EUROPEAN UNION RISK MANAGEMENT PLAN (RMP) FOR DATOPOTAMAB DERUXTECAN

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP:

Not applicable for an initial marketing authorisation submission.

Summary of significant changes in this RMP:

Not applicable – this is Version 1 of the RMP.

Qualified Person for Pharmacovigilance (QPPV) name: Dr. Stefan Freudenthaler

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

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LIST OF ACRONYMS AND ABBREVIATIONS

Acronym/Abbreviation	Definition
AC	adjudication committee
ADC	antibody drug conjugate
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BRCA1/2	breast cancer gene 1/2
CDK4/6	cyclin-dependent kinase 4/6
Cmax	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P540
Dato-DXd	datopotamab deruxtecan (DS-1062a)
DXd	deruxtecan
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU-27	the 27 member state countries of the European Union
GnRH	gonadotropin hormone-releasing hormone
HCP	Healthcare Professional
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HR	hormone receptor
IgG1	Immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
ISH	in situ hybridisation
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NSCLC	non-small cell lung cancer
NIH SEER	National Institutes of Health Surveillance, Epidemiology, and End Results
PL	Patient Leaflet

Acronym/Abbreviation	Definition
PK	pharmacokinetic
PT	preferred term
Q3W	every 3 weeks
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
SERD	selective oestrogen receptor degrader
SERM	selective oestrogen receptor modulator
SmPC	Summary of Product Characteristics
SOC	System Organ Class (MedDRA)
TROP2	trophoblast cell surface antigen 2
ULN	upper limit of normal
US	United States
WHO	World Health Organization

PART I. PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) (INN or common name):	Datopotamab deruxtecan (Dato-DXd; DS-1062a)
Pharmacotherapeutic group(s) (ATC Code):	Not yet assigned
Marketing Authorisation Applicant:	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers:	One
Invented name(s) in the EEA:	Not yet available
Marketing authorisation procedure:	Centralised
Brief description of the product:	**Chemical class**: TROP2-directed ADC
	Summary of mode of action: The antibody is a humanised anti-TROP2 IgG1 attached to deruxtecan (DXd), a topoisomerase I inhibitor bound by a tetrapeptide-based cleavable linker. The antibody binds to TROP2 expressed on the surface of certain tumour cells. After binding, Dato-DXd undergoes internalisation into the tumour cells. Subsequently, the release of DXd results in DNA damage and apoptotic cell death via topoisomerase I inhibition.
	Important information about its composition: The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology. The topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 4 molecules of DXd are attached to each antibody molecule.
Hyperlink to the Product Information:	[Product Information]
Indication(s) in the EEA:	**Current**: Dato-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.
Dosage in the EEA:	**Current**: 6.0 mg/kg given as an IV infusion Q3W (21-day cycle) until disease progression or unacceptable toxicity.

Table I.1: Product Overview

Pharmaceutical form(s) and strengths:	**Current**: The Dato-DXd drug product is supplied as a white to yellowish-white lyophilised powder, which has a cake-like appearance. One vial of powder for concentrate for solution for infusion contains 100 mg of Dato-DXd. It must be reconstituted and diluted by a healthcare professional and administered as an IV infusion. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of Dato-DXd.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = Anatomical Therapeutic Chemical; DNA = deoxyribonucleic acid; INN = international non-proprietary name

PART II. SAFETY SPECIFICATION

PART II. MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. Breast Cancer

Incidence

Breast cancer is the most commonly diagnosed cancer worldwide, accounting for approximately 24.5% of all cancer cases and 15.5% of cancer deaths in 2020. Approximately 11.7% of all new cancers are female breast cancer, which has an annual incidence rate of 47.8 per 100,000 worldwide. Australia/New Zealand, Europe, and North America have the highest incidence rate by region. Hormone Receptor-positive, HER2-negative breast cancer is the most common subtype, accounting for approximately 70% of breast cancer diagnoses.

Europe: In the EU-27, 374,800 new cases of female breast cancer were diagnosed in 2022, comprising approximately 29.4% of all cancers in women. In men, 4400 new cases of breast cancer were diagnosed in 2022, estimated to account for 0.3% of all diagnosed cancers in men. In Europe, the estimated annual age-standardised (worldwide) incidence rate of breast cancer in 2020 was 74.3 per 100,000. In a cohort study based on healthcare administrative data (covering a population of >10 million patients in Italy in 2013), the crude incidence of HR-positive, HER2-negative metastatic breast cancer was 6.9 per 100,000 women aged ≥18 years.

United States: The age-adjusted rate of new cases of female breast cancer (2016 to 2020) in the US was 126.9 per 100,000 women per year, and estimates suggest that there were to be 297,790 new cases of female breast cancer in 2023. Furthermore, HR-positive, HER2-negative was the most common subtype of breast cancer in the US, with an age-adjusted rate of 87.2 new cases per 100,000 women based on 2016 to 2020 cases.

Prevalence

The WHO estimated that in 2020 there were 2.3 million women diagnosed with breast cancer globally, and 7.8 million women alive globally who were diagnosed with breast cancer in the previous 5 years.

***Europe*:** In 2020, there were an estimated 2,138,117 women living with breast cancer in Europe who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 552.2 per 100,000.

***United States*:** There were an estimated 1,097,918 women alive who were diagnosed with breast cancer from 2015 to 2019. In the US, HR-positive, HER2-negative tumours are the most common subtype of breast cancer, accounting for approximately 73% to 77% of breast cancer cases.

Demographics of the population - age, gender, racial and/or ethnic origin, and risk factors for the disease

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

Age: Worldwide, 48% of the newly diagnosed breast cancer patients are 45 to 64 years old. In the EU and in the US, breast cancer is most frequently diagnosed in women aged 55 to 75 years. In both the EU and the US, breast cancer incidence is much higher among adults and increases with age, with the highest incidence and prevalence rates among those ≥65 years. Similarly, the risk of HR-positive, HER2-negative breast cancer increases significantly with age, with median age at diagnosis of approximately 65 years.

Race and/or Ethnicity: In the US, the incidence and prevalence of both breast cancer overall and of HR-positive, HER2-negative breast cancer is highest among white non-Hispanic women. Furthermore, in a NIH SEER data registry covering an estimated 28% of the US population in 2010, racial and ethnic differences in HR-positive, HER2-negative breast cancer rates peaked at 75 to 79 years of age, with higher rates for white non-Hispanic (342.7 per 100,000), followed by Black non-Hispanic (236.8 per 100,000), Asian or Pacific Islander non-Hispanic (176.4 per 100,000), and Hispanics (190.3 per 100,000).

Risk factors for breast cancer comprise the following:

- ***Family history***: Women with a family history, especially a mother, sister, or daughter who has or had breast cancer, have a higher risk of having breast cancer. In western countries, genetic predisposition is the cause of up to 10% of breast cancer cases. The most common inherited causes are mutation in the BRCA1 and BRCA2 genes. Among women undergoing screening mammography, those with a family history of breast cancer (ie, first-degree relatives with breast cancer) had a significantly higher risk of developing HR-positive, HER2-negative breast cancer compared to women without a family history of the disease.
- ***Reproductive factors***: Women who have early menarche (before age 12) or late menopause (after age 55) have a higher risk of developing breast cancer. Nulliparous women and women who are over age 30 at their first birth may have a greater chance of developing breast cancer.
- ***Obesity***: Obesity is associated with a greater probability of breast cancer, which is intensified in obese postmenopausal females. Similarly, among women undergoing screening mammography, those with high BMI (25 to 29 kg/m^2 and >30 kg/m^2) have a significantly higher risk of developing HR-positive, HER2-negative breast cancer than those with low BMI (<25 kg/m^2).
- ***Breast density***: Greater breast tissue density correlates with higher breast cancer risk; this trend is observed in premenopausal and postmenopausal females. Higher breast density was also associated with increased risk of HR-positive, HER2-negative breast cancer compared to those with low breast density.
- ***Atypical hyperplasia***: Presence of atypical hyperplasia has been associated with increased risk of HR-positive, HER2-negative breast cancer.

- ***Hormonal replacement therapy***: Females who use hormonal replacement therapy for a prolonged period (especially longer than 5 or 7 years) are also at increased risk of breast cancer.
- ***Physical activity***: Lack of physical activity is associated with higher risk of breast cancer.
- ***Birth control pills***: Oral contraceptive use may slightly increase the risk of developing breast cancer. 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 breast cancer.
- ***Combined postmenopausal hormone therapy***: Women who use combined hormone therapy after menopause have increased risk of developing breast cancer. There is a dose-response relationship, with larger risks corresponding with longer durations of combined hormonal therapy use.
- ***Radiation exposure***: Children or young adults exposed to radiation therapy to the chest area have significantly increased risk of developing breast cancer later in life.

The main existing treatment options

The choice of therapy for HR-positive, HER2-negative breast cancer depends on several variables, such as disease stage, menopausal status, biomarker status, therapy objectives, prior therapies, and patient health. Differences in the healthcare systems and reimbursement across countries also influence therapeutic options.

In general, endocrine therapy (eg, SERMs, SERDs, AIs or GnRH agonists) or surgery at primary stage are the mainstay for the majority of patients with HR-positive metastatic breast cancer, with palliative chemotherapy reserved for life-threatening advanced disease or patients with visceral crisis.

In patients with locally advanced metastatic HR-positive, HER2-negative breast cancer, the recommended first-line standard-of-care is endocrine therapy, with either AI or fulvestrant, plus a CDK4/6 inhibitor for metastatic HR-positive, HER2-negative breast cancer.

In patients who have exhausted or are not suitable for endocrine therapy, sequential single-agent chemotherapy (such as doxorubicin, paclitaxel, eribulin, capecitabine, gemcitabine, vinorelbine) is the next therapeutic option; however, no specific sequence of cytotoxic therapies has been advocated, and such treatments are associated with poor prognosis and declining response rates, disease control rates, and increased toxicity which can have a significant impact on patient quality of life.

More recently, ADCs have been approved for the treatment of breast cancer following demonstration of their superior clinical benefit over existing treatments. Enhertu™ (trastuzumab deruxtecan) was first approved in 2022 for treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Trodelvy™ (sacituzumab govitecan) was first approved in 2023 for the treatment of adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who

have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

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

Approximately 6% of women diagnosed with breast cancer in the US have metastatic disease at time of diagnosis, and up to 30% of women with early-stage non-metastatic breast cancer will subsequently develop metastatic disease.

In patients with metastatic breast cancer, bone is the most common site for metastasis (reported in 70.6% of patients). Among patients with breast cancer who had bone metastases, 47.7% developed skeletal-related events, defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopaedic surgery.

The liver is also a common site for metastasis (reported in 54.5% of patients with breast cancer) and liver metastases represent a frequent cause of mortality among these patients. In the majority of cases, liver metastases have been reported as primarily asymptomatic at the time of diagnosis; however, some patients do present with epigastric pain or fullness, palpable hepatomegaly, and/or ascites.

Approximately 31% of patients with metastatic breast cancer also experience lung metastasis. Metastases to the lung are associated with poor prognosis and presents with clinical symptoms such as pain, cough, haemoptysis, pleural effusion, and pulmonary dysfunction.

The estimated number of deaths attributable to breast cancer globally increased from 380,910 deaths in 1990 to 700,660 deaths in 2019. Whilst Asia and Africa reported relatively high death rates in 2020, Europe, Australasia, and the US have exhibited a consistent decrease in death rates over time. This decline is most likely due to high socioeconomic status, widespread use of mammography for early-stage diagnosis, and improvements in treatment facilities.

Despite recent advances in treatment, approximately 684,996 women died from breast cancer worldwide in 2020, with a 5-year age-adjusted mortality rate of 13.6 per 100,000. Patients with HR-positive, HER2-negative advanced/metastatic breast cancer typically have a 5-year survival rate of <30%.

Based on US NIH SEER data from 2013 to 2019, the HR-positive, HER2-negative breast cancer subtype exhibited the highest relative survival rate (94.8%) over 5 years, than the HR-positive, HER2-positive (91%) and the HR-negative, HER2-positive (85.6%) subtypes). However, evidence suggests that the stage at which breast cancer is diagnosed has a greater influence over relative survival than subtype. For HR-positive, HER2-negative breast cancer, 5-year relative survival rates in the US were 100% for localised disease, 90.3% for regional disease, and 34% for distant disease.

Important comorbidities

Most breast cancer patients have one or more comorbid medical conditions at diagnosis or at baseline, the most common being cardiovascular conditions, particularly hypertension (which varies from 9% to 43%).

Other comorbidities, with their reported prevalences, include pain or pain-inflammation (34.8% to 50%), obesity (41.9%), hyperlipidaemia (37%), mental health disorders such as depression associated with anxiety (21.5%), COPD (19.9%), rheumatologic disease (1.4% to 18.6%), chronic gastritis or gastric disorders (14.3% to 18.4%), diabetes mellitus (2% to 16.7%), coronary heart disease (3.5% to 5.0%), stroke (1.4% to 2.2%), and chronic hepatitis (1.8%).

The literature suggests that there is an association between ethnicity and prevalence of comorbidities among breast cancer patients; eg, Black patients in the US were found to be twice as likely to have a diagnosis of type 2 diabetes and 1.4 times more likely to have a diagnosis of hypertension than White patients. Some estimates indicate that comorbidities such as hypertension, diabetes, coronary heart disease, or stroke are associated with older age, being overweight (BMI 25 to <30 kg/m^2) or obese (BMI ≥30 kg/m^2), and not being treated with chemotherapy and radiotherapy.

Estimates of comorbid conditions that are present at HR-positive, HER2-negative diagnosis suggest that hypertension is the most prevalent comorbidity, ranging from 15.8% to 73.9%. Other prevalent comorbidities include dyslipidaemia (66.5%), diabetes (34.6%), COPD (19.8%), stroke (10.6%), coronary heart failure (8.2%), chronic kidney disease (7.9%) and chronic liver disease (0.9%). Among HR-positive, HER2-negative patients, incidence of comorbidities such as hypertension and diabetes mellitus are higher among older patients (65 to 87 years) than younger patients (25 to 64 years): 61.1% vs 15.8% for hypertension and 26.4% vs 6.5% for diabetes mellitus.

Adverse events anticipated to occur in the target population

Frequently reported AEs for the different drug classes commonly used in patients with HR-positive, HER2-negative breast cancer are presented in Table II-SI.1.

Table II-SI.1: Frequently Reported Adverse Events in Patients with HR-positive, HER2-negative Breast Cancer

Drug Class	Adverse Events
Hormonal therapy (*SERMs/AIs/SERDs/GnRH agonists*)	Cognitive impairment, depression, joint and bone pain, osteoporosis, nausea, weakness, reactions at injection sites, elevated liver enzymes, hot flashes/sweats, night sweats, vaginal discharge, vaginal dryness, sexual dysfunction, arthralgia, myalgia, thromboembolic disease, ischaemic cardiovascular/ cerebrovascular diseases, hair thinning, and mood changes.
Chemotherapy (*taxanes/ anthracyclines/ platinum-based agents*)	Alopecia, constipation, cognitive changes, diarrhoea, oesophagitis, fatigue, infection, joint pain, kidney damage, myelosuppression, nausea, ototoxicity, peripheral neuropathy, rash, stomatitis, vomiting, and weight changes.
Targeted therapy (*CDK4/6 inhibitors and mTOR/PI3K inhibitors*)	Anaemia, hyperglycaemia, leukopenia (less common with abemaciclib), fatigue, nausea, diarrhoea (more common with abemaciclib), liver dysfunction, stomatitis, non-infective pneumonitis, lipid alterations, and neutropenia.

mTOR = Mammalian target of rapamycin; PI3K = Phosphoinositide

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

Information on the key safety findings from the nonclinical studies with Dato-DXd and/or released drug and their relevance to human usage is presented in Table II-SII.1.

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
TOXICITY	
Acute or repeat-dose toxicity studies:	
Pulmonary toxicity: • *Dato-DXd*: The most significant change related with Dato-DXd was severe lung toxicity in monkeys at ≥30 mg/kg. Histopathological findings in the lung included oedema and haemorrhage in the alveolus, aggregation of foamy alveolar macrophages, and inflammation in the alveolus/interstitium. Consolidation in the chest computed tomography examination, an increase in serum surfactant protein D, and/or decreases in oxygen partial pressure and haemoglobin oxygen saturation in the blood gas analysis were also observed at ≥30 mg/kg. • *DXd*: Non-severe pulmonary findings such as haemorrhage, infiltration of neutrophils in the alveolus, regeneration of the alveolar epithelium, and infiltration of foamy alveolar macrophages were also observed in rats at 200 mg/kg. On the other hand, no pulmonary toxicity was induced by DXd monohydrate in rats up to 30 mg/kg or in monkeys up to 12 mg/kg.	TROP2 expression in human lungs has been reported; however, comprehensive mechanisms of pulmonary toxicity related to Dato-DXd remain unclear. Nonclinical studies in monkeys suggested that Dato-DXd could potentially lead to pulmonary toxicity. Similarly, events of ILD/pneumonitis have been observed in clinical studies. Therefore, considering the importance of detection and management as well as the potential for serious and life-threatening consequences if left unmanaged, ILD/pneumonitis is considered to be an important identified risk in this RMP (see Section SVII.3.1.1).
Corneal toxicity: • *Dato-DXd*: Single cell necrosis and brown pigmentation in the corneal epithelium, which was accompanied by corneal pigmentation in ophthalmology, were observed in monkeys at ≥30 mg/kg of Dato-DXd. In addition, atrophy of the corneal epithelium was observed in monkeys at 80 mg/kg. The corneal findings showed reversibility, except pigmentation after the 2-month recovery period. • *DXd*: A corneal toxicity also occurred in rats at ≥3 mg/kg and in monkeys at 12 mg/kg of DXd monohydrate. Therefore, corneal toxicity in the animals given Dato-DXd, as well as DXd monohydrate, would be attributable to the cytotoxic mechanism of action of DXd.	TROP2 expression in the cornea was detected in eye tissue in humans and has similarly been reported in cynomolgus monkeys, and nonclinical studies suggested a potential for adverse corneal effects. Based on data from clinical studies, eye disorders (eg, increased lacrimation, dry eye, conjunctivitis, blurred vision, and visual impairment) are considered to be identified risks for Dato-DXd; however, these events were rarely reported as severe and therefore do not impact the benefit-risk balance. Furthermore, and based on the potential for serious consequences if left unmanaged, keratitis is additionally considered to be an important identified risk for Dato-DXd in this RMP (see Section SVII.3.1.2).

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Skin toxicity: • *Dato-DXd*: Non-severe skin toxicity was observed in rats at 200 mg/kg and in monkeys at ≥30 mg/kg of Dato-DXd. Alopecia in rats, abnormal skin colour, excoriation, erosion, and crust in monkeys were observed. Histopathological findings included necrosis of the epidermis and single cell necrosis in the hair follicle in rats, pigmentation in the epidermis, fibrosis, and cell infiltration in the epidermis/dermis, crust, and erosion in monkeys. These changes, except a histopathological finding of brown pigmentation in the epidermis in monkeys at ≥30 mg/kg, showed reversibility after the recovery period in rats and monkeys. • *DXd*: In the 4-week toxicity studies of DXd monohydrate, no similar finding was noted in rats up to 30 mg/kg and in monkeys up to 12 mg/kg either.	TROP2 expression in the human and monkey epidermis has been reported; however, the involvement of Dato-DXd via TROP2 in the skin toxicity was undetermined as rats (a non-cross-reactive species of Dato-DXd) also showed similar lesions. Several skin AEs (eg, rash, pruritus, dry skin, skin hyperpigmentation) are considered identified risks for Dato-DXd based on the evaluation of clinical study data; however, these events were rarely reported as severe and therefore do not impact the benefit-risk balance of Dato-DXd. Thus, this topic is not considered relevant for inclusion as an important identified risk in this RMP.
Liver Toxicity • *Dato-DXd*: Single cell necrosis in hepatocytes was observed in a monkey at 30 mg/kg of Dato-DXd. These findings were reversible and not observed anymore after 2 months of withdrawal. No apparent finding was seen in rats up to 200 mg/kg of Dato-DXd. • *DXd*: Single cell necrosis, focal necrosis, and increased mitosis in hepatocytes, dilatation and bile thrombus of the bile canaliculus, and brown pigment deposition in Kupffer cells in the liver were noted in monkeys at 12 mg/kg of DXd monohydrate, which were accompanied by increases in hepatic enzyme parameters. No apparent finding was seen in rats up to 30 mg/kg of DXd monohydrate.	Nonclinical studies in monkeys suggested that Dato-DXd could potentially lead to liver toxicity; however, no evidence of liver toxicity has been identified from clinical studies. Thus, this topic is not considered relevant for inclusion as a safety concern in this RMP.

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Gastrointestinal toxicity • *Dato-DXd*: Vomiting, salivation, loose stool, and mucus in the faeces were noted in a monkey at 30 mg/kg of Dato-DXd in the exploratory study for 6 weeks (Q3W, three times in total, dose level: 10 and 30 mg/kg). In the 3-month toxicity studies, single cell necrosis of the crypt epithelium in the intestines of rats at ≥60 mg/kg and in monkeys at ≥10 mg/kg of Dato-DXd was observed. These changes showed reversibility after the recovery period in rats and monkeys. • *DXd*: The intestinal toxicity related to Dato-DXd also occurred in the toxicity studies of DXd monohydrate in rats and monkeys.	Nonclinical studies in rats and monkeys indicated a potential for gastrointestinal effects (eg, diarrhoea and vomiting) with Dato-DXd and released drug, and gastrointestinal toxicity is a typical dose-limiting toxicity of topoisomerase I inhibitors in humans. Gastrointestinal toxicity is attributable to the cytotoxic mechanism of action of DXd, and Dato-DXd-related intestinal toxicity might be caused, at least in part, by DXd released into plasma. Several gastrointestinal AEs (eg, nausea, vomiting, diarrhoea, constipation) are considered identified risks for Dato-DXd based on the evaluation of clinical study data; however, these events were rarely reported as severe and therefore do not impact the benefit-risk balance of Dato-DXd. Thus, this topic is not considered relevant for inclusion as a safety concern in this RMP.
Stomatitis/Mucosal Inflammation In a 2-week exploratory toxicity study of MAAP-9002b (a former TROP2 ADC candidate comprised of the same components as Dato-DXd), comprising once weekly (twice in total) dosing at 11, 33, and 89 mg/kg, mucosal necrosis and cell infiltration in the oesophagus were observed in monkeys at a dose level of ≥11 mg/kg. • *Dato-DXd:* No similar finding was noted in rats up to 200 mg/kg and in monkeys up to 80 mg/kg in the 3-month toxicity studies of Dato-DXd. • *DXd*: No similar finding was noted in rats up to 30 mg/kg and in monkeys up to 12 mg/kg in the 4-week toxicity studies of DXd monohydrate.	The stratified squamous epithelium in the human oesophagus expresses TROP2 protein; therefore, the findings in the oesophagus from monkeys given MAAP-9002b may be TROP2-mediated. However, MAAP-9002b has a higher average drug-to-antibody ratio than that of Dato-DXd (7 vs 4, respectively), and therefore this difference, in addition to differences in dosing regimens, could explain why Dato-DXd was not involved in mucosal injuries in Dato-DXd-treated monkeys. Based on the evaluation of clinical study data, stomatitis is considered an identified risk for Dato-DXd; however, events were predominantly reported as mild or moderate in severity, rarely resulted in treatment discontinuation, and can be adequately managed by guidance provided in the product label. Stomatitis therefore does not impact the benefit-risk balance of Dato-DXd, and thus this topic is not considered relevant for inclusion as a safety concern in this RMP.

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Lymphatic/Haematopoietic Toxicity • *Dato-DXd*: As lymphatic organ toxicity, an increased number of tingible body macrophages in the thymus was observed in rats at ≥20 mg/kg of Dato-DXd. Atrophy of the cortex in the thymus and of periarteriolar lymphoid sheaths in the spleen was seen in rats at 200 mg/kg. Thymic atrophy was also observed in monkeys at ≥30 mg/kg of Dato-DXd. As haematopoietic organ toxicity decreases in reticulocyte, white blood cell, neutrophil, and lymphocyte counts were noted in rats at 200 mg/kg of Dato-DXd. The haematological changes in rats seemed to be associated with a decreased number of haematopoietic cells in the bone marrow. These changes showed reversibility after the recovery period in rats and monkeys. • *DXd*: The lymphatic/haematopoietic organ toxicity also occurred following the administration of DXd monohydrate in rats and monkeys.	Nonclinical data suggest that the effects of Dato-DXd are attributable to the cytotoxic mechanism of action of DXd, and that the Dato-DXd-related lymphatic/haematopoietic organ toxicity could be caused, at least in part, by DXd released into plasma. Based on the evaluation of clinical study data and biological plausibility, anaemia is considered an ADR for Dato-DXd; however, events were infrequently reported as severe and therefore do not impact the benefit-risk balance of Dato-DXd. Thus, this topic is not considered relevant for inclusion in this RMP as a safety concern. No other haematological toxicities have been observed based on clinical data.
Renal Toxicity • *Dato-DXd*: Slight renal tubular changes were observed in rats at ≥60 mg/kg and in monkeys at 80 mg/kg of Dato-DXd. In addition, a glomerular lesion (ie, degeneration of podocytes) was noted in rats at 200 mg/kg. In urinalysis, an increase in protein in rats at 200 mg/kg and a decrease in urinary pH and an increase in ketone body in monkeys at ≥30 mg/kg were observed. In blood chemistry, decreases in albumin and albumin/globulin ratio, and an increase in urea nitrogen were noted in rats at 200 mg/kg. These changes showed reversibility after the recovery period in rats and monkeys. • *DXd*: In the 4-week toxicity studies of DXd monohydrate, no similar finding was either noted in rats up to 30 mg/kg and in monkeys up to 12 mg/kg.	Nonclinical findings in rats and monkeys were reversible, and the renal tubular findings in monkeys may be due to an off-target effect by Dato-DXd, since no TROP2 expression in the proximal tubule has been reported in immunohistochemistry. In humans, the major excretion pathway of DXd (payload of Dato-DXd) from Dato-DXd is primarily through faeces via the biliary route, with minimal renal excretion based upon mass balance studies of DXd in monkeys. Nevertheless, as the mechanism of renal toxicity in monkeys and rats remains unknown, renal toxicity is considered as a potential risk not categorised as important in this RMP (see Section SVII.1.1 for further details).

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Cardiotoxicity	When taken together, nonclinical data suggest that it is unlikely that Dato-DXd would cause cardiotoxicity in humans; and therefore, cardiotoxicity is not considered relevant for inclusion in this RMP as a safety concern.
• *Dato-DXd*: No toxicity finding in the heart was noted in rats up to 200 mg/kg and in monkeys up to 80 mg/kg of Dato-DXd. • *DXd*: DXd caused myocardial degeneration/necrosis in a moribund monkey at 12 mg/kg. • In a safety pharmacology study, Dato-DXd did not affect cardiovascular parameters (ie, electrocardiography, heart rate, or blood pressure) in telemetered monkeys receiving a single intravenous dose of Dato-DXd at up to 80 mg/kg. Moreover, DXd has no inhibitory effects on hERG channel current at up to 10 µmol/L (approximately 5000 ng/mL).	
Reproductive / developmental toxicity:	
Reproductive organ toxicity:	Nonclinical data from rats and monkeys indicate changes to the reproductive organs of females and males, and a hypothetical risk of adverse effects on fertility in humans cannot be excluded. These data are therefore deemed to be of potential relevance to human use, and this topic is considered to be a potential risk not categorised as important in this RMP (see Section SVII.1.1 for further details).
• *Dato-DXd*: Degeneration of the germinal epithelium and atrophy of seminiferous tubules in the testis were seen in rats at 200 mg/kg of Dato-DXd. Cell debris, decreased number of spermatozoa in ducts, and single cell necrosis of the ductal epithelium in the epididymis were also observed at 200 mg/kg. The seminiferous tubular atrophy in rats at 200 mg/kg remained after the recovery period; therefore, no clear tendency toward recovery was suggested. An increased number of atretic follicles in the ovary and single cell necrosis of mucosal epithelium in the vagina were observed in rats at 200 mg/kg of Dato-DXd. These changes in female rats showed reversibility. No apparent finding was seen in monkeys up to 80 mg/kg of Dato-DXd. • *DXd*: In the 4-week toxicity studies of DXd monohydrate, no similar finding was noted in rats up to 30 mg/kg and in monkeys up to 12 mg/kg either.	

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Foetal and development toxicity:	
• No reproductive and developmental toxicity studies for Dato-DXd have been conducted, and therefore a literature-based assessment was made to evaluate the importance of TROP2 in embryonic development and pregnancy. TROP2 has been identified as a causative gene for GDLD, with the loss of function of TROP2 gene leading to decreased expression and change in the subcellular localisation of tight junction-related proteins in the cornea. No other specific congenital disorder has been identified in humans. • Toxicity studies in rats and monkeys with Dato-DXd or DXd indicated toxic effects on rapidly dividing cells (ie, lymphatic/haematopoietic organs, intestines, or testes). DXd was genotoxic in an in vitro chromosome aberration study with mammalian cultured cells and an in vivo micronucleus study in rats.	The characteristics of Dato-DXd and the released drug indicate that Dato-DXd can potentially cause foetal harm when administered to a pregnant woman. Embryo-foetal toxicity is considered an important potential risk for inclusion in this RMP (see Section SVII.3.1.3).
Genotoxicity:	
• *Dato-DXd*: Not applicable. • *DXd*: In vitro genotoxicity studies of DXd indicated that DXd had no potential to induce gene mutations in bacteria but had the potential to induce structural chromosome aberrations in mammalian cultured cells. An in vivo micronucleus study in the bone marrow of male rats indicates that DXd has the potential to induce micronuclei following the single IV administration of DXd monohydrate at ≥0.05 mg/kg (calculated as DXd).	Based on toxicokinetic data, plasma exposure levels of DXd in humans (at a Dato-DXd dose of 6.0 mg/kg) are anticipated to be higher than the dose causing chromosomal aberration in rat bone marrow; and therefore the possibility of human genotoxicity cannot be ruled out. However, as Dato-DXd is only for use in the advanced cancer setting, the theoretical risk of genotoxicity (and associated clinical consequences) in patients in the target populations is unlikely to impact the benefit-risk balance. Nevertheless, as the released drug DXd was considered to be genotoxic, Dato-DXd may potentially result in foetal harm following exposure during pregnancy, and consequently embryo-foetal toxicity is considered an important potential risk for inclusion in this RMP (see Section SVII.3.1.3).

Table II-SII.1: Summary of Nonclinical Findings for Dato-DXd

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Carcinogenicity:	
In accordance with the ICH S6(R1) and S9 guidelines, studies evaluating carcinogenicity of Dato-DXd have not been conducted and are not planned given the characteristics of this product and the intended clinical use in patients with advanced cancer.	Not applicable as Dato-DXd is being developed for the treatment of patients with advanced cancer.
GENERAL SAFETY PHARMACOLOGY	
Cardiovascular, Respiratory, and Central Nervous Systems:	
Following the administration of Dato-DXd at a dose levels of 10 mg/kg or 80 mg/kg, and evaluation for 3 weeks post-dose, no treatment-related changes in heart rate, blood pressure, any ECG parameter, frequency of arrhythmia, physical condition, respiratory rate, any blood gas parameter, body temperature, any functional observational battery parameter, body weight, or food consumption were observed at either dose level.	As Dato-DXd had no effect on the cardiovascular, respiratory, or central nervous systems, no safety concerns relevant for inclusion in this RMP have been identified.
OTHER TOXICITY-RELATED INFORMATION	
Phototoxicity:	
• *Dato-DXd*: Not applicable. • *DXd*: An in vitro 3T3 NRU phototoxicity testing of DXd suggested its potential risk for phototoxicity. However, no phototoxic reaction was noted in a single dose phototoxicity study of DXd in pigmented rats at up to 3 mg/kg (the highest dose).	In the phototoxicity study, the plasma concentration of DXd in rats at 3 mg/kg was 90.5 ng/mL, which was 29 times higher than the Cmax (3.13 ng/mL, single dose [Cycle 1]) in NSCLC subjects given 6 mg/kg of Dato-DXd in clinical study DS1062-A-J101 (NCT03401385). Based on the findings, the risk of phototoxicity following the administration of Dato-DXd in humans is considered limited; therefore, phototoxicity is not considered relevant for inclusion in this RMP.

ECG = electrocardiogram; GDLD = gelatinous drop-like corneal dystrophy; ICH = International Council for Harmonisation; NRU = neutral red uptake.

PART II. MODULE SIII - CLINICAL TRIAL EXPOSURE

Dato-DXd is an anticancer agent indicated for use as monotherapy. A summary of exposure to Dato-DXd in patients with advanced/unresectable HR-positive, HER2-negative breast cancer is provided in Section SIII.1.

The key features of all studies included in this RMP are summarised in Table II-SIII.1.

Table II-SIII.1: Summary of Studies Included in the RMP

Study number (name) [NCT number] Data cut-off	Study design	Treatment arms	Patient population
D9268C00001 (TB-01) [NCT05104866] 24 Jul 2024	Phase 3, open-label, randomised, multicentre	• Dato-DXd (6 mg/kg) • Investigator's choice of chemotherapy	Patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable or metastatic setting.

SIII.1 Breast Cancer

The pivotal safety dataset in support of the use of Dato-DXd in patients with advanced/unresectable HR-positive, HER2-negative breast cancer was derived from the Dato-DXd arm of the TB-01 study, in which patients received Dato-DXd 6 mg/kg via IV infusion Q3W until Investigator-defined disease progression (according to RECIST 1.1), or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation was met.

Exposure to Dato-DXd by weeks, age group and sex, and race is presented in Table II-SIII.2, Table II-SIII.3, and Table II-SIII.4, respectively.

Table II-SIII.2: Duration of Exposure to Dato-DXd (TB-01 Study) (N = 360)

Duration of exposure (months)[a]	Number of patients (%)
>0 to ≤3	83 (23.1)
>3 to ≤6	85 (23.6)
>6 to ≤9	70 (19.4)
>9 to ≤12	37 (10.3)
>12 to ≤18	48 (13.3)
>18 to ≤24	28 (7.8)
>24	9 (2.5)
Median duration of exposure (months)	**6.83**
Total patient-years[b]	**249**

[a] Treatment duration (months) = (date of last dose - first dose date + 21) / 30.4375
[b] Patient-years of exposure = sum (duration of exposure [months]) / 12

Table II-SIII.3: Exposure to Dato-DXd by Age Group and Sex (TB-01 Study) (N = 360)

Age Group[a]	Male		Female	
	Number of patients (%)	Patient-years exposure[b]	Number of patients (%)	Patient-years exposure[b]
<65 years	3 (0.8)	2	266 (73.9)	179
65 to 74 years	2 (0.6)	1	70 (19.4)	51
75 to 84 years	0	0	18 (5.0)	15
≥85 years	0	0	1 (0.3)	1

[a] Age in years is calculated using the date of birth and the date of informed consent.
[b] Patient-years of exposure = sum (duration of exposure [months]) / 12

Table II-SIII.4: Exposure to Dato-DXd by Race (TB-01 Study) (N = 360)

Race	Number of patients (%)
Caucasian or White	179 (49.7)
Asian	142 (39.4)
Black or African American	4 (1.1)
Other	3 (0.8)
Missing[a]	32 (8.9)

[a] Missing includes both Missing and Not Reported/Unknown

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 exclusions from the pivotal studies supporting the approved indication (study TB-01; see Table II-SIII.1 for further details).

- ***Age less than the years of maturity (eg, <18 years)***
  - Reason for exclusion: This population was excluded from Dato-DXd clinical studies based on the general principle that paediatric patients are not exposed to investigational products where the benefit-risk profile for the intended adult population has not yet been established.
  - Is it considered to be included as missing information: No
  - Rationale: HR-positive, HER2-negative breast cancer is primarily a disease of adults, with only exceptional occurrence in the paediatric population. Consequently, use in paediatric and adolescent patients is not indicated or anticipated for the target indication, and therefore this population is not relevant for inclusion as missing information.

- ***Eastern Cooperative Oncology Group performance status ≥2***
  - Reason for exclusion: Patients with poor performance status are generally excluded from clinical studies to ensure that included patients are well enough to attend the study site and comply with study procedures, and to ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: There is no scientific rationale to suspect that the safety profile of Dato-DXd in patients with a performance status of ≥2 would differ from that of the general target patient populations. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Known HIV infection that is not well controlled, or active hepatitis B or C infection***
  - Reason for exclusion: Patients with known HIV infection that is not well controlled, or active hepatitis B or C infection, are generally excluded from clinical studies to eliminate comorbidities that may increase the risk of AEs, to ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: There is no scientific rationale to suspect that the safety profile of Dato-DXd in patients with uncontrolled HIV or hepatitis B or C infection would differ

from that of the general target patient populations. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Preexisting severe renal impairment (creatinine clearance <30 mL/min)***
  - Reason for exclusion: Patients with preexisting severe renal impairment are generally excluded from clinical studies in order to eliminate comorbidities that may increase the risk of AEs and ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: Based on mass balance studies of DXd (payload of Dato-DXd) in monkeys, the major excretion pathway of DXd in humans was determined to be through faeces via the biliary route, with minimal renal excretion. In relation to clinical data, renal function had no clinically meaningful impact on exposure in patients with mild and moderate renal impairment based on a population PK analysis, and no evidence of a different safety profile was observed between patients with normal, mild, and moderate renal impairment who received Dato-DXd in pivotal clinical studies. When taken together, no difference in the safety profile of Dato-DXd is expected in patients with renal impairment, and therefore the use of Dato-DXd in these patients is not relevant for inclusion as missing information.

- ***Preexisting severe hepatic impairment (defined as total bilirubin >3.0 × ULN and any AST, regardless of Gilbert's syndrome or liver metastases at baseline)***
  - Reason for exclusion: CYP3A4 is the primary CYP isoform involved in the metabolism of DXd. Consequently, effects on the elimination and exposure of Dato-DXd in patients with impaired hepatic function is possible. This patient population was therefore excluded from pivotal clinical studies in order to eliminate comorbidities that may increase the risk of AEs and ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: Whilst there is a theoretical risk to this patient population based on the elimination pathway of Dato-DXd, population PK analyses did not find hepatic impairment to be a statistically significant covariate on the exposure of Dato-DXd, and mild hepatic impairment did not have a clinically relevant impact on Dato-DXd and DXd PK. This is supported by limited data from patients with moderate and severe hepatic impairment in the TB-01 study, where no difference in safety profile was observed in relation to patients with normal hepatic function at baseline. Furthermore, epidemiological data suggest that the number of patients with severe hepatic impairment in the approved indication is likely to be limited. Consequently, as exposure in this population is anticipated to be very low and available data do not warrant further characterisation, the use of Dato-DXd in patients with severe hepatic impairment is not considered relevant for inclusion as missing information.

- ***History of myocardial infarction, recent troponin levels consistent with myocardial infarction, or recent unstable angina***
  - Reason for exclusion: Patients with a history of myocardial infarction or unstable angina are generally excluded from clinical studies in order to eliminate comorbidities that may increase the risk of AEs and ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: Clinical data do not support an association between Dato-DXd and cardiotoxicity manifesting as ischaemic cardiac events, such as myocardial infarction. This lack of cardiac liability suggests that the safety profile in this population would not be different from that of the indicated population, and therefore the use of Dato-DXd in these patients is not relevant for inclusion as missing information.

- ***Left ventricular ejection fraction <50% or recent symptomatic congestive heart failure***
  - Reason for exclusion: Patients with a notable preexisting reduction in cardiac function are generally excluded from clinical studies in order to eliminate comorbidities that may increase the risk of AEs and ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: In a safety pharmacology study, a single dosing of Dato-DXd did not induce any effects on the cardiovascular system in cynomolgus monkeys at dose levels up to 80 mg/kg. This lack of cardiac liability suggests that the safety profile in this population would not be different from that of the indicated population, and therefore the use of Dato-DXd these patients is not relevant for inclusion as missing information.

- ***Corrected QT interval using Fridericia's formula >470 ms or recent serious cardiac arrhythmia***
  - Reason for exclusion: Patients with notable preexisting cardiac arrythmias are generally excluded from clinical studies in order to eliminate comorbidities that may increase the risk of AEs and ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: In a safety pharmacology study, a single dosing of Dato-DXd did not induce any effects on the cardiovascular system (including electrocardiogram parameters such as QT interval) in cynomolgus monkeys at single doses of up to 80 mg/kg. Moreover, DXd had no effects on the hERG channel current at concentrations up to 10 μmol/L. Further data from an exposure-response analysis of 195 patients with NSCLC also indicated that at the recommended Dato-DXd dose of 6.0 mg/kg, the upper bound of the 90% confidence interval for QTc change from baseline at the geometric mean Cmax for Dato-DXd and DXd ranged from 1.11 to 1.99 ms, well below the 10 ms threshold at which QT prolongation would be

associated with pro-arrhythmic effects (Study DS1062-A-J101). Consequently, there is no evidence that Dato-DXd exerts a clinically meaningful QTc prolongation effect, and no evidence to suggest that the safety profile in this population would be different from that of the general target population.

- ***History of ILD requiring corticosteroid treatment or active or suspected ILD***
  - Reason for exclusion: Lung toxicity, such as inflammation in the alveolus and/or the interstitium, was observed in the intermittent dose toxicity studies in cynomolgus monkeys. Consequently, patients with a history of ILD were excluded from the Dato-DXd clinical development programme to minimise potential risk to patients.
  - Is it considered to be included as missing information: No
  - Rationale: ILD/pneumonitis is considered an important identified risk for Dato-DXd based on an evaluation of data obtained in clinical studies; see Section SVII.3.1.1 for further details.

- ***Clinically significant corneal disease***
  - Reason for exclusion: Single cell necrosis and brown pigmentation in the corneal epithelium were observed in the intermittent dose toxicity studies in cynomolgus monkeys. Consequently, patients with clinically significant corneal disease were excluded from the Dato-DXd clinical development programme to minimise potential risk to patients.
  - Is it considered to be included as missing information: No
  - Rationale: Keratitis is considered an important identified risk for Dato-DXd based on an evaluation of data obtained in clinical studies; see Section SVII.3.1.2 for further details.

- ***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: Toxicity studies in rats and monkeys with Dato-DXd or DXd indicated toxic effects on rapidly dividing cells (ie, lymphatic/haematopoietic organs, intestines, or testes). DXd was genotoxic in an in vitro chromosome aberration study with mammalian cultured cells and an in vivo micronucleus study in rats. Therefore, the characteristics of DXd indicate that Dato-DXd could cause foetal harm when administered to a pregnant woman.
  - Is it considered to be included as missing information: No
  - Rationale: Embryo-foetal toxicity is considered an important potential risk for Dato-DXd based on nonclinical findings; see Section SVII.3.1.3 for further details.

- ***Clinically active brain metastases (symptomatic and untreated or requiring treatment)***
  - Reason for exclusion: Patients with these conditions have significantly worse prognoses and a reduced life expectancy and are therefore generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: 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 Programmes

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

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

A summary of exposure of special populations in the clinical study development programme is provided in Table II-SIV.1.

Table II-SIV.1: Exposure of Special Populations Included or Not in the Clinical Study Development Programme

Type of special population	Exposure TB-01 (6 mg/kg) (N = 360)
Pregnant women or breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment:[a]	
• Moderate hepatic impairment	5 patients
• Severe hepatic impairment	1 patient
Patients with renal impairment:[b]	
• Moderate renal impairment	40 patients
• Severe renal impairment	0 patients
Patients with clinically relevant cardiovascular impairment	Not included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin:	
• Caucasian or White	179 patients
• Asian	142 patients
• Black or African American	4 patients
• Other	3 patients
Subpopulations carrying relevant genetic polymorphisms	No data are available regarding relevant genetic polymorphisms

[a] The definitions for hepatic impairment are as follows: moderate hepatic impairment = total bilirubin >1.5 to ≤3 × ULN and any AST; and severe hepatic impairment = total bilirubin >3 × ULN and any AST.
[b] The definitions for renal impairment are as follows: moderate renal impairment: creatinine clearance = ≥30 to <60 mL/min, and severe renal impairment: creatinine clearance = ≥15 to <30 mL/min.

PART II. MODULE SV - POST-AUTHORISATION EXPERIENCE

Not applicable.

PART II. MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

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

SVI.2 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.

PART II. MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

The reasons for not including a potential or identified risk in the list of safety concerns in the initial RMP (Version 1) are presented below:

- *Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice):*
  - **Infusion-related reaction**: Infusion-related reactions are a common occurrence with intravenously administered compounds, and have been reported in the pivotal TB-01 clinical study as common events which were generally mild or moderate in severity. Specific recommendations regarding premedication, infusion times, and post-infusion observation periods in order to mitigate against the potential for more severe reactions are provided in the SmPC, and this is fully aligned with standard clinical practice. All infusion-related reactions will also continue to be monitored as part of routine pharmacovigilance activities.

- *Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):*
  - **Alopecia, anaemia, dyspnoea, dysgeusia, neutropenia, leukopenia, aspartate aminotransferase increased, alanine aminotransferase increased, madarosis, dry skin, diarrhoea, vomiting, nausea, constipation, dry mouth, fatigue, decreased appetite, rash, pruritus, and skin hyperpigmentation**: These risks are frequently reported with anticancer medications, and in the pivotal TB-01 clinical study were primarily reported as non-serious, of low-grade severity, and/or were self-limiting/manageable without intervention. Given the severity of the indication being treated therefore, these risks were all deemed to have a limited clinical impact on patients.
  - **Renal toxicity**: In the pivotal TB-01 clinical study, the incidence of AEs in the MedDRA SOC of Renal and Urinary Disorders was low and generally balanced between treatment arms, and upon individual case review, no clustering of specific renal AEs was noted. The majority of renal AEs reported for the Dato-DXd treatment arm were non-serious, of low-grade severity, and did not lead to treatment discontinuation. Nevertheless, as renal changes were observed in non-clinical studies with Dato-DXd (for which the underlying mechanism was unknown; see Part II. Module SII for details), renal toxicity is considered a potential risk which is not categorised as important due to the minimal clinical impact in relation to the severity of the disease being treated. All events of renal toxicity will continue to be monitored as part of routine pharmacovigilance activities.

- *Other reasons for considering risks not important:*
  - **Dry eye, conjunctivitis, blurred vision, visual impairment, photophobia, increased lacrimation, blepharitis, and meibomian gland dysfunction**: Corneal toxicity was observed in a nonclinical study of the payload of Dato-DXd and has been reported in drugs of a similar class. Whilst keratitis has been confirmed as an important identified risk for Dato-DXd (see Section SVII.1.2), these more general ocular effects (some of which may also manifest as signs and symptoms of keratitis) were primarily reported in the pivotal TB-01 clinical study as non-serious, of low-grade severity, and did not require dose modifications.
  - **Stomatitis**: Stomatitis has been observed with other TROP2-directed ADCs, and has been reported in the pivotal TB-01 clinical study as a very common ADR. Whist it is acknowledged that stomatitis may influence patient quality of life, the clinical impact of this risk is considered minimal in relation to the severity of the disease being treated, and events of stomatitis in pivotal studies were primarily reported to be non-serious and mild or moderate in severity, and were manageable with dose modifications. Few events resulted in the permanent discontinuation of Dato-DXd treatment. Guidance on dose modifications, appropriate oral care measures, and specific information regarding prophylaxis and treatment to reduce the occurrence of stomatitis (or prevent worsening) is provided in the SmPC, which is aligned with standard clinical practice. All events of stomatitis will also continue to be monitored as part of routine pharmacovigilance activities.
  - **Adverse effects on fertility**: Reproductive tract toxicity in both male and female rats was observed in non-clinical studies with Dato-DXd, and consequently there exists a hypothetical risk of impaired fertility during clinical use. However, effects on fertility following Dato-DXd use is not considered relevant for inclusion in the RMP due to the risk prevention guidance and robust contraception guidelines provided in the Dato-DXd SmPC and PL for both women of childbearing potential and men with female partners of childbearing potential. Consequently, this potential risk is deemed manageable through routine risk minimisation measures, and is not considered to impact the benefit-risk balance of Dato-DXd.

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

The following topics were classified as important risks for Dato-DXd in the initial RMP (Version 1):

Important identified risks

- **Interstitial lung disease/pneumonitis**
  - *Risk benefit impact*: Events of ILD/pneumonitis (as confirmed by an independent AC) were reported more frequently in the Dato-DXd arm of the pivotal TB-01 clinical study in comparison to the control arm. Interstitial lung disease/pneumonitis is a potentially life-threatening event that requires immediate medical evaluation/intervention, as if not recognised or managed appropriately may result in a fatal outcome. Specific clinical

measures (described in the SmPC) are therefore deemed necessary in order to reduce the risk of serious adverse outcomes.

- **Keratitis**
  - *Risk benefit impact*: Events of keratitis were reported more frequently in the Dato-DXd arm of the pivotal TB-01 clinical study in comparison to the control arm. If not recognised or managed appropriately, keratitis may lead to persistent or significant disability (impaired vision or loss of sight), and therefore routine risk minimisation measures (eg, guidance on preventive measures in the SmPC) are deemed necessary in order to minimise severe outcomes.

Important potential risk

- **Embryo-foetal toxicity**
  - *Risk benefit impact*: Based on the composition and mechanism of action of Dato-DXd, data from similar products of the same class, and information on the DXd payload, there is a theoretical concern that Dato-DXd may cause embryo-foetal harm if exposure occurs during pregnancy. No events of pregnancy in a patient or a female partner of a male patient have been reported to date and therefore the teratogenic potential of Dato-DXd has not been established; however, any potential embryo-foetal toxicity is expected to be serious. Specific measures are therefore necessary to ensure that the pregnancy status of females of childbearing potential be verified prior to the initiation of Dato-DXd (to ensure pregnant patients do not receive treatment), and that females of childbearing potential and male patients with female partners of childbearing potential are advised to use effective contraception.

Missing information

There are no areas of missing information for Dato-DXd.

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

Not applicable.

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

SVII.3.1.1 Important Identified Risk: Interstitial Lung Disease/Pneumonitis

Potential mechanisms

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

Evidence source(s) and strength of evidence

Dose-dependent changes in the lung were seen in nonclinical data (see Part II. Module SII), and have been observed with drugs of a similar class.

In the pivotal TB-01 clinical study, events of ILD/pneumonitis (as confirmed by an independent AC), including those with a fatal outcome, were reported more frequently in the Dato-DXd arm in comparison to the control arm.

Characterisation of the risk

This risk is characterised in Table II-SVII.1.

These data were derived from the assessment of all events of potential ILD/pneumonitis reported by investigators by an independent, external ILD AC to ensure a comprehensive and standardised assessment of the relevant events. The ILD AC adjudicated each potential ILD/pneumonitis event with regard to whether it was ILD/pneumonitis and whether it was related to study drug (regardless of the determination made by the investigator), as well as determining onset dates and adjudicating CTCAE grades for events that the AC considered to be ILD/pneumonitis. For patients who experienced a potential ILD/pneumonitis event and died with the outcome of the potential ILD/pneumonitis event marked as not recovered/not resolved, fatal, or unknown, the death event was also adjudicated as to whether it was due to ILD/pneumonitis.

Table II-SVII.1: Important Identified Risk: Interstitial Lung Disease/Pneumonitis

Indication	Treatment group	Number of patients (%)								
		Frequency and severity			Event outcome			Action taken with study treatment		
		Any AE	CTCAE Grade ≥3	Serious	Resolved	Not resolved	Outcome of death	Dose reduction	Dose delay	Discontinuation
Advanced/ unresectable HR-positive, HER2-negative breast cancer *(TB-01 study)*	Dato-DXd 6 mg/kg (N = 360)	14[a] (3.9)	3 (0.8)	4 (1.1)	6 (1.7)	8 (2.2)	1 (0.3)	2 (0.6)	3 (0.8)	6 (1.7)

These data represent all confirmed events of drug-related ILD, as assessed by an independent AC. CTCAE Grade is assigned by the AC after adjudication is complete.

[a] Note: One additional patient in the Dato-DXd arm of Study TB-01 had a drug-related CTCAE Grade 1 ILD event according to the AC, which was subsequently removed from the database by the Investigator.

Risk factors and risk groups

There are no known risk factors for the development of ILD/pneumonitis following Dato-DXd administration; however, patients with a prior personal or family history of ILD/pneumonitis may be at increased risk, in addition to those who are current/former smokers, have underlying health conditions (such as sarcoidosis, autoimmune diseases, and connective tissue disorders), and/or those who have experienced long-term exposure to specific environmental or occupational toxins/pollutants (eg, mould, silica dust, asbestos fibres, grain dust, etc).

Preventability

Whilst ILD/pneumonitis is not completely preventable, actions can be taken to reduce the risk of serious adverse outcomes.

As described in the Dato-DXd SmPC, HCPs should closely monitor patients for the signs and symptoms of potential ILD/pneumonitis (eg, cough, fever, and dyspnoea) and suspected cases should be evaluated by radiographic imaging. Dato-DXd administration should be delayed, and corticosteroid treatment considered for asymptomatic events of ILD/pneumonitis (CTCAE Grade 1). Symptomatic events of ILD/pneumonitis (CTCAE Grade ≥2) should be proactively managed with corticosteroid treatment and patients should permanently discontinue Dato-DXd.

Per detailed guidance in the PL, patients are also educated to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms to ensure prompt diagnosis/management of potential ILD/pneumonitis.

Impact on the benefit-risk balance of the product

Interstitial lung disease/pneumonitis is a potentially life-threatening event that requires immediate medical evaluation/intervention, as if not recognised or managed appropriately, may result in a fatal outcome.

Potential public health impact

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

SVII.3.1.2 Important Identified Risk: Keratitis

Potential mechanisms

The mechanism for corneal toxicity with Dato-DXd remains unclear; however, ocular surface toxicity is one of the most common AE associated with ADCs.

Although the mechanisms for ADC-mediated damage are not fully understood, it has been proposed that such events may be a result of both on- and off-target effects: on-target toxicity may occur via receptor-mediated endocytosis in ocular surface cells that express the target antigen for a specific ADC; off-target toxicity may occur through Fc-receptor-mediated entry, macropinocytosis of the ADC, or bystander toxicity due to premature cleavage of the linker in the bloodstream and liberation of the cytotoxic payload. Passive diffusion of the cytotoxic payload through the permeable cell membrane could also cause off-target toxicity.

Evidence source(s) and strength of evidence

Corneal toxicity was observed in nonclinical data (see Part II. Module SII), and has been observed with drugs in a similar class.

In the pivotal TB-01 clinical study, events of keratitis were reported more frequently in the Dato-DXd arm in comparison to the control arm.

Characterisation of the risk

This risk is characterised in Table II-SVII.2.

Table II-SVII.2: Important Identified Risk: Keratitis

Indication	Treatment group	Number of patients (%)								
		Frequency and severity		Serious	Event outcome			Action taken with study treatment		
		Any AE	CTCAE Grade ≥3		Resolved	Not resolved	Outcome of death	Dose reduction	Dose delay	Discontinuation
Advanced/ unresectable HR-positive, HER2-negative breast cancer *(TB-01 study)*	Dato-DXd 6 mg/kg (N = 360)	72 (20.0)	3 (0.8)	1 (0.3)	34 (9.4)	35 (9.7)	0	5 (1.4)	6 (1.7)	1 (0.3)

Keratitis is a medical concept which includes the following PTs: keratitis, punctate keratitis, and ulcerative keratitis.

Risk factors and risk groups

No risk factors for Dato-DXd-induced keratitis have been identified; however, general risk factors for the development of keratitis include wearing contact lenses, reduced immunity, local corticosteroid use, preexisting ocular surface disorders (eg, dry eye), and eye injury.

Preventability

Actions can be taken to reduce the possibility of events of keratitis progressing to a more severe outcome.

As described in the Dato-DXd SmPC, HCPs should advise patients against the use of contact lenses (unless directed by an eye care professional), and on the regular prophylactic use of preservative-free lubricant eye drops. Patients should also be promptly referred to an eye specialist in the event of any new or worsening ocular symptoms that could suggest keratitis. If a diagnosis is confirmed, Dato-DXd should be delayed, dose reduced, or permanently discontinued (dependent on severity).

Per detailed guidance in the PL, patients are also educated to report any ocular symptoms to their HCP to ensure the prompt diagnosis/management of potential keratitis.

Impact on the risk-benefit balance of the product

Keratitis, if not recognised or managed appropriately, may lead to persistent or significant disability (impaired vision or loss of sight).

Public health impact

There is no potential public health impact beyond that within the treated populations.

SVII.3.1.3 Important Potential Risk: Embryo-foetal Toxicity

Potential mechanisms

Based on the results from general animal toxicity studies, Dato-DXd and its topoisomerase I inhibitor component (DXd) were toxic to rapidly dividing cells (ie, lymphatic/haematopoietic organs, intestines, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

Evidence source(s) and strength of evidence

The findings from nonclinical data, the potential mechanism of the payload of Dato-DXd and the known effects of anti-TROP2 agents on embryo-foetal toxicity suggest that Dato-DXd may potentially cause foetal harm.

Characterisation of the risk

No pregnancy in women of childbearing potential or in female partners of male patients has been reported in clinical studies with Dato-DXd.

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

Risk factors and risk groups

No risk factors or risk groups associated with embryo-foetal toxicity have been identified for Dato-DXd.

Preventability

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

Impact on the benefit-risk balance of the product

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

Potential public health impact

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

SVII.3.2 Presentation of the Missing Information

There are no areas of missing information for Dato-DXd.

PART II. MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

The safety concerns for Dato-DXd are summarised in Table II-SVIII.1.

Table II-SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risk	• Interstitial lung disease / pneumonitis • Keratitis
Important potential risk	• Embryo-foetal toxicity
Missing information	None

Part III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Not applicable – there are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

Not applicable – there are currently no planned additional pharmacovigilance activities for Dato-DXd.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

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

V.1 Routine Risk Minimisation Measures

A summary of routine risk minimisation measures per safety concern is provided in Table V.1.

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

Safety concern	Routine risk minimisation activities
Important Identified Risk	
Interstitial lung disease / pneumonitis	**Routine risk communication:** • SmPC Section 4.8 • PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.2 and 4.4: – Dose modification guidance. – Recommendations for monitoring and detecting early respiratory signs and symptoms. – Guidance as to the use of corticosteroid treatment. • PL Section 2: – How to detect early signs and symptoms **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription-only medicine
Keratitis	**Routine risk communication:** • SmPC Section 4.8 • PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.2 and 4.4: – Dose modification guidance. – Recommendations for the prompt assessment of new or worsening ocular signs and symptoms. – Guidance as to the regular use of prophylactic preservative-free lubricant eye drops and avoidance of contact lens wear. • PL Section 2: – How to detect early signs and symptoms **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription-only medicine

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

Safety concern	Routine risk minimisation activities
Important Potential Risk	
Embryo-foetal toxicity	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 and 4.6: – Recommendations for pregnancy monitoring and contraception usage • PL Section 2: – Recommendations for pregnancy monitoring and contraception usage **Other routine risk minimisation measures beyond the Product Information:** • Legal status: Prescription-only medicine

V.2 Additional Risk Minimization Measures

Not applicable - routine risk minimisation measures (as described in Section V.1) are sufficient to manage the safety concerns of Dato-DXd.

V.3 Summary of Risk Minimization Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table V.2.

Table V.2: 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 Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Keratitis	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Table V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Embryo-foetal toxicity	**Routine risk minimisation measures:** • SmPC Sections 4.4 and 4.6 • PL Section 2 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Datopotamab Deruxtecan (Dato-DXd)

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

Dato-DXd's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Dato-DXd should be used.

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

Important new concerns or changes to the current ones will be included in updates of Dato-DXd's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Dato-DXd is authorised:

- As monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

It contains Dato-DXd as the active substance and is given intravenously.

Further information about the evaluation of Dato-DXd's benefits can be found in Dato-DXd's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Dato-DXd, together with measures to minimise such risks and the proposed studies for learning more about Dato-DXd's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

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

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

List of Important Risks and Missing Information	
Important identified risk	• Interstitial lung disease / pneumonitis • Keratitis
Important potential risk	• Embryo-foetal toxicity
Missing information	None

II.B Summary of Important Risks

Table VI.2: Important Identified Risk: Interstitial lung disease / Pneumonitis

Important Identified Risk: Interstitial lung disease / Pneumonitis	
Evidence for linking the risk to the medicine	Dose-dependent changes in the lung were seen in nonclinical data and have been observed with drugs of a similar class. In the pivotal TB-01 clinical study, events of interstitial lung disease (ILD)/pneumonitis (as confirmed by an independent Adjudication Committee), including those with a fatal outcome, were reported more frequently in the Dato-DXd arm in comparison to the control arm.
Risk factors and risk groups	There are no known risk factors for the development of ILD/pneumonitis following Dato-DXd administration; however, patients with a prior personal or family history of ILD/pneumonitis may be at increased risk, in addition to those who are current/former smokers, have underlying health conditions (such as sarcoidosis, autoimmune diseases, and connective tissue disorders), and/or those who have experienced long-term exposure to specific environmental or occupational toxins/pollutants (eg, mould, silica dust, asbestos fibres, grain dust, etc).

Table VI.2: Important Identified Risk: Interstitial lung disease / Pneumonitis

Important Identified Risk: Interstitial lung disease / Pneumonitis	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None

Table VI.3: Important Identified Risk: Keratitis

Important Identified Risk: Keratitis	
Evidence for linking the risk to the medicine	Corneal toxicity was observed in nonclinical data and has been observed with drugs in a similar class. In the pivotal TB-01 clinical study, events of keratitis were reported more frequently in the Dato-DXd arm in comparison to the control arm.
Risk factors and risk groups	No risk factors for Dato-DXd-induced keratitis have been identified; however, general risk factors for the development of keratitis include wearing contact lenses, reduced immunity, local corticosteroid use, preexisting ocular surface disorders (eg, dry eye), and eye injury.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None

Table VI.4: Important Potential Risk: Embryo-foetal Toxicity

Important Potential Risk: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	The findings from nonclinical data, the potential mechanism of the payload of Dato-DXd and the known effects of anti-trophoblast cell surface antigen 2 (TROP2) agents on embryo-foetal toxicity suggest that Dato-DXd may potentially cause foetal harm.
Risk factors and risk groups	No risk factors or risk groups associated with embryo-foetal toxicity have been identified for Dato-DXd.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.4 and 4.6 • PL Section 2 • Legal status: Prescription-only medicine **Additional risk minimisation measures:** • None

II.C Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Dato-DXd.

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

There are no studies required for Dato-DXd.

PART VII. ANNEXES

Not applicable.