic/hematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity (SmPC Section 5.3).

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

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

No clinical data on the effect of trastuzumab deruxtecan on fertility are available.

Risk factors and risk groups:

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

Preventability:

Contraception guidelines for both women of childbearing potential and men with female partners of childbearing potential are provided in SmPC Section 4.4 and SmPC Section 4.6. The pregnancy status of females of childbearing potential should be verified prior to the initiation of trastuzumab deruxtecan. 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 trastuzumab deruxtecan 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 antibody-drug conjugate 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 color 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 [59] and 2 spontaneous cases are evident for Kadcyla in the Eudravigilance database (DLP 31-AUG-2020) reporting PT ‘Wrong drug administered’ or ‘Product name confusion’. Both cases involve two trastuzumab-containing products and both cases were not associated with an adverse event.

As of 31-AUG-2020 there have been no case reports of product confusion-related medication errors associated with trastuzumab deruxtecan.

Characterisation of the risk:

There is a potential for serious clinical consequences (e.g. 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 trastuzumab deruxtecan have

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

Furthermore, trastuzumab deruxtecan 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 Moderate and Severe Hepatic Impairment

Evidence source:

The safety profile of trastuzumab deruxtecan may be different in subjects with moderate or severe hepatic impairment as the drug is primarily hepatically metabolised.

Population in need of further characterisation:

Patients with metastatic BC who have moderate or severe hepatic impairment.

Data from ongoing studies will be reviewed to further characterise the safety profile of trastuzumab deruxtecan in this patient population.

Missing information: Long-term safety

Evidence source:

Trastuzumab deruxtecan 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. Long-term safety will be further characterised through ongoing Phase 3 clinical studies (DS8201-A-U301 and DS8201-A-U302).

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 moderate or severe hepatic impairment • Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION 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:** The planned purpose of the follow-up questionnaire for spontaneous ILD/pneumonitis events is to capture 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 post-marketing setting.
- **LV dysfunction:** The planned purpose of the follow-up questionnaire for spontaneous LVEF decrease (including cardiac failure) events is to capture 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 post-marketing setting.

Batch related activities:

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

III.2 Additional Pharmacovigilance Activities

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

Furthermore, the collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies with trastuzumab deruxtecan is planned to provide an overall assessment of these 10 subjects with moderate hepatic impairment.

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 authorization: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 - Required additional pharmacovigilance activities				
Prescriber Survey planned	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis	ILD	Final Report	Q3 2023
Phase 2 or 3 studies planned	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies	Use in patients with moderate or severe hepatic impairment	Final report (for 10 subjects)	Q4 2023

EU = European Union; ILD = interstitial lung disease

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

The MAH is currently conducting the Phase 3 clinical trial DS8201-A-U301 which is a multicenter, randomized, open-label, active-controlled study conducted in subjects with HER2 positive, unresectable and/or metastatic breast cancer. Study U301 is proposed as a confirmatory study expected to provide comprehensive evidence of the clinical benefit of trastuzumab deruxtecan treatment in subjects with unresectable or metastatic HER2-positive breast cancer. For protocol details please see Annex 5.

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

Study: **Status**	**Summary of objectives**	**Efficacy uncertainty addressed**	**Milestones**	**Due dates**
DS-8201-A-U301: A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pretreated with prior standard of care HER2 therapies, including T-DM1 On-going	To examine the efficacy and safety of , compared with reference treatment, in subjects who received study treatment in the pivotal sponsored study for treatment of HER2-positive, unresectable and/or metastatic breast cancer	Overall efficacy and safety	submission of results	Q 1 2022

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.

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. Other routine risk minimisation measures beyond the Product Information: Legal status: Trastuzumab deruxtecan 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: Trastuzumab deruxtecan 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: Trastuzumab deruxtecan 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: Trastuzumab deruxtecan 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 moderate or 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: Trastuzumab deruxtecan 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: Trastuzumab deruxtecan is subject to medical prescription.

ILD = interstitial lung disease; SmPC = Summary of Product Characteristics; PIL = Patient Information Leaflet

V.1 Additional Risk Minimisation Measures

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

For the important potential risk of product confusion-related medication errors, an HCP Guide will be 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 will improve 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 will potentially minimise the occurrence of more serious ILD/pneumonitis cases. The guide will also improve the adherence to the key risk minimisation measures for ILD/pneumonitis defined in the trastuzumab deruxtecan SmPC.

Target audience and planned distribution path:

Where trastuzumab deruxtecan is supplied, all HCPs will be provided with the HCP Guide to use as a reminder/quick reference material before the administration of trastuzumab deruxtecan.

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

The Applicant will verify distribution of the HCP Guide and test the understanding and knowledge of the key messages by the HCPs and evaluate the effectiveness using a survey.

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

Additional risk minimisation 2: Patient Card

Objectives:

The objective of the Patient Card 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 will provide the PC to the patient before initial administration of trastuzumab deruxtecan. The PC will have a compact design for portability.

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

The MAH will verify distribution of the PC in the prescriber survey.

The frequency of all ILD/pneumonitis including ILD/pneumonitis cases with a fatal outcome in the post-marketing setting will be evaluated periodically and will be 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 trastuzumab deruxtecan and not other trastuzumab-containing products or the HER2-targeted antibody-drug conjugate trastuzumab emtansine (Kadcyla).

Rationale for the additional risk minimisation activity:

The HCP Guide will improve 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 will ensure the adherence to labelled language during the prescription, preparation and administration processes with trastuzumab deruxtecan.

Target audience and planned distribution path:

Where trastuzumab deruxtecan is supplied, all HCPs will be provided with the HCP Guide for prevention of medication errors to use as a reminder/quick reference material before the administration of trastuzumab deruxtecan.

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

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

V.2 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. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: Prescriber survey
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None

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 colors for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
		Additional pharmacovigilance activities: None

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

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ENHERTU

This is a summary of the RMP for trastuzumab deruxtecan. The RMP details important risks of trastuzumab deruxtecan, how these risks can be minimised, and how more information will be obtained about trastuzumab deruxtecan's risks and uncertainties (missing information).

The SmPC and package leaflet for trastuzumab deruxtecan give essential information to HCPs and patients on how trastuzumab deruxtecan should be used.

This summary of the RMP for trastuzumab deruxtecan 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 trastuzumab deruxtecan'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 2 or more prior anti-HER2-based regimens. It contains trastuzumab deruxtecan as the active substance and it is given intravenously.

Further information about the evaluation of trastuzumab deruxtecan's benefits be found in trastuzumab deruxtecan's EPAR (https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu), including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of trastuzumab deruxtecan, 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 trastuzumab deruxtecan, 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 trastuzumab deruxtecan, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of trastuzumab deruxtecan 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 trastuzumab deruxtecan. 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 Moderate or Severe Hepatic Impairment • Long-term safety

II.B Summary of Important Risks

Important identified risks with trastuzumab deruxtecan 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 trastuzumab deruxtecan, including fatal outcomes. An independent Adjudication Committee adjudicated all potential events of ILD.
Risk factors and risk groups	Recognised risk factors for ILD/pneumonitis include country of Japan and use of ≥10 prior chemotherapy/targeted therapies.
Risk minimisation measures	Routine risk communication: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Routine risk minimisation measures: 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. Additional risk minimisation measures: Healthcare Professional Guide and Patient Card
Additional pharmacovigilance activities	Prescriber survey

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 trastuzumab deruxtecan.
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

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 trastuzumab deruxtecan and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that trastuzumab deruxtecan 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 trastuzumab deruxtecan 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

Missing information with trastuzumab deruxtecan includes use in patients with moderate or severe hepatic impairment, as outlined below.

Missing Information 1: Use in Patients with Moderate or Severe Hepatic Impairment	
Evidence for linking the risk to the medicine	Trastuzumab deruxtecan has not been studied in subjects with severe hepatic impairment. A maximum of 10 subjects with moderate hepatic impairment were eligible for inclusion in Study DS8201-A-U201; however, only 1 subject in the HER2-positive BC 5.4 mg/kg Pool had moderate hepatic impairment at baseline. Based on a population PK analysis, clearance of the released drug of trastuzumab deruxtecan is decreased 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
Additional pharmacovigilance activities	Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies.

AST = aspartate aminotransaminase; BC = breast cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; SmPC = Summary of Product Characteristics

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

II.C Post-Authorisation Development Plan

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

The Phase 3 clinical trial (DS8201-A-U301) serves as the confirmatory trial (see also RMP Part IV). Details are provided in the table below.

DS8201-A-U301	
Short title	A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pretreated with prior standard of care HER2 therapies, including T-DM1
Purpose of the study	Primary objective: To compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Key secondary objective: To compare overall survival (OS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Other secondary Objectives: To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice on: Confirmed objective response rate (ORR); Duration of response (DoR); To further determine pharmacokinetics (PK) of trastuzumab deruxtecan. To further evaluate safety of trastuzumab deruxtecan compared to investigator's choice. To evaluate Health Economics and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to investigator's choice. Safety concern addressed: overall safety, long-term safety.

II.C.2 Other Studies in Post-Authorisation Development Plan

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

PK and safety data analysis in patients with moderate hepatic impairment	
Short title	Collection and analysis of PK and safety data in subjects with moderate hepatic impairment from ongoing clinical studies
Purpose of the study	Overall assessment of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies. Safety concern addressed: Missing information: Use in patients with moderate or severe hepatic impairment.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

Available in electronic format only and is electronically submitted as per guidelines.

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table Part VII.1: Planned and Ongoing Studies/Pharmacovigilance Activities

Study/Activity	Summary of Objectives	Safety Concerns Addressed	Milestones
Prescriber survey	EU survey of relevant healthcare professionals on understanding of additional risk minimisation measures pertaining to ILD/pneumonitis	ILD/pneumonitis	Final Report, Q3 2023
On-going Phase 2 or 3 studies	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing clinical studies	Use in patients with moderate or severe hepatic impairment	Final assessment report (for 10 subjects), Q4 2023

EU = European Union; ILD = interstitial lung disease; PK = pharmacokinetic.

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Prescriber Survey on understanding of key risk minimization measures related to ILD/pneumonitis with Trastuzumab Deruxtecan treatment

Milestones and timelines

Milestone	Timeline (Quarter/Year)
Start vendor selection	After Day 80 Questions are received
Protocol final by sponsor	3 months after EC decision
Registration in the ENCePP EU PAS register	3 months after EC decision
Study initiation	1 year after launch of the product in each participating country

Background and Rationale

Trastuzumab deruxtecan is an antibody drug conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2 regimens. Interstitial lung disease has been identified as an important identified risk for patients treated with trastuzumab deruxtecan, and fatal outcomes have been observed. Therefore, the Marketing Authorization applicant proposes additional risk minimization measures for ILD/pneumonitis in form of a Healthcare Professional (HCP) Guide and a Patient Card (PC) to minimise the occurrence of severe ILD/pneumonitis cases.

This survey study aims to evaluate the effectiveness of additional risk minimization measures in terms of distribution of the guide and assessment of the knowledge and understanding of HCPs in relation to key elements of the distributed trastuzumab deruxtecan material.

Objectives

The primary objective is to evaluate the effectiveness of proposed educational material as risk minimization measures by:

- Evaluating the level of knowledge of educational materials by HCPs of risks, early recognition, diagnosis and management of ILD/pneumonitis.
- Evaluating the extent to which HCPs receive the HCP guide and distribute the PC to patients.

Secondary objective(s):

N/A

Methods

Study design

A cross-sectional study to assess distribution of HCP guide as well as to evaluate knowledge of HCPs on key elements of the trastuzumab deruxtecan guide using a survey.

Within 1 year after product launch in each participating EU country a diverse set of oncology centers will be recruited randomly to participate in the survey based on the distribution list of the HCP guide. HCPs who have been treating at least 1 breast cancer patient with trastuzumab deruxtecan will be asked to provide information on the receipt of the HCP guide and distribution of the PC to the patient(s).

In addition, a self-administered questionnaire will be employed to collect information on HCP knowledge about the risks, diagnosis and management of ILD/pneumonitis as described in the HCP guide. The data collection will last for 12 months or until intended number of enrolled subjects has been reached, whichever comes first.

Data source

Short self-administered web-based questionnaire.

Population selection

HCPs from multiple European countries will be selected for participation in the survey.

Inclusion criteria:

HCPs must meet the following inclusion criteria for survey participation:

- HCPs on the HCP guide distribution list
- Work at an oncology center and treat or treated at least one patient with trastuzumab deruxtecan since EMA market authorization

Exclusion criteria:

HCPs that meet the following criteria will be excluded:

- Employed (or have an immediate family member employed) by the MAH or a European Regulatory Agency

Study variables

HCP questionnaire data:

- Receipt and reading of the HCP guide (yes/no)
- Number of patients treated with trastuzumab deruxtecan (as reported by HCP)
- Distribution of the PC to the patient(s) (yes/no)
- Test score on HCP knowledge check of risks, diagnosis and management of ILD/pneumonitis included in the HCP guide

Survey size

[redacted]

Statistical methods

Analysis of trastuzumab deruxtecan HCP guide and PC distribution, and evaluation of HCP knowledge will be descriptive in nature and will entail the tabular display of summary statistics and the frequency distribution of item responses. The percentage of HCPs that achieved a desirable test score will be calculated. A detailed analysis plan describing methods of analysis and presentation, as well as table shells, will be developed prior to starting analysis of data. All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS Institute Inc., Cary, North Carolina, USA).

For the protocol synopsis of the two ongoing Phase 3 studies please see Annex 5 of the RMP as both belong to the category of post-authorisation efficacy studies.

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) [Heart Failure] Event 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 (e.g. 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) (e.g. 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 (e.g. 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 (e.g. 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 (e.g. Lymphangitis Carcinomatosis)	☐ Past ☐ Present	
☐ Prior lung surgery		Location:
☐ Asthma		
☐ Chronic obstructive pulmonary disease (COPD)		
☐ Radiation pneumonitis		
☐ Respiratory infection (e.g. pneumonia)		
☐ Other(s) (e.g. 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® Left Ventricular Ejection Fraction (LVEF) [LV dysfunction] Event Follow-up Questionnaire

Date:		**Daiichi Sankyo ARGUS #**	
Reporter Information			
Reporter:	**Name:**		**Signature:**
HCP	☐ Yes / ☐ No		If no, please specify:
Phone:	**Fax:**		**E-Mail:**
Patient Demographics			
Initials:		Date of Birth (dd/mm/yyyy) or age:	
Gender:		Race/Ethnicity:	
Weight (units):		Height (units):	
LVEF Adverse Event Details *Please provide start date and details of the LVEF adverse event.*			
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		
Event Outcome			
☐ Recovered	☐ Recovered with Sequelae If sequelae, please specify		☐ Recovering
☐ Not Recovered	☐ Fatal (if conducted, please provide copy of post-mortem report)		☐ Unknown

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 (e.g. 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 (e.g. 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 (e.g. anthracycline [doxorubicin])?	☐ Yes ☐ No Details (e.g. 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		NHYA class:
☐ Prior heart surgery		Location:
☐ Acute coronary syndrome (e.g. 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)		
☐ Ischemic heart disease		
☐ Valvular heart disease		
☐ Cardiomyopathy		
☐ Smoker		
☐ Alcohol use		
☐ Others (e.g. Occupational/environmental exposure), please specify		

Concomitant Medications

(Prescription, illicit drug use, over the counter, nutritional supplements, herbals)

Drug	Indication	Dose/ Route/ Frequency	Causality (Related/ Not related/ unknown)	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Other

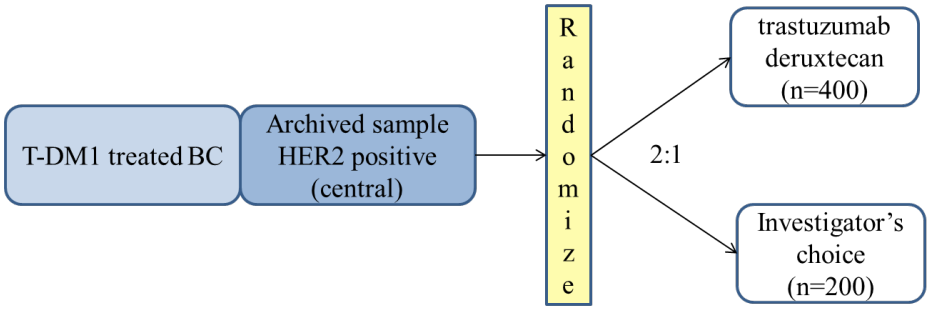
Are there any other contributing factors to the adverse event?	☐ Yes ☐ No If yes, details:

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

See next page for protocol synopsis of study: DS8201-A-U301

PROTOCOL SYNOPSIS

EudraCT:	2018-000221-31
IND Number:	127553
NCT Number:	NCT03523585
Protocol Number:	DS8201-A-U301 (DESTINY-Breast02)
Investigational Product:	trastuzumab deruxtecan (DS-8201a)
Active Ingredients:	Trastuzumab deruxtecan consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a.
Study Title:	A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-Antibody Drug Conjugate, Versus Treatment of Investigator's Choice for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1 (DESTINY-Breast02)
Study Phase:	Phase 3
Indication Under Investigation:	Unresectable/metastatic breast cancer with human epidermal growth factor receptor 2 (HER2)-positive expression
Study Objectives:	Primary Objective: • To compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Key Secondary Objective: • To compare overall survival (OS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Other Secondary Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice on: – Confirmed objective response rate (ORR); – Duration of response (DoR); • To further determine pharmacokinetics (PK) of trastuzumab deruxtecan. • To further evaluate safety of trastuzumab deruxtecan compared to investigator's choice. • To evaluate Health Economics and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to investigator's choice. Exploratory Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice by clinical benefit rate (CBR) and progression-free survival on the next line of therapy (PFS2) • To evaluate potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD]). • To evaluate exposure-response relationships for efficacy and safety endpoints.

Study Design:	This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of trastuzumab deruxtecan versus the investigator's choice in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1). Approximately 600 subjects will be randomized 2:1 to trastuzumab deruxtecan versus the investigator's choice of • Trastuzumab/capecitabine, or • Lapatinib/capecitabine Randomization will be stratified by: • Hormone receptor status (positive, negative) • Prior treatment with pertuzumab (yes, no) • History of visceral disease (yes, no) **Study Design Schema of DS8201-A-U301**  There will be follow-up visits after permanent discontinuation of study treatment to obtain information about subsequent treatment(s) and survival status.
Study Duration:	Enrollment is planned to occur over approximately 30 mo. The end of the study hypothesis-testing period is defined as the date when approximately 434 OS events have been observed, which is estimated as approximately 71 months from first subject randomization. For each subject there will be a 40-Day (+ 7 d) Follow-up after the last study treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up every 3 mo (± 14 d) from the date of 40-Day (+ 7 d) Follow-up, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.
Study Sites and Location:	Approximately 230 sites including but not limited to: North and South America, Europe, and Asia.
Subject Eligibility Criteria:	Key Inclusion Criteria: • Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old.) • Pathologically documented breast cancer that: – is unresectable or metastatic – has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines evaluated at a central laboratory. – was previously treated with T-DM1.

- Documented radiologic progression (during or after most recent treatment or within 6 mo after completing adjuvant therapy).
  - Subjects must be HER2-positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, a fresh biopsy is required.
    - Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 mo after the last dose of trastuzumab deruxtecan, 6 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine. Male subjects must agree to inform all potential female partners that they are participating in a clinical trial of a drug that may cause birth defects. Male subjects must also agree to either avoid intercourse or that he and/or any female partner of reproductive/childbearing potential will use a highly effective form of contraception during and upon completion of the study and for at least 4.5 mo after the last dose of trastuzumab deruxtecan, 3 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine.
- Adequate renal function, defined as:
  - Creatinine clearance ≥ 30 mL/min, as calculated using the Cockcroft-Gault equation,
- Adequate hepatic function, defined as:
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and
  - Aspartate transaminase/alanine transaminase ≤ 2.5 × ULN

Key Exclusion Criteria:

- Ineligible for the comparator arm treatment for reasons including but not limited to the following:
  - Prior treatment with capecitabine;
  - History of any contraindication included in the approved local label for capecitabine or for both trastuzumab and lapatinib;
  - Concurrent treatment with any medication prohibited in the applicable approved local label for capecitabine or for both trastuzumab and lapatinib.
- Prior participation in a study involving an antibody drug conjugate produced by Daiichi Sankyo Inc (DSI).
- Uncontrolled or significant cardiovascular disease, including any of the following:
  - History of myocardial infarction within 6 mo before randomization
  - History of symptomatic congestive heart failure (New York Heart Association Class II to IV)
  - Troponin levels consistent with myocardial infarction as defined according to the manufacturer within 28 d prior to randomization

	– Corrected QT interval prolongation to >470 ms (females) or >450 ms (male) based on average of screening triplicate 12 lead electrocardiogram (ECG) – Left ventricular ejection fraction (LVEF) < 50% within 28 d prior to randomization • Has a history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening. • Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. – Subjects with clinically inactive brain metastases may be included in the study. – Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.
Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan for injection 100 mg: A trastuzumab deruxtecan lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. The starting dose of trastuzumab deruxtecan will be 5.4 mg/kg. The drug for intravenous (IV) infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight to a 100 mL or 250 mL infusion bag. The study treatment will be administered as an IV infusion every 21 d, initially for approximately 90 min, then, if there is no infusion related reaction, for a minimum of 30 min thereafter. Investigator's choice comparative therapy will be administered in accordance with the locally approved label in cycles of every 21 d. The choice needs to be predefined at time of randomization from the following options: • Trastuzumab/capecitabine • Lapatinib/capecitabine
Study Endpoints:	<u>Primary Efficacy Endpoint:</u> • PFS based on blinded independent central review (BICR) <u>Key Secondary Efficacy Endpoint</u> • OS <u>Other Secondary Efficacy Endpoints:</u> • ORR based on BICR and investigator assessment (confirmation of complete response [CR]/partial response [PR] is required) • DoR based on BICR • PFS based on investigator assessment <u>Exploratory Efficacy Endpoints:</u> • Time to response based on BICR • Best percent change in the sum of the diameter of measurable tumors based on BICR • CBR based on BICR

	• PFS2 based on investigator assessment Health Economic and Outcomes Research Endpoints: • European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) – C30 – BR45 • EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L) • Hospitalization-related endpoints Pharmacokinetic Endpoints: • Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a Biomarker Endpoints: • Serum biomarkers (eg, HER2 extracellular domain [HER2ECD]) • Other potential biomarkers (eg, cell free deoxyribonucleic acid, RNA profiling) Safety Endpoints: • Serious adverse events (SAEs) • Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 • Adverse events of special interest (AESIs) • TEAEs associated with discontinuation of study treatment • Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS]) • Vital sign measurements • Standard clinical laboratory parameters • ECG parameters • Echocardiogram (Echo)/multigated acquisition scan (MUGA) findings • Anti-drug antibodies (ADA)
Planned Sample Size:	The target sample size will be approximately 600 subjects, randomized in a 2:1 ratio into 2 treatment groups (trastuzumab deruxtecan versus investigator's choice).
Statistical Analyses:	The primary analysis for PFS will be performed when approximately 372 BICR-assessed PFS events are observed. Efficacy Analyses The primary efficacy analyses will be performed for the Full Analysis Set (FAS) that consists of all randomized subjects. The primary efficacy endpoint is PFS based on BICR. The primary efficacy analyses will compare PFS per BICR between the 2 treatment groups, using stratified log-rank test stratified by stratification factors per Interactive Web/Voice Response System (IXRS). PFS will be tested for statistical significance at an overall 2-sided alpha of 0.05. Kaplan-Meier estimates and survival curves will also be presented for each treatment group. The median survival times and 2-sided 95% confidence intervals (CIs) for the medians will be provided using Brookmeyer and Crowley method for each treatment

group. The hazard ratio (HR) and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by stratification factors per IXRS.

The key secondary efficacy endpoint is OS, and other secondary efficacy endpoints are confirmed ORR (the proportion of subjects who achieved a best overall response of CR or PR) based on BICR and investigator assessment, DoR based on BICR, and PFS based on investigator assessment.

Group sequential testing will be used to compare OS between the 2 treatment groups hierarchically, provided PFS is significant. Kaplan-Meier estimates and survival curves will also be presented for each treatment group. The median survival times and 2-sided 95% CIs for the medians will be provided using Brookmeyer and Crowley method for each treatment group. In addition, Kaplan-Meier estimates at fixed time points along with their 2-sided 95% CIs will be provided for each treatment group. The HR and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by stratification factors per IXRS. Up to 3 analyses of OS could be performed:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant), at which point a total of 208 OS events (48% information fraction) are expected.
- If the OS interim analysis is not significant, a second interim analysis for OS is planned when approximately 304 OS events (70% information fraction) are expected.
- If the second OS interim analysis is not significant, a final analysis for OS after approximately 434 OS events have been observed (expected 71 months from date of first subject to be randomized).

Cochran-Mantel-Haenszel tests stratified by stratification factors per IXRS will be used to compare ORR (based on BICR/investigator assessment) between the treatment groups. The estimates of ORR and the 2-sided 95% CIs will be provided using Clopper-Pearson method.

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

The survival distribution of PFS based on investigator assessment will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS and its 2-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (eg, 3, 6, 9, 12 months) and the 2-sided 95% CIs will be provided for each treatment group. The treatment effect HR and its 2-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the same stratification factors as the randomization stratification factors taken from IXRS. The survival distribution of PFS based on investigator assessment between the 2 treatment groups will be compared at a 2-sided significance level of 0.05, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at the time when primary analysis of PFS per BICR is statistically significant.

Health Economic and Outcomes Research Analyses:

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

Descriptive analyses of HEOR endpoints based on the following patient reported outcome questionnaires will be summarized. For the European Organization for

	Research and Treatment of Cancer quality of life questionnaires (EORTC QLQ)-C30 and EORTC QLQ-BR45: changes from baseline over time on the global QoL scale, the functioning scales, symptom scales, and single-item scales of the EORTC QLQ-C30 and in each of the subscales of EORTC QLQ-BR45. For the EQ-5D-5L visual analogue scale, all 5 dimensions and associated utility scores; and for hospitalization-related endpoints: time to hospitalization as well as reason, discharge diagnosis, intensive care unit stay, and length of stay will be reported. Time to definitive deterioration on the 'breast symptoms' and 'arm symptoms' subscales of the EORTC QLQ-BR45, and the pain symptom subscale of the EORTC QLQ-C30 will also be assessed. Time to definitive deterioration will be compared between the 2 treatment groups using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at a 2-sided significance level of 0.05. The survival distributions will be estimated by Kaplan-Meier method and results will be presented graphically. The median time to definitive deterioration and the proportion of patients without definitive deterioration at specific time points will be reported as well as the 2-sided 95% CIs for the medians. A stratified Cox regression model will be used to estimate the HR of time to definitive deterioration, along with 95% CI. Pharmacokinetic Analyses Descriptive statistics will be provided for all serum concentration data (trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a) at each time point. The population PK (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of trastuzumab deruxtecan, and if appropriate, total anti-HER2 antibody and MAAA-1181a will be characterized including available PK data. After establishment of the pop-PK model, a pop-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and toxicity. The results of the nonlinear mixed effects pop-PK and pop-PK/pharmacodynamic models may be reported separately from the clinical study report. Biomarker Analyses Archived tissue will be requested for re-analysis of HER2 status by immunohistochemistry and/or in situ hybridization as well as exploratory biomarkers. Biomarkers will be summarized by treatment group using descriptive statistics Safety Analyses: Safety endpoints will include SAEs, TEAEs, AESIs, DAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings, and ADAs. TEAEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

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

The educational programme is aimed at:

I) ensuring early recognition of interstitial lung disease (ILD)/pneumonitis, to allow prompt appropriate treatment and to mitigate worsening of the condition

II) improving HCP awareness of the potential risk for product confusion-related medication errors due to the availability of multiple trastuzumab-containing products and trastuzumab emtansine

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

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

The HCP Guide will contain the following key elements:

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

Patient Card

The Patient Card will contain the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan

- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber
- Cross-reference to Patient Information Leaflet

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

The HCP Guide will contain the following key elements:

- Alert to HCPs about a potential risk of confusion between TRADENAME (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 TRADENAME (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

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

List of References

1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018. Available from: https://gco.iarc.fr/today; Last accessed 17 March 2020.
2. Cortet M, Bertaut A, Molinié F, et al. Trends in molecular subtypes of breast cancer: description of incidence rates between 2007 and 2012 from three French registries. BMC Cancer. 2018;18(1):161.
3. Santa-Maria CA, Nye L, Mutonga MB, et al. Management of metastatic HER2-positive breast cancer: Where are we and where do we go from here? Oncology. 2016 Feb; 30(2):148-55.
4. Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: pathophysiology, clinical use, and new advances in therapy. Chemother Res Pract. 2012; 743193.
5. Taucher S, Rudas M, Mader RM, et al. Do we need HER-2/neu testing for all patients with primary breast carcinoma? Cancer Dec. 2003; 98:2547-53.
6. DeKoven M, Bonthapally V, Jiao X, et al. Treatment pattern by hormone receptors and HER2 status in patients with metastatic breast cancer in the UK, Germany, France, Spain and Italy (EU-5): results from a physician survey. J Comp Eff Res. 2012;1(5):453-63.
7. Ottini L, Capalbo C, Rizzolo P, et al. HER2-positive male breast cancer: an update. Breast Cancer: Targets and Therapy 2010;2:45-58.
8. Noone AM, Howlader N, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Available from https://seer.cancer.gov/csr/1975_2015/. Last accessed 17 Mar 2020.
9. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence. Available at: https://canques.seer.cancer.gov/cgi-bin/cq_submit?dir=seer2016&db=3&rpt=TAB&sel=1^1^0^51^2^0,1,2,4,5^2^0&y=Race/ethnicity^0,1,2,4,5&dec=1,1,1&template=null). Last accessed 17 Mar 2020.
10. Bilimoria M, Morrow M. The woman at increased risk for breast cancer: Evaluation and management strategies. CA Cancer J Clin. 1995; 45:263–78.
11. Kelsey JL, Gammon MD, John EM. Reproductive and Hormonal Risk Factors. Reproductive Factors. 1993;15(1):36-47.
12. Munsell MF, Sprague BL, Berry DA, et al. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev. 2014; 36:114–36.
13. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: Breast cancer—Epidemiology, risk factors, and genetics. British Med J. 2000;321(Sep):624-28.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53,297 women with breast

cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet. 1996; 347:1713-27.

15. Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and breast cancer: A systematic review and meta-analysis. Menopause. 2005; 12(6):668–78.
16. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: A review of current evidence. Breast Cancer Res. 2005: 7:21-32.
17. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017; 31:244-59.
18. Baselga J, Cortés J, Kim S, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366(2):109-19.
19. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. New Engl J Med. 2012; 367(19):1783-91.
20. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer (Version 2.2020). 5 Feb 2020.
21. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: Analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015; 385:977-1010.
22. Carioli G, Malvezzi M, Rodriguez T, et al. Trends and predictions to 2020 in breast cancer mortality in Europe. The Breast. 2017;36:89-95.
23. Savci-Heijink CD, Halfwerk H, Hooijer GKJ, et al. Retrospective analysis of metastatic behavior of breast cancer subtypes. Breast Cancer Res Treat. 2015;150:547-57.
24. Dent R, Hanna WM, Trudeau M, et al. Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat. 2009;115:423-8.
25. Jensen AO, Jacobsen JB, Norgaard M, et al. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer. 2011;11:29.
26. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol. 2004;22(14):2865-72.
27. Pestalozzi BC, Zahrieh D, Price KN, et al for the International Breast Cancer Study Group. Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol. 2006;17:935-44.
28. Rostami R, Mittal S, Rostami P, et al. Brain metastasis in breast cancer: a comprehensive literature review. J Neurooncol. 2016;127:407-14.
29. Witzel I, Laakmann E, Weide R, et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer. 2018;102:1-9.
30. Jones LW, Haykowsky MJ, Swartz JJ, et al. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007;50:1435-41.

31. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131:1981-8.
32. Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer (review). Cochrane Database of Systematic Reviews 2014;6.
33. Matos E, Jug B, Bagus R, et al. A prospective cohort study on cardiotoxicity of adjuvant trastuzumab therapy in breast cancer patients. Arq Bras Cardiol. 2016; 107(1):40-7.
34. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.
35. Hoe AL, Royle GT, Taylor I. Breast liver metastases – incidence, diagnosis and outcome. J R Soc Med. 1991;84(12):714-6.
36. Xie J, Xu Z. A population-based study on liver metastases in women with newly diagnosed breast cancer. Cancer Epidemiol Biomarkers Prev. 2019;28(2):283-92.
37. Wyld L, Gutteridge E, Pinder SE, et al. Prognostic factors for patients with hepatic metastases from breast cancer. Br J Cancer. 2003;89(2):284-90.
38. Dieras V, Harbeck N, Budd GT, et al. Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. J Clin Oncol. 2014;32(25):2750-7.
39. Omarini C, Thanopoulou E, Johnston SRD. Pneumonitis and pulmonary fibrosis associated with breast cancer treatments. Breast Cancer Res Treat. 2014;146:245-58.
40. Jin L, Han B, Siegel E, et al. Breast cancer lung metastasis: molecular biology and therapeutic implications. Cancer Biol Ther. 2018;19(10)858-68.
41. Ording AG, Cronin-Fenton DP, Jacobsen JB, et al. Comorbidity and survival of Danish breast cancer patients from 2000–2011: A population-based cohort study. Clin Epidemiol. 2013;5:39-46.
42. Berglund A, Wigertz A, Adolfsson J, et al. Impact of comorbidity on management and mortality in women diagnosed with breast cancer. Breast Cancer Res. Treat 2012; 135:281-9.
43. Louwman WJ, Janssen-Heijnen MLG, Houterman S, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. Eur J Cancer. 2005; 41:779-85.
44. McPherson CP, Swenson KK, Lee MW. The effects of mammographic detection and comorbidity on the survival of older women with breast cancer. J Am Geriatr Soc. 2002; 50:1061-8.
45. Land LH, Dalton SO, Jørgensen TL, et al. Comorbidity and survival after early breast cancer. A review. Crit Rev Oncol/Hemat. 2012; 81:196-205.
46. Yancik R, Wesley MN, Ries LAG, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. J Am Med Assoc. 2001;285(7):885-92.

47. Houterman S, Janssen-Heijnen MLG, Verheij CDGW, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer. 2004; 90:2332-7.
48. Braithwaite D, Moore DH, Satariano WA, et al. Prognostic impact of comorbidity among long-term breast cancer survivors: Results from the LACE study. Cancer Epidemiol Biomark Prev. 2012; 21(7):1115-25.
49. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: Where these entities intersect a scientific statement from the American Heart Association. Circulation. 2018;137:e30-66.
50. Janssen-Heijnen MLG, Houterman S, Lemmens VEPP, et al. Prognostic impact of increasing age and co-morbidity in cancer patients: A population-based approach. Crit Rev Oncol/Hemat. 2005;55:231-40.
51. Ording AG, Garne JP, Nyström PMW, et al. Comorbid diseases interact with breast cancer to affect mortality in the first year after diagnosis—A Danish nationwide matched cohort study. PLOS ONE. 2013;8(10):e76013.
52. Guidance for Industry: Estimating the Maximum Safety Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Rockville, Md.: U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Pharmacology and Toxicology; July 2005.
53. S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. Rockville, Md.: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research; 2018.
54. Liu Z, Carvajal M, Carraway CA, et al. Expression of the receptor tyrosine kinases, epidermal growth factor receptor, ErbB2 and ErbB3 in human ocular surface epithelia. Cornea. 2001;20(1):81-5.
55. Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012;13(1):39.
56. Kondapalli L. Cardiotoxicity: An Unexpected Consequence of HER2-Targeted Therapies. American College of Cardiology. 2016. https://www.acc.org/latest-in-cardiology/articles/2016/06/06/09/32/cardiotoxicity. Published 07 June 2016. Last accessed 17 Mar 2020.
57. Mohan N, Jiang J, Dokmanovic M, et al. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. Antib Ther. 2018;1(1):13-7.
58. Florido R, Smith KL, Cuomo KK, et al. Cardiotoxicity from human epidermal growth factor receptor-2 (HER 2) targeted therapies. J Am Heart Assoc. 2017; 6(9):e006915.
59. European Medicines Agency. Kadcyla: EPAR Public Assessment Report. EMA/CHMP/641539/2013. available at: https://www.ema.europa.eu/en/documents/assessment-report/kadcyla-epar-public-assessment-report_en.pdf

ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Table Part VII.2: Summary of Change to the Risk Management Plan Over Time

Version	Approval date Procedure	Change
1.0	Marketing authorisation application	Not applicable - initial version of RMP