THE EU RISK MANAGEMENT PLAN FOR KADCYLA®/TRASTUZUMAB EMTANSINE

RMP version to be assessed as part of this application:

RMP Version number: 16.0

Data lock point for this RMP: 22 May 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
26-Jun-2024 13:27:25	Deputy QPPV	Tanrikulu, Yusuf (tanrikuy)
27-Jun-2024 13:42:05	Company Signatory (PV)	PPD

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Rationale for submitting an updated RMP:

The last patient last visit (LPLV) for Study BO27938 (KATHERINE), a Phase III, two-arm, randomized, multicenter, multinational, open-label study in patients with HER2-positive primary breast cancer, was 23 May 2024, as significant overall survival results were shown at the second planned interim analysis for OS, in which the stopping boundary was crossed. Patients were already off treatment at the time of the primary analysis in July 2018, and the long-term follow-up data obtained at the time of this second interim analysis led to the study's termination. Therefore, this trastuzumab emtansine European Union Risk Management Plan (EU RMP) has been updated from Version 15.0 to Version 16.0 to remove Study BO27938 (KATHERINE) from the lists of required Post-Authorization Efficacy Studies (PAESs), and additional pharmacovigilance (PV) activities pertaining to missing information on “use in elderly patients” and “clinical impact of anti-drug antibodies (ADAs)” and to important identified risks on “left ventricular dysfunction”. Furthermore, no additional PV activities or additional risk minimization measures are required to further characterize the risks of “use in elderly patients” and “clinical impact of ADAs”, and routine PV activities are deemed sufficient; therefore, the safety concerns are removed from the EU RMP.

Summary of significant changes in this RMP:

- Deletion of Study BO27938 (KATHERINE) from the Additional Pharmacovigilance Activities for “Left ventricular dysfunction”, “Use in elderly patients”, and “Clinical impact of anti-drug antibodies (ADAs)” in Part III.2 (Additional Pharmacovigilance Activities), Part V.3 (Summary of Risk Minimization Measures), and Part VI: IIB (Summary of Important Risks).

- Deletion of Study BO27938 (KATHERINE) from Part III.3 (Summary Table of Additional Pharmacovigilance Activities), Part VI: II.C.1 (Studies which are conditions of the marketing authorization) and Part VI: II.C.2 (Other Studies in Post−Authorization Development Plan) following the completion of the Category 3 additional PV activities.
- Deletion of Study BO27938 (KATHERINE) from Part IV (Plans for post-authorization efficacy studies) as no longer required.
- Removal of the safety concerns “Use in elderly patients” and “Clinical impact of anti-drug antibodies (ADAs)” from Part II. SVII.3.2 (Presentation of the Missing Information), Part V: V.1 and V.3 (Risk minimization measures), Part VI. II.A and II.B (Summary of the risk management plan)
- Deletion of “Use in patients with left ventricular ejection fraction (LVEF) < 50%” in Part III.2 (Additional Pharmacovigilance Activities) as this PV commitment was fulfilled by Study BO39807 (Variation EMEA/H/C/002389/II/0048/G with a positive opinion December 2019) and the information was inadvertently not deleted during the RMP Version 10.0 update.

- In Part II. SVII.2, a rationale for the removal of “Use in elderly patients” and “Clinical impact of anti-drug antibodies (ADAs)” from the list of safety concerns has been added.
- The enhanced PV pregnancy programs have been removed from Annex 4 as this information may constitute Commercially Confidential Information (CCI) and details concerning the program have been updated in Part II Module SVII.3.1. (Presentation of important identified risks and important potential risks) Section 2.1 (Fetal harm).

In addition, the following updates were made:

- Part II Module SI (Epidemiology of the indication(s) and target population(s)) has been updated with the most recent epidemiological data.
- Part II Module SIV.3 (Limitations in respect to populations typically under-represented in clinical trial development program) has been updated to include a section on ‘Use in Pregnancy and Lactation’.
- Part II Module SV.1 (Post-Authorization Exposure) has been updated until the date closest to the data lock point (DLP) of the latest Periodic Benefit Risk Evaluation Report (PBRER; 21 February 2024 [Report 1128810]), which is 28 February 2024. The table for Cumulative Exposure from Marketing Experience has been moved to Annex 7 and a reference to Annex 7 has been added in its place, as post-marketing exposure data (patient exposure and sales volume) by country may constitute as CCI.
- In Part II Module SVII.3.1. (Presentation of important identified risks and important potential risks) the characterization of the safety concerns were updated with the available safety data from the Study BO27938 (KATHERINE).
- In Part II Module SVII.3.1. (Presentation of important identified risks and important potential risks) the preferred term (PT) pulmonary radiation injury was removed from Table 13.
- In Part II Module SVII.3.1. (Presentation of important identified risks and important potential risks) Section 2.1 (Fetal harm) details about pregnancy cases have been removed as there is no cumulative assessment in the periodic benefit-risk evaluation report (PBRER).
- To align with the SmPC the following sections have been updated with the sentence “Male patients or their female partners should also use effective contraception.”: Part II Module SVII.3.1. (Presentation of important identified risks and important potential risks) and Part V.1 (Routine Risk Minimization Measures).
- In Part V: V.1 and V.3 (Risk minimization measures) further details have been added to the safety concern “Use in patients with left ventricular ejection fraction (LVEF) <50%”.
- Outdated statistical and biostatistical outputs have been removed from Annex 7 and in place a reference to Study BO27938 (KATHERINE) Interim CSR, literature references and the “Summary Tabulations of Prospective and Retrospective Individual Case Safety Reports on Pregnancy” have been added.

- Annex 8 has been updated to reflect changes to this RMP.
- Minor editorial/formatting changes have been undertaken in this RMP.

Other RMP versions under evaluation:

There are no other versions under evaluation.

Details of Currently Approved RMP:

Version number: 15.0

Approved with procedure: EMEA/H/C/002389/II/0064

Date of approval (opinion date): 7 July 2022

See page 1 for signature and date

Yusuf Tanrikulu (Deputy QPPV)	Date

See page 1 for signature and date

PPD	Date

PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	Trastuzumab emtansine
Pharmacotherapeutic group(s) (ATC Code)	L01FD03
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Kadcyla®
Marketing authorization procedure	Centrally authorized procedure
Brief description of the product including:	Chemical Class: Antibody-drug conjugate
	Summary of mode of action: Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1: • Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fc γ receptors and complement C1q. In addition, trastuzumab emtansine, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signalling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2. • DM1, the cytotoxic component of trastuzumab emtansine, binds to tubulin. By inhibiting tubulin polymerization, both DM1 and trastuzumab emtansine cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from in vitro cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids. • The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

	Important information about its composition: Kadcyla, trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.
Hyperlink to the Product Information	EU SmPC
Indication(s) in the EEA	**Current:** Metastatic Breast Cancer (MBC) Kadcyla, as a single agent, is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for locally advanced or metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy. Early Breast Cancer (EBC) Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.
	Proposed: Not applicable
Dosage in the EEA	**Current:** The recommended dose of trastuzumab emtansine is 3.6 mg/kg body weight administered as an intravenous infusion every 3 weeks (21-day cycle). Early Breast Cancer (EBC): Patients should receive treatment for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

	Metastatic Breast Cancer (MBC): Patients should receive treatment until disease progression or unmanageable toxicity.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** • 100 mg powder for concentrate for solution for infusion, designed to deliver 5 mL of 20 mg/mL of trastuzumab emtansine after reconstitution. • 160 mg powder for concentrate for solution for infusion designed to deliver 8 mL of 20 mg/mL of trastuzumab emtansine after reconstitution.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No
ADCC = Antibody-dependent cell-mediated cytotoxicity; ECD = Extracellular domain; ECD = extracellular domain; EU = European Union; HER2 = Human Epidermal Growth Factor 2; MCC = 4-[N-maleimidomethyl]cyclohexane-1-carboxylate; SmPC = Summary of Product Characteristics.	

ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activity of daily living
AE	adverse event
AEGT	Adverse Events Group Term
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BC	breast cancer
CCI	Commercially Confidential Information
CHF	congestive heart failure
CI	confidence interval
CSR	clinical study report
DLP	data lock point
EBC	early breast cancer
ECD	extracellular domain
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Fc	fragment crystallizable
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HER2	Human Epidermal Growth Factor 2
HR	hazard ratio
HRT	hormone replacement therapy
IBD	international birth date
ILD	interstitial lung disease
INN	international non-proprietary name
IRRs	infusion-related reactions
LVEF	left ventricular ejection fraction
MAH	Marketing Authorization Holder
MBC	metastatic breast cancer
MCC	4-[N-maleimidomethyl] cyclohexane-1-carboxylate

Abbreviation	Definition
NAbs	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRH	nodular regenerative hyperplasia
OS	overall survival
PAES	Post-Authorization Efficacy Studies
PBRER	periodic benefit-risk evaluation report
pCR	pathological complete response
PSUR	periodic safety update report
PT	preferred term
PV	pharmacovigilance
Q3W	every 3 weeks
QoL	quality of life
QW	once a week
RMP	Risk Management Plan
RoW	rest of the world
SAEs	serious adverse events
SEER	Surveillance, Epidemiology and End Results
SMQ	Standardized MedDRA Query
SmPC	Summary of Product Characteristics
T-DM1	trastuzumab emtansine; Kadcyla
US	United States
ULN	Upper limit of normal

PART II: SAFETY SPECIFICATION

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

SI.1 Metastatic Breast Cancer

Incidence:

The epidemiologic evidence specific to the human epidermal growth receptor 2 (HER2)-positive metastatic breast cancer (MBC) patient population is limited; we therefore present data from the general breast cancer (BC) population to supplement our report.

Breast cancer is among the most commonly diagnosed cancer in the world, with close to 2.3 million new cases comprising 11.6% of all cancer cases (IARC Breast Cancer 2022; Bray et al. 2024). The disease is the fourth leading cause of cancer mortality worldwide with approximately 666,103 deaths in 2022 (IARC Breast Cancer 2022). Breast cancer accounts for approximately one in four cancer cases and one in six cancer deaths in women worldwide, with the highest incidence rates seen in France, Australia, New Zealand (Bray et al. 2024).

In the more developed nations, it is the second most common cause of cancer death. This is a disease affecting 10–12% of women worldwide (Benson et al. 2009).

Europe experienced 557,532 new cases of breast cancer among women in 2022, representing approximately 24.3% of the total new cases in women worldwide (IARC Breast cancer 2022). Women living in transitioned countries have considerably higher incidence rates compared with those in transitioning countries (54.1 vs. 30.8 per 100,000), respectively (Bray et al. 2024). In Netherlands, MBC incidence was reported as 6.8 per 100,000 in 2014 (Vondeling et al. 2018). Table 1 depicts the breast cancer epidemiology in 2022 (IARC Breast Cancer 2022).

Table 1 Epidemiology of breast cancer in 2022

Country	Number: (Incidence in million)	Incidence per 100,000 (World age-standardized rate)	Number Mortality	Mortality per 100,000 (World age-standardized rate)	5-year Prevalence (Number)	5-year Prevalence proportion (per 100,000)
Worldwide	2,296,840	46.8	666,103	12.7	8,178,393	209.0
United States	274,375	95.9	42,900	12.2	1,194,271	706.1
Europe	557,532	75.6	144,439	14.6	2,296,495	594.5

Source: IARC Breast cancer 2022

Since HER2-positive disease accounts for approximately 15–20% of cases of BC (He et al. 2023; Loibl et al. 2017; Mercogliano et al. 2023), it is estimated that approximately

264,000 new cases of HER2-positive BC occur each year globally and approximately 92,620 cases in the European Union (EU).

There is limited data on the secular trends associated with the incidence of HER2-positive BC. Koninki et al. 2009 reported the results from three cohorts (years 1982 to 1986 [n = 310],1989 to 1992 [n = 108], and 2004 to 2005 [n = 713]) to estimate time trends of HER2-positive BC: the age-adjusted incidence of HER2-positive BC increased only slightly from 1982 to 2005 (12.2 per 100,000 to 13.0 per 100,000, respectively), whereas the incidence of HER2-negative BC doubled over the same period (44.1 per 100,000 to 82.3 per 100,000, respectively). Numbers for incidence of HER2-positive BC may vary as other factors like demographic parameters, histology/type of BC and/or HER2 testing quality have an impact on positivity rates (Rüschoff et al. 2017; Wolff et al. 2007).

In the US, among 298,937 cases of invasive breast cancer with known HER2 status diagnosed during 2010 and 2011 from National Cancer Database, 14.5% (43,485 cases) were HER2-positive (Killelea et al. 2017).Population based cancer registry data on women with breast cancer reported a slight decline in incidence for HER2-positive BC during the time period between 2009 and 2016 in Scotland. An incidence of 13.6 for ER-positive/HER2-positive (Luminal B like) BC and 7.1 for ER-negative/HER2-positive (HER2 enriched like) BC was reported in 2016 compared to 17.4 and 9.0 in 2009 respectively (Mesa-Eguiagaray et al. 2020).

Another population-based cohort reported incidence patterns and early survival for premenopausal women with breast cancer by receptor-based subtypes and reported HER2-positive cancers increased in each age decade. The greatest increases in incidence were observed for HER2-positive among women aged 20-49 years during 2010-2016. Also, Hispanic women aged 30-49 years experienced larger increases of HER2-positive/HR-positive cancer compared to the total analytic sample for these respective age decades (Thomas et al. 2020).

The overall incidence of MBC (i.e., including patients initially presenting with early disease who subsequently relapse) is probably best indicated by annual mortality rates (refer to the mortality section below) since most patients who die from BC, die from metastatic disease.

Prevalence:

In 2022, the 5-year limited duration prevalence (i.e., BC cases diagnosed between 2018 and 2022) in the EU-27 was estimated to be 1,564,925 (IARC Breast Cancer 2022). An estimated 44,642 women were living with MBC in Brazil with a prevalence of 41 per 100,000 (Reinert et al. 2020). To our knowledge, there have been no epidemiologic studies reporting on the prevalence of HER2-positive MBC. However, based on the prevalence of BC in general, the 5-year limited duration prevalence of HER2-positive

disease is estimated to be 266,000 (or ~20% of all BC cases) in the EU-27. It was suggested that improvements in treatment and aging of the population could lead to increased prevalence of MBC (Mariotto et al. 2017).

Demographics:

In EU, the risk of BC incidence rates, increase with age with a change around age 50 years (i.e., around menopause). In 26 European countries, the incidence rate in postmenopausal women tends to increase compared to premenopausal women. The 1-year survival rate is around 90% for younger patients, while the highest 5-year survival is observed for the 45- to 54-year-old group. Both 1- and 5-year relative survival rates decrease in women with BC aged 55 years and older, with a steeper decline at older ages (over 75 years) (Dafni et al. 2019).

The median age at initial diagnosis of invasive BC is 62 years in women (Gucalp et al. 2019). HER2-positive BC tends to occur in the mid-50s (around 5 years younger than the general BC population (Karihtala et al. 2021).

The incidence of HER2-positive breast cancer is more common in younger women, ranging from 28% in women under 30 to only 11% in those over 70 (Killelea et al. 2017).

In MBC, HER2+ subtype is more frequent in patients <40 years (26.6%) compared to 40-60 years (21.2%) and >60 years (16.1%) (Frank et al. 2020).

The average age of diagnosis of BC for men is 68 years, which is 5–10 years later than the average age of diagnosis for women. BC in males is considered to account for less than 1% of all cases of breast malignancy (Gucalp et al. 2019); however, prevalence has been reported to be higher (2.5–5.9%) in HER2-positive BC. This discrepancy is possibly due to differences in geography and race (Onami et al. 2010; Barh et al. 2009).

Racial differences in the incidence of different BC sub-types have been described in females. HER2- positivity has been reported greatest in Asian/Pacific Islanders (18.6%) and least in Whites (14.1%) and is more common in Hispanics (17.8%) compared with non-Hispanics (14.4%) (Killelea et al. 2017).

The main existing treatment options:

All patients with HER2-positive MBC should receive HER2-directed systemic therapy in combination with cytotoxic chemotherapy or endocrine therapy (NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 4.2023 and European Society for Medical Oncology [ESMO] Guidelines 2023 Review) (Gradishar et al. 2023; Antonarelli et al. 2023). HER2 targeting is a cornerstone of advanced breast cancer (ABC) treatment, both in the early and in the advanced setting, for HER2-positive disease. The current upfront standard-of-care (SOC), first-line treatment of HER2-positive ABC is represented by taxane-based chemotherapy in combination with dual HER2 blockade with

trastuzumab and pertuzumab.
For most patients progressing to trastuzumab- or pertuzumab-based chemotherapy in the first line, trastuzumab-deruxtecan (T-DXd1) monotherapy should be considered the standard second-line therapy. These include patients relapsing within 6 months from (neo)adjuvant therapy.

While the clinical scenario of the first and second treatment lines is clearly defined, there is currently no consensus on subsequent treatment lines, as currently there are no available clinical data of therapies beyond T-DXd progression. Among various available treatment options, decision making must be supported by patient- and disease-related factors, including overall tolerability, clinical benefit to prior therapies, disease burden, and eventual central nervous system (CNS) involvement. In the third-line setting and beyond, several new emerging anti-HER2 therapies are becoming available, including tucatinib, lapatinib, neratinib, and margetuximab. Tucatinib in combination with capecitabine and trastuzumab is recommended as third-line therapy and preferred for those with CNS metastases.

Risk factors for the disease:

Risk factors for BC include the following (NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 1.2019):

- Gender: Breast cancer is about 100 times more common in women than men. This is because men have less of the female hormones estrogen and progesterone which can promote BC cell growth.
- Age: The incidence of BC increases with age, doubling about every ten years until menopause.
- Age at menarche and menopause: Women that start menstruating early in life or who have late menopause have an increased risk of developing BC.
- Age at first pregnancy: Nulliparity and late age at first birth both increase the lifetime incidence of BC.
- Family history: Having a first-degree relative with BC approximately doubles a women's risk. Having 2 first-degree relatives increases her risk about three-fold.
- Inherited genes that increase cancer risk: Certain gene mutations (BRCA1 and BRCA2) can greatly increase a women's risk of breast and other cancers.
- Previous benign or malignant breast disease: Women with severe atypical epithelial hyperplasia have a 4-5 times higher risk of developing BC than women who do not have proliferative changes in the breast. In addition, if a woman has had cancer in one breast, she is at increased risk of developing BC in the other breast.
- Lifestyle: Obesity is associated with a 2-fold increase in risk of BC in postmenopausal women. Some studies have shown a link between alcohol consumption and incidence of BC, but the relationship is inconsistent.

- Oral contraception: Studies have found that women using oral contraceptives have a slightly greater risk of BC than women who never used them. This risk seems to go back to normal over time once the oral contraceptives are stopped.
- Hormone replacement therapy (HRT): Women who take HRT that combine estrogen and progesterone to treat signs and symptoms of menopause have an increased risk of BC.

Natural history of the indicated condition in the untreated population:

Mortality: Approximately 666,103 deaths due to BC were recorded worldwide in 2022. Of these, 42,900 deaths in the US and 144,439 deaths in Europe due to BC were reported (IARC Breast Cancer 2022). According to SEER database, from 2017 to 2021, the age-adjusted mortality due to BC was reported to be 19.3 per 100,000 women per year (SEER website). According to an analysis of the SEER data (n =1800), stage IV BC is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al. 2001). As per SEER database, across racial and ethnic groups, the BC death rate declined annually during 2016-2020 by 1.0%–1.4% in Hispanic, Black, and White women respectively, by 0.6% in Asian/Pacific Islander women, and was relatively stable in American Indian/Alaska Native women (Giaquinto et al. 2022).

Outcome of the (untreated) target disease: MBC is almost always fatal. Five-year relative survival for newly diagnosed patients with distant metastases is 24% (Howlader et al. 2016). Depending on stage, tumor biology and the treatments utilized, between 20% and 89% of women with EBC develop distant metastases.

Discussion of the possible stages of disease progression to be treated: Most BCs in the Western world (around 94%–95% of patients in the US and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Zielonke et al. 2020; Howlader et al. 2016; Sant et al. 2003) i.e., only around 5–6% of new cases are locally advanced or metastatic at diagnosis.

Important co-morbidities: In UK, the most frequent comorbidities among BC patients across age group 18-80 years were atrial hypertension (24.5%), depression (21.1%), anxiety disorder (15.5%), thyroid gland disorders (10.1%), obesity (8.1%), diabetes mellitus (6.7%), lipid metabolism disorders (6.5%), renal insufficiency (4.2%), ischemic heart diseases (4.1%). Age [Hazard Ratio (HR): 1.03; 95% CI (1.02-1.04)], diabetes mellitus [HR: 1.46 (1.07-1.99)], depression [HR: 1.44; 95% CI (1.17–1.78)], and sleep disorders [HR: 1.37; 95% CI (1.02–1.84)] were significantly associated with death within 5 years of BC follow-up. Higher comorbidity burden is associated with lower survival of BC patients (Bach et al. 2021).

Data from eight US cancer care centers suggest that hypertension is the most common comorbidity among BC patients (34.5%). The next most common conditions among BC patients are: previous solid tumors (12.4%), diabetes (10.4%), respiratory disease

(8.2%), psychiatric disease (5.8%), angina (4.2%), obesity (3.9%), myocardial infarct (3.1%), and stroke (2.8%) (Piccirillo et al. 2008).

SI.2 Early Breast Cancer

Incidence:

The epidemiologic evidence has been limited in the HER2-positive EBC patient population; we therefore present data from the general BC population to supplement our findings. Refer to Section SI.1 for information regarding the incidence of overall BC and HER2-positive disease.

As mentioned in Section SI.1, most BCs in the Western world (around 94% – 95% of patients in the US and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al. 2016; Sant et al. 2003; Zielonke et al. 2020) (i.e., EBC at diagnosis).

The global incidence of early-onset breast cancer was observed as 13.7 per 100,000 in 2019 (Zhao et al. 2023). The age-adjusted incidence rate of EBC among white women in the US aged ≥ 20 years, from 2005 to 2009, was reported to be 163.2 per 100,000 person-years, while among non-white women, it was reported to be 56.6 per 100,000 person-years (Crabbe et al. 2015). The incidence of diagnosis of EBC increases with advanced age (De Glas et al. 2014). In Netherlands, EBC incidence was reported as 62.3 per 100,000 in 2014 (Vondeling et al. 2018).

Prevalence:

The prevalence of HER-2 positive BCs in 12 population-based SEER registries was estimated at 19% (95%CI: 13; 25%) of women aged 49 years or younger and 15% (95%CI: 9; 21%) of women aged 50 years or older with early-stage breast cancer. The overall prevalence estimate for the SEER population was 16% (95%CI: 12; 21%) for stages I, II, and IIIa BC among women diagnosed in the year 2005 (Cronin et al. 2010).

Demographics:

The demographic profile of EBC is similar to that in MBC (refer to Section SI.1 although patients tend to be a few years younger. The incidence of BC increases with age, and is higher in females than males and in Caucasians compared with other racial groups (Howlader et al. 2010; Anderson WF et al. 2010; Crabbe et al. 2015; Iqbal et al. 2015).

The main existing treatment options:

ESMO 2023 guidelines (Loibl et al. 2024) recommends HER2-directed therapy (with initial concurrent chemotherapy) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment in patients with HER2-positive EBC.

Administration can be combined with radiotherapy and endocrine therapy, if indicated. For patients with stage I HER2-positive EBC, primary surgery may be carried out, followed by adjuvant administration of 12 weeks of paclitaxel plus 1 year of trastuzumab.

For patients with clinical stage II-III HER2-positive early breast cancer, neoadjuvant systemic chemotherapy with dual blockade anti-HER2 therapy comprising trastuzumab-pertuzumab (versus trastuzumab alone) is the preferred option. For the chemotherapy backbone, a regimen of anthracycline taxane or taxane-carboplatin is evidence-based independent of neoadjuvant or adjuvant use. In patients with node-positive disease, the addition of pertuzumab to trastuzumab should be strongly considered in the adjuvant setting irrespective of HR status. Patients with high-risk HR-positive tumours, extended treatment with neratinib (concurrent with endocrine therapy) for 1 year after completion of 1 year of trastuzumab-based therapy can be considered.

Patients with residual disease in the breast and/or axilla after HER2-targeted neoadjuvant therapy have a worse prognosis compared to those who achieve pathological complete response (pCR) (Cortazar et al. 2014). For those patients (i.e., HER2-positive disease without pCR after preoperative treatment) who are at increased risk of recurrence, trastuzumab emtansine is recommended as treatment for 14 cycles (NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 1.2021). If trastuzumab emtansine is discontinued for toxicity, then trastuzumab ± pertuzumab is continued to complete one year of therapy. In addition, those patients with hormone receptor–positive disease are recommended to receive hormonal therapy after surgery.

Risk factors for the disease:

Major risk factors for developing BC (of all types) are described in Section SI.1.

Natural history of the indicated condition in the untreated population:

Mortality: Global mortality due to early-onset BC was 3.5 per 100,000 (Zhao et al. 2023). Mortality from BC is typically due to metastatic disease. According to the SEER database, the mortality among patients with EBC due to BC, from 2004 to 2012, was found to be 1.9% (3889/206,625) (Iqbal et al. 2017). Based on SEER data (2010), approximately 57% of deaths from BC occur in those aged > 65 years, and the median age at death from BC is 68 years. Stage IV BC is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al. 2001).

Outcome of the (untreated) target disease: Based on a review of 107 published studies, Ross et al. 2009 reported that the relative risk for adverse clinical outcome of untreated HER2-positive BC is 2.74 (range, 1.39 – 6.93). It is estimated that up to 1 in 4 patients will experience recurrence within 10 – 11 years of diagnosis (Slamon et al. 2015; Cameron et al. 2017; Perez et al. 2014).

Important co-morbidities:

Important co-morbidities for EBC are similar to those for MBC and are described in Section SI.1.

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

SII.1 TOXICITY

SII.1.1 Genotoxicity

The genotoxicity of trastuzumab emtansine was confirmed in an in vivo rat bone marrow micronucleus assay. A single IV dose of 0.05, 0.1, or 0.2 mg/kg DM1 induced a dose-dependent increase in micronucleus frequency, which is an indicator of genotoxicity either via aneugenic and/or clastogenic mechanisms. The mean serum DM1 concentrations that resulted in genotoxicity (aneugenicity and/or clastogenicity) in rats are in the range of circulating unconjugated DM1 measured in humans given 3.6 mg/kg trastuzumab emtansine (the recommended human dose).

Relevance to human usage: Yes

Discussion:

The genotoxic potential of DM1 (and therefore trastuzumab emtansine) is consistent with the mechanism of action of DM1 (i.e. microtubule inhibition), which is expected to be translatable to humans. Patients administered trastuzumab emtansine will be exposed to concentrations of DM1 that resulted in genotoxicity in animals and therefore may lead to genotoxicity in humans.

SII.1.2 Embryo-fetal Toxicity

Reproductive studies, including embryo-fetal developmental and peri- and post-natal, have been conducted in cynomolgus monkeys with trastuzumab (Herceptin® US Prescribing Information, Section 8.1/EU SmPC, Sections 4.6, 5.3 [Herceptin (trastuzumab) Summary of Product Characteristics]), the antibody component of trastuzumab emtansine. No embryo-fetal toxicities were observed in non-clinical studies. Teratogenic effects have been observed with maytansine (nearly chemically identical to DM1), consistent with its mechanism of action (Sieber et al. 1978). Given the mechanism of action of DM1 and the known or expected reproductive/developmental toxicity hazards with trastuzumab and DM1, no reproductive and developmental toxicology studies of trastuzumab emtansine have been conducted.

Relevance to human usage: Yes

Discussion:

Although non-clinical data revealed no embryo-fetal toxicities in the case of trastuzumab, post-marketing cases of oligohydramnios in the second and third trimesters of pregnancy were observed, some associated with fatal pulmonary hypoplasia of the fetus. Given the mechanism of DM1 and the teratogenic effects seen with maytansine, trastuzumab emtansine is expected to have additional risks compared to trastuzumab alone via its targeting of rapidly dividing cells. Additionally, patients administered trastuzumab emtansine will be exposed to concentrations of DM1 that resulted in genotoxicity in animals and therefore may lead to genotoxicity in humans. Per advice from the European Medicines Agency's Committee for Medicinal Products for Human Use dated 16 December 2010, it was agreed that trastuzumab emtansine presents a high risk for embryotoxic, teratogenic, and clastogenic effects in human pregnancy and will have to be handled as a potential reprotoxicant with a malformative potential.

SII.1.3 Decreased Fertility

Dedicated fertility studies have not been conducted with trastuzumab emtansine. However, based on results from general animal toxicity studies and the mechanism of action of DM1, adverse effects on fertility can be expected. In a single-dose, general toxicity study of trastuzumab emtansine in rats, male rats had degeneration of seminiferous tubules with hemorrhage in testes at a non-tolerated and severely toxic dose level (60 mg/kg; about 5 times the clinical exposure based on area under the curve), associated with decreased weights of male reproductive organs. In female rats at the same dose level, hemorrhage and necrosis of the corpus luteum in ovaries was noted. The reversibility of these effects has not been evaluated. In monkeys dosed with trastuzumab emtansine once every three weeks for 12 weeks (four doses), at up to 30 mg/kg (about 7 times the clinical exposure based on AUC), there were decreases in the weights of epididymides, prostate, testes, seminal vesicles and uterus. Although the interpretation of these effects is unclear due to the varied sexual maturity of enrolled animals, it may be consistent with the observations in rats and the mechanism of action of DM1 (and trastuzumab emtansine).

Relevance to human usage: Yes

Discussion:

Although not completely known, the effects of trastuzumab emtansine on reproductive organs in rats and monkeys may be consistent with the mechanism of action of DM1 (i.e. microtubule inhibition), on rapidly dividing cells, which would be expected to be translatable to humans. Exposure to trastuzumab emtansine may impair fertility in humans. Long-term effects of treatment with trastuzumab emtansine on fertility are unknown.

SII.1.4 Pulmonary Toxicity

Pulmonary toxicity was not observed in studies of trastuzumab or trastuzumab emtansine in monkeys. In a single-dose study of trastuzumab emtansine in rats, increased absolute lung and lung-to-brain weight ratio and correlating microscopic findings including alveolar histiocytosis, type II pneumocyte hyperplasia, and/or alveolar neutrophilic infiltration were observed. Given that this finding was not seen in other rat studies with trastuzumab emtansine at equivalent dose levels and was minimal in severity, this finding is of unknown toxicologic significance. However, the histologic features are compatible with clinical pulmonary toxicities observed in patients.

Relevance to human usage: Yes

Discussion:

The histologic findings in rats were of unknown toxicologic significance since they were not observed consistently across rat studies with trastuzumab emtansine at equivalent dose levels and were minimal in severity. Regardless, the histologic findings in rats are compatible with clinical pulmonary toxicities observed in patients given trastuzumab emtansine.

SII.1.5 Hepatic Toxicity

Toxicology studies in rats and monkeys showed that trastuzumab emtansine and DM1 caused reversible dose-dependent hepatotoxicity, indicated by transient elevations of aspartate transaminase, alanine transaminase, alkaline phosphatase, and in some cases gamma glutamyl transpeptidase, and total bilirubin, and microscopic findings in the liver (e.g. vacuolation and/or atrophy and degeneration/necrosis of hepatocytes, Kupffer cells, and sinusoidal endothelium). These effects on the liver are attributed to the pharmacology of DM1, given that hepatotoxicity was not observed in studies of trastuzumab in monkeys, yet was observed in both antigen-binding (cynomolgus monkey) and non-binding (rats) species administered either trastuzumab emtansine or DM1. Maytansine, the parent compound of DM1, is also known to cause liver toxicity based on non-clinical and clinical experience (Issell et al. 1978).

Relevance to human usage: Yes

Discussion:

The trend in transient cyclic elevations in liver enzymes, attributed to the DM1 component of trastuzumab emtansine, has been consistent between non-clinical species and patients.

SII.1.6 Cardiotoxicity

Effects of trastuzumab emtansine on the cardiovascular system were investigated in monkeys in single and repeat-dose (3- and 6-month) toxicity studies, and in a single-dose cardiovascular safety pharmacology study. In the cardiovascular safety pharmacology study, there were no clear treatment-related changes to electrocardiogram parameters, including QT interval. Modest increases in systolic, diastolic, and mean arterial pressures were observed in the high dose group of 30 mg/kg (about 7 times the clinical exposure based on area under the curve); these effects were variable in onset and duration with changes most consistently observed four days post-dose. Hemodynamic effects were not observed in the repeat-dose toxicity studies, nor were tissue changes (e.g., tissue congestion or vascular or glomerular changes) that might reflect sustained hypertensive effects identified at necropsy or in the microscopic examination of tissues from these studies. Also, there was no evidence of cardiomyocyte damage in the ventricle, atrium, or atrial-ventricular valve evaluated histopathologically in single- or repeat-dose monkey studies.

In vitro, DM1 did not inhibit the HERG channel current at concentrations in the range of circulating unconjugated DM1 measured in humans given the recommended dose of trastuzumab emtansine (3.6 mg/kg)

Relevance to human usage: Yes

Discussion:

Cardiomyocyte injury was identified clinically for trastuzumab and is considered to be a risk with trastuzumab emtansine also.

SII.1.7 Neurotoxicity

In monkeys, treatment with trastuzumab emtansine caused dose-dependent axonal degeneration in the sciatic nerve with hypertrophy or hyperplasia of the Schwann cells, and axonal degeneration of the dorsal funiculus in the spinal cord. Ex vivo tissue cross-reactivity experiments also showed HER2-dependent staining in monkey and human glial cells and peripheral nerve spindle cells (presumptive Schwann cells). Given the mechanism of action of the cytotoxic component DM1 as a microtubule inhibitor, as well as the observed HER2-dependent staining in monkey and human cells,

trastuzumab emtansine effects on the nerve may be attributed to both antigen-dependent and antigen-independent mechanisms.

Relevance to human usage: Yes

Discussion:

The irreversible axonal degeneration observed in monkeys has translated to patients as a low incidence of Grades 1 and 2 peripheral neuropathy.

SII.1.8 Thrombocytopenia

Toxicology studies in rats and monkeys showed that trastuzumab emtansine and DM1 caused dose-dependent thrombocytopenia that was partially or completely reversible between 3-week dose cycles. Effects on other myeloid and erythroid populations were mild and transient, and included increases in neutrophils, decreases in lymphocytes, monocytes, reticulocytes, and red blood cells, and lymphoid depletion in the spleen and thymus. In vitro mechanistic studies in hematopoietic stem cells, megakaryocytes, and platelets suggest that trastuzumab emtansine does not have a direct effect on platelet function but likely impairs megakaryocyte and platelet production in bone marrow (Mahapatra et al. 2011). Results from these studies also suggest that the uptake of DM1 conjugated antibodies into megakaryocytes is antigen independent and partially Fc mediated, and the subsequent intracellular release of DM1 appears to result in a reduction of the stem cell population. The impairment of megakaryocyte and platelet production caused by the antigen-independent uptake of trastuzumab emtansine is consistent with the mechanism of action of DM1 (i.e. microtubule inhibition).

Relevance to human usage: Yes

Discussion:

Minimal to mild decreased platelet counts observed in the non-clinical species manifested as the patient dose limiting toxicity in the Phase I clinical trial, as was true in rats and monkeys, have generally been reversible between dose cycles or with cessation of dosing or by dose reduction.

SII.2 GENERAL SAFETY PHARMACOLOGY

SII.2.1 Infusion-Related Reactions (IRRs)

Adverse events of infusion reactions were not observed in preclinical studies.

Relevance to human usage: Yes

Discussion:

Infusion reactions were identified clinically for trastuzumab and are considered to be a risk with trastuzumab emtansine also.

SII.2.2 Hypersensitivity

Adverse events of hypersensitivity reactions were not observed preclinically.

Relevance to human usage: Yes

Discussion:

Hypersensitivity reactions were identified clinically for trastuzumab and are considered to be a risk with trastuzumab emtansine also.

SII.2.3 Medication Error

No relevant data have been identified in non-clinical studies of trastuzumab emtansine.

Relevance to human usage: Yes

Discussion:

Medication error has been noted in the clinical trial program (see Section SVII.3.2 for additional details).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Clinical trial exposure data are presented below for each indication by duration of exposure, age group, dose and racial origin in Sections SIII.3.1 (MBC) and SIII.3.2 (EBC).

The clinical safety data presented are derived primarily from the following trials:

- **MBC:** Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- **EBC:** Data of 740 patients from a single, large pivotal Phase III study BO27938 (KATHERINE).

SIII.3.1 Metastatic Breast Cancer (MBC)

Table 2 Exposure Data from Pooled MBC Clinical Trials

Study	Patients	Study Treatment Arms	Pooled Treatment Arms	Data Cut-Off
TDM4788g/ BO22589	Randomized patients who took at least one dose of study drug	Trastuzumab+Taxane (N=353) T-DM1+Pertuzumab (N=366) T-DM1+Placebo (N=361)	T-DM1 (N=361)	16 Sep 2014
TDM4997g/BO25734	Randomized patients who took at least one dose of T-DM1	T-DM1 3.6 mg/kg (N=403) 87 crossed to T-DM1	T-DM1 (N=403+87)	31 Jan 2014
TDM4370g/BO21977	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=490) 136 crossed to TDM1	T-DM1 (N=490+136)	31 Dec 2014
TDM4374g	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=110)	T-DM1 (N=110)	26 Apr 2011
TDM4258g	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=112)	T-DM1 (N=112)	25 Jun 2009
TDM4688g	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=51) 20 switched to T-DM1+Pertuzumab	T-DM1 (N=51)	30 May 2011
TDM3569g	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=15)	T-DM1 (N=15)	24 Aug 2009
TDM4529g/ BO25430*	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=59) T-DM1+Pertuzumab (N=9)	T-DM1 (N=59)	31 Jan 2014
TDM4450g/BO21976	Patients treated with T-DM1 3.6 mg/kg	T-DM1 (N=69) 37 crossed to T-DM1	T-DM1 (N=69+37)	23 May 2012 (different to SCE)

*Extension of studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976.

Table 3 summarizes the exposure details for patients with HER2-positive advanced breast cancer in the total trastuzumab emtansine-exposed patient group described above. Table 4 provides demographic details for these populations.

Table 3 Clinical Trial Exposure by Dose and Duration: Total Trastuzumab Emtansine-Exposed Population with MBC

Parameter	Total Trastuzumab Emtansine-Exposed (n = 1871)
Number of doses received	
N	1871
Mean (SD)	15.8 (16.2)
Median	10.0
Range	1.0 – 98.0
Average dose received (mg/kg)	
N	1868*
Mean (SD)	3.47 (0.28)
Median	3.54
Range	0.1 – 6.00
Dose intensity[1] (%)	
N	1871
Mean (SD)	95.11 (10.70)
Median	98.76
Range	1.5 – 206.5
Treatment duration (months)	
N	1871
Mean (SD)	10.77 (11.79)
Median	6.31
Range	0.03 – 70.44
Duration on treatment	
<=2 years	1654 (88.4%)
>2 - <= 3 years	114 (6.1%)
>3 years	103 (5.5%)
Dose ever interrupted/stopped?	
n	1871
No	1574 (84.1%)
Yes	297 (15.9%)
T-DM1 dose ever reduced?[2]	
n	1871
No	1546 (82.6%)
Yes	325 (17.4%)
T-DM1 Reduced to 3.0 mg/kg	206 (63.4%)
T-DM1 Reduced to 2.4 mg/kg	119 (36.6%)

Table 3 Clinical Trial Exposure by Dose and Duration: Total Trastuzumab Emtansine-Exposed Population with MBC (cont.)

* Average dose missing for 3 patients

(1) Dose intensity is defined as total dose received divided by the expected total dose.

(2) Dose ever reduced does not include patients from study TDM3569g and TDM4258g since data collection differed from the other studies and this data was not explicitly collected on the CRFs. Percentages of T-DM1 reduced to 3.0mg/kg and 2.4mg/kg are based on overall number of patients who reduced T-DM1. Pooled T-DM1 includes patients from TDM4788g/ BO22589, TDM4997g/ BO25734, TDM4370g/ BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, TDM4450g/BO21976.

Program: /opt/BIOSTAT/prod/cdt3502m/t_ex_03.sas

Output: /opt/BIOSTAT/prod/cdt3502m/reports/t_ex_03_TPL.out

14JUL2015 14:13. Cut-off date 31 Dec 2014.

Table 4 Demographic Details of Patients with MBC: Total Trastuzumab Emtansine-Exposed Population

Parameter	Total Trastuzumab Emtansine-Exposed (n=1871)*
Age (yr)	
N	1871
Mean (SD)	53.0 (10.8)
Median	53.0
Range	24 – 89
Age Group	
N	1871
<65	1590 (85.0%)
>=65 - <75	225 (12.0%)
>=75	56 (3.0%)
Sex	
N	1871
Female	1861 (99.5%)
Male	10 (0.5%)
Race Group	
N	1871
White	1425 (76.2%)
Asian **Black/African American**	281 (15.0%) / 85 (4.5%)
American Indian or Alaska Native	22 (1.2%)
Native Hawaiian or Other Pacific Islander	3 (0.2%)
Other	13 (0.7%)
Not available	42 (2.2%)
Region	
N	1871
United States	637 (34.0%)
Western Europe, Canada and Australia/Pacific	652 (34.8%)
Asia	238 (12.7%)
Other	193 (10.3%)

Table 4 Demographic Details of Patients with MBC: Total Trastuzumab Emtansine-Exposed Population (cont.)

Parameter	Total Trastuzumab Emtansine-Exposed (n=1871)*
Ethnicity	
N	1871
Hispanic or Latino	195 (10.4%)
Not Hispanic or Latino	1525 (81.5%)
Not Available	151 (8.1%)

*Pooled T-DM1 includes patients from TDM4788g/ BO22589, TDM4997g/ BO25734, TDM4370g/ BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, TDM4450g/BO21976 who have received at least one dose of trastuzumab emtansine. Cut-off date 31 Dec 2014.

Patients Exposed to Trastuzumab Emtansine Doses other than 3.6 mg/kg Every 3 Weeks

Among the studies included in the pooled population from which safety data are derived for this risk management plan (RMP), TDM3569g was a dose-ranging single-arm study in which patients received escalating doses at different frequencies for a determination of maximal tolerated dose. Only the patients receiving trastuzumab emtansine 3.6 mg/kg every 3 weeks (Q3W) are included in the total trastuzumab emtansine-exposed and single-arm study populations. The other regimens within this study, and the number of patients exposed, are summarized below in Table 5.

Table 5 Exposure to Trastuzumab Emtansine at Doses other than 3.6 mg/kg in Studies Included in the initial MAA

Study	Dose (mg/kg)	Subjects
TDM3569g Q3W	0.3	3
	0.6	1
	1.2	1
	2.4	1
	3.6	15
	4.8	3
TDM3569g QW	1.2	3
	1.6	3
	2.0	3
	2.4	16
	2.9	3
Total exposure to doses other than 3.6 mg/kg q3wk	N/A	37

N/A=Not applicable; QW=every week; Q3W=every 3 weeks.

SIII.3.2 Early Breast Cancer (EBC)

Table 6 Exposure Data from EBC Clinical Trial

Study	Patients	Study Treatment Arms	Data Cut-Off
BO27938	Randomized patients who took at least one dose of study drug	Trastuzumab (N=720) T-DM1 (N=740)	5 Oct 2023

Table 7 summarizes the exposure details for patients with HER2-positive EBC in the total trastuzumab emtansine-exposed patient group described above. Table 8 provides demographic details for these patients.

Table 7 Clinical Trial Exposure by Dose and Duration: Total Trastuzumab Emtansine-Exposed Population with EBC

Parameter	Total Trastuzumab Emtansine-Exposed (n = 740)
Number of doses received	
N	740
Mean (SD)	11.9 (3.9)
Median	14.0
Range	1—14
Average dose received (mg/kg)	
N	740
Mean (SD)	3.57 (0.24)
Median	3.60
Range	0.8—6.4
Treatment duration (months)	
N	740
Mean (SD)	8.55 (2.80)
Median	9.72
Range	0.7—12.5
Number of cycles of Trastuzumab Emtansine treatment	
N	740
Median	14
Range	1–14
Number of Cycles completed of any study treatment– including switch therapy	
N	740
Median	14
Range	1–14
Number (%) of patients completing at least a total of X cycles of Trastuzumab Emtansine treatment:	
1 cycle	740 (100.0%)
4 cycles	677 (91.5%)
7 cycles	637 (86.1%)
11 cycles	579 (78.2%)
14 cycles	528 (71.4%)

Table 7 Clinical Trial Exposure by Dose and Duration: Total Trastuzumab Emtansine-Exposed Population with EBC (cont.)

Parameter	Total Trastuzumab Emtansine-Exposed (n = 740)
Number (%) of patients completing at least a total of X cycles of all study treatment [a]:	
1 cycle	740 (100.0%)
4 cycles	698 (94.3%)
7 cycles	673 (90.9%)
11 cycles	639 (86.4%)
14 cycles	593 (80.1%)
Infusion ever modified?	
n	740
No	652 (88.1%)
Yes	88 (11.9%)
T-DM1 dose ever reduced?[2]	
n	740
No	634 (85.7%)
Yes	
T-DM1 Reduced to 3.0 mg/kg	77 (10.4%)
T-DM1 Reduced to 2.4 mg/kg	29 (3.9%)

[a] "All treatment" refers to any study treatment including the switch therapy.

Program:root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ex_rmp.sas
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Program:root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/program/t_ex_tdm1.sas
Output:root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_INTERIM/prod/output/t_ex_tdm1_SE.out
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Table 8 Demographic Details of Patients with EBC: Total Trastuzumab Emtansine-Exposed Population

Parameter	Total Trastuzumab Emtansine-Exposed (n=740)
Age (yr)	
N	740
Mean (SD)	48.9 (10.4)
Median	49.0
Range	24 - 79
Age Group	
N	740
<40	143 (19.3%)
40–64	540 (73.0%)
65–74	55 (7.4%)
>=75	2 (0.3%)
Sex	
N	740
Female	738 (99.7%)
Male	2 (0.3%)
Race Group	
N	740
American Indian or Alaska Native	36 (4.9%)
Asian	64 (8.6%)
Black/African American	20 (2.7%)
Native Hawaiian or Other Pacific Islander	0
White	550 (74.3%)
Multiple	1 (0.1%)
Unknown	69 (9.3%)
Region	
N	740
North America	168 (22.7%)
Western Europe	401 (54.2%)
Rest of World	171 (23.1%)

Program:root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_Final_IDFS/prod/program/t_dm.sas

Output: root/clinical_studies/RO5304020/CDPT3519/BO27938/data_analysis/CSR_Final_IDFS/prod/output/t_dm_SE.out

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PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients	Treatment with trastuzumab emtansine has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions. Treatment with trastuzumab emtansine is not recommended in these patients.	No	Hypersensitivity to the active substance or to any of the excipients is a contraindication in the EU SmPC. Hypersensitivity is an identified risk for trastuzumab emtansine. See Section VII.3.1
Pregnancy	Based on the clinical data for trastuzumab and the teratogenic properties of maytansine, it was considered inappropriate for pregnant women to be exposed to trastuzumab emtansine in the absence of data on treatment benefit.	Yes	Not applicable 'Use in pregnant women' is considered a missing information for trastuzumab emtansine. See Section VII.3.2
History of symptomatic CHF or serious cardiac arrhythmia requiring treatment. History of myocardial infarction or unstable angina within 6 months of randomization	Left ventricular dysfunction is an identified risk for trastuzumab emtansine. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with trastuzumab emtansine. Patients with underlying cardiac disease are in general at an increased risk for a cardiac event.	No	Detailed information regarding cardiac dysfunction is included in Section 4.4 Special Warnings and Precautions for use in the EU SmPC.

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Untreated brain metastases[1]	Such patients were initially excluded from MBC clinical trials due to concerns regarding the therapeutic efficacy of trastuzumab emtansine alone on brain metastases.	No	This exclusion criterion was not related to the safety of the patients.
Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy.	Patients with dyspnea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events.	No	Information regarding pulmonary events and pulmonary toxicity is included in Section 4.4, Special Warnings and Precautions for use of the EU SmPC.
Peripheral neuropathy Grade $\geq$ 3 per NCI CTCAE Version 4.0	Peripheral neuropathy is an identified risk for trastuzumab emtansine; irreversible axonal degeneration has been observed in non-clinical toxicology studies.	No	Peripheral neuropathy is an identified risk for trastuzumab emtansine. See Section VII.3.1 Information regarding peripheral neuropathy is included in Section 4.4, Special Warnings and Precautions for use of the EU SmPC.
Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)	The benefit-risk evaluation for treatment may vary in patients with systemic disorders in addition to the underlying malignancy.	No	Information regarding cardiac dysfunction and pulmonary toxicity is included in Section 4.4 Special Warnings and Precautions for use of the EU SmPC.

[1] Untreated brain metastases were an exclusion criterion in MBC clinical trials. Patients with any metastases were excluded in EBC study BO27938 (KATHERINE).

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with serious infection with HIV, hepatitis B virus, or hepatitis C virus[2]	The benefit-risk evaluation for treatment may vary in patients with active viral infection which may impact liver function in addition to the underlying malignancy.	No	Detailed information regarding hepatic toxicity as well as dose modification guidelines are included in sections 4.2 Posology and Method of administration and 4.4 Special Warnings and Precautions for use of the EU SmPC.

CHF = Congestive heart failure; EU = European Union; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; HIV = Human Immunodeficiency Virus; LVEF = Left ventricular ejection fraction; SmPC = Summary of product characteristics

[2] EBC study BO27938 (KATHERINE) excluded patients with any known active liver disease, for example, disease due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis. Patients who had positive HBV or HCV serologies without known active disease were required to meet the eligibility criteria for ALT, AST, TBILI, INR, aPTT, and alkaline phosphatase (ALK) on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period to be able to participate.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program 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.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAM

Information available for use of trastuzumab emtansine in populations typically under-represented in clinical development program is provided in Table 10; additional details for use in pregnancy and lactation are presented below in the Section 'Use in Pregnancy and Lactation.

Table 10 Exposure of Special Populations Included or not in Clinical Trial Development Program

Type of special population	**Exposure**[1]
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant co-morbidities	
Patients with hepatic impairment	Phase I study BO25499[2]: 10 Patients
Patients with renal impairment	Patients with clinically significant renal impairment were excluded from the clinical trial population.
Patients with cardiovascular impairment	Patients with clinically significant cardiac impairment were excluded from clinical trials of trastuzumab emtansine.
Immuno-compromised patients	Not included in the clinical development program
Population with relevant different ethnic origin	Please refer to Table 4 (MBC patients) and Table 8 (EBC patients).
Subpopulations carrying relevant genetic polymorphisms	Study TDM4370g/BO21977 (EMILIA): 894 Patients A/A genotype: 269 G/G genotype: 107
Other	
Children:	Not included in the clinical development program
Elderly:	• ≥65 - <75 years[3]: 225 • ≥75 years[3]: 56

Type of special population	Exposure[1]
Immunogenicity (Anti-Drug Antibodies)	- Positive anti-drug antibodies (ADA) (previously referred to as anti-therapeutic antibodies (ATA) have been detected in 24 of 376 patients (6.4%) across five previous Phase I and II clinical trials (Studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, and TDM4450g/BO21976) - Study TDM4788g/BO22589 (MARIANNE): Post-baseline positive ADA responses were detected in 48 of 638 (7.5%) ADA-evaluable patients treated with trastuzumab emtansine (28 patients in the trastuzumab emtansine + placebo arm and 20 patients in the trastuzumab emtansine + pertuzumab arm). - Study BO28408 (KRISTINE): 16 (7.5%) had positive ADA results in the T-DM1 + pertuzumab arm in the neoadjuvant phase. 25 (13.1%) had positive ADA results in the T-DM1 + pertuzumab arm in the adjuvant phase. - In Study TDM4370g/BO21977 (EMILIA), 24 of 466 patients (5.2%) were ADA-positive. Thirteen of 24 ADA-positive patients were also positive for neutralizing antibodies (NAbs). - In the pivotal EBC Study BO27938 (KATHERINE), at the time of the interim analysis (clinical cut-off date: 5 Oct 2023), 16 of 401 patients (4.0%) were ADA-positive. Five of 16 ADA-positive patients were also positive for NAbs.
Men	10 Patients[3]

[1]Only completed studies are included.

[2] Patients with clinically significant impaired hepatic function were excluded from the clinical trial population, with the exception of BO25499 (patients with HER2-positive metastatic breast cancer and normal or reduced hepatic function).

[3] Pooled data from studies TDM4788g/ BO22589, TDM4997g/ BO25734, TDM4370g/ BO21977 (EMILIA), TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, TDM4450g/BO21976. Cut-off date 31 Dec 2014

ADA=anti-drug antibody; ATA=anti-therapeutic antibody; EBC=Early Breast Cancer; MBC=Metastatic Breast Cancer.

Use in Pregnancy and Lactation

No clinical trials have been performed with trastuzumab emtansine in pregnant women and there are no data from the use of trastuzumab emtansine in pregnant women.

Trastuzumab, a component of trastuzumab emtansine, can cause foetal harm or death when administered to a pregnant woman. In addition, developmental toxicity of maytansine has been identified in non-clinical studies which suggests that DM1, the microtubule-inhibiting cytotoxic maytansinoid drug component of trastuzumab emtansine, is expected to be teratogenic and potentially embryotoxic. Therefore, the

administration of trastuzumab emtansine to pregnant women is not recommended. Section 4.6 of the E.U. Summary of Product Characteristics (SmPC) advises women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception (see information for important potential risk 'fetal harm' in SVII 3.1., Section 2.1). Section 4.6 of the E.U. SmPC also advises breast-feeding mothers to discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine as it is not known whether trastuzumab emtansine is excreted in human milk, and thus a risk for newborns/ infants cannot be excluded.

Interval and cumulative data of the pregnancy outcome (Overall Exposure, Exposure by Parents [mother and farther], Exposure by Source) is present in Annex 7 of the RMP.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 METHOD USED TO CALCULATE EXPOSURE

Market exposure to trastuzumab emtansine was estimated based on internal information on the actual mass of commercial product shipped to each country where trastuzumab emtansine has been launched. The volume sold by Roche is sourced from Roche supply chain and financial systems (COntrolling Profitability Analysis [COPA]). The sales data are provided on a monthly basis; therefore, the exposure is available from the International Birth Date (IBD; 22 February 2013) to the date closest to the DLP of the latest PBRER (21 February 2024 [Report 1128810]), which is 28 February 2024.

The vial volume is converted to patient exposure using the estimations on epidemiology, treatment duration, dosing, and patient compliance from the market research and trial data.

Roche market research with oncologists is used to estimate gender distribution and age of patients on therapy in the US. Exposure data for US is stratified by age and sex. The sex and age split for EEA (European Economic Area) have been assumed to be 1% male/99% female and 60% <65 years. Exposure data stratified by sex and age was not available from Japan and Rest of the World (RoW).

Trastuzumab emtansine (Kadcyla) is currently available to the market in the form of 100 mg and 160 mg vials. It was assumed that all patients received the approved regimen of 333 mg per patient per month.

Exposure data in subgroups may not equal the overall totals due to rounding errors.

SV.1.2 Exposure

Since the IBD (22 February 2013) to 21 February 2024, an estimated cumulative total of 324,192 patients have received Kadcyla (trastuzumab emtansine) from marketing experience (including Japan); see Annex 7 for further details.

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

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The risk of abuse or misuse of trastuzumab emtansine, on the basis of its pharmacological properties, is low.

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

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

“Use in elderly patients” and “clinical impact of ADAs” are no longer considered missing information. Study BO27938 (KATHERINE) was listed as an additional PV activity in the EU RMP to evaluate the use of trastuzumab emtansine in patients with HER2-positive primary breast cancer. Reasons for removal of “use in elderly patients” and “clinical impact of ADAs” from the list of safety concerns, include:

- While subgroup analyses in Study BO27938 (KATHERINE) of safety were limited by the low number of patients aged 65 and over, no notable clinically meaningful differences were observed and there were no major additional safety concerns associated with trastuzumab emtansine in patients aged 65-74. The incidence of Grade 3 or above AEs was similar across both treatment groups. The number of patients ≥ 75 years old was too small (n= 9 in total) to draw any firm conclusions on the safety profile in this group. Of note, no patient was reported to have experienced any SAE in this age group. Therefore, the use of trastuzumab emtansine in elderly patients will continue to be closely monitored by routine PV activities. Furthermore, based on Study MO28231 (KAMILLA), Section 4.2 of the SmPC was updated (approved 17 August 2021) to include additional information for elderly patients experiencing higher incidences of AEs leading to drug discontinuation/interruption (procedure EMEA/H/C/002389/IB/0059/G).
- Given the low number of patients with positive ADA/NAb, a definitive conclusion on the impact on efficacy cannot be made. Therefore, the clinical impact of anti-therapeutic antibodies will continue to be monitored by routine PV activities.
- Following the completion of the Category 3 additional PV activities Study BO27938 (KATHERINE), there are no further additional PV activities pertaining to missing

information on “use in elderly patients” and “clinical impact of ADAs” required to further characterize the risks, and routine PV activities are deemed sufficient. Therefore, in accordance with Good Pharmacovigilance Practices (GVP) Module V(R2), “use in elderly patients” and “clinical impact of ADAs” have been removed as missing information from the EU RMP. “Use in elderly patients” and “clinical impact of ADAs” will continue to be monitored via routine PV.

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

1. INFORMATION ON IMPORTANT IDENTIFIED RISKS

1.1 INTERSTITIAL LUNG DISEASE/ACUTE RESPIRATORY DISTRESS SYNDROME (ILD/ARDS)

MedDRA terms: Kadcyla Specific Adverse Events Group Term (AEGT) - Pulmonary Toxicity/Pneumonitis

Potential mechanisms: The mechanism of trastuzumab emtansine-associated lung injury is not known. Additionally, the role of the DM1 component of trastuzumab emtansine in mediating pulmonary toxicity is unknown.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Table 11 Characterization of Risk of ILD/ARDS

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	24 (1.3%)	20 (2.7%) [a, b]
95% CI for Incidence Rate (Clopper-Pearson)	(0.82, 1.9)	(1.66, 4.14)
Overall number of events	32	20
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	7 (0.4%)	3 (0.4%)
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	9 (0.5%)	5 (0.7%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	10 (0.5%)	11 (1.5%)
No. of Patients with at least one AE resulted in Fatal outcome	2 (0.1%) [c]	0

AE=adverse event; ARDS=acute respiratory distress syndrome; EBC=early breast cancer; ILD=interstitial lung disease; MBC=metastatic breast cancer.

[a] The events reported in majority of EBC patients (17/20) were Grade 1-2 in intensity (refer to Table 13 for further details regarding PTs/seriousness assessment for these events).

[b] Includes 12 events of radiation pneumonitis reported in 12 patients (1.6%) (refer to Table 13 for further details regarding PTs/seriousness assessment for these events). Adjuvant radiotherapy with trastuzumab emtansine was permitted as part of standard of care treatment in EBC Study BO27938 and thus the majority of patients in the study had concurrent radiation with trastuzumab emtansine.

[c] One case reporting fatal outcome was identified as a post-marketing report of a trastuzumab AE of ILD. However, as it occurred within 30 days of the patient's last dose of trastuzumab emtansine in a MBC clinical trial, it is included in the clinical database for trastuzumab emtansine, per protocol.

Source: `t_ae_12_ILD_TPL; t_ae_rmp_RMP1_SE.`

Table 12 ILD/ARDS Events Reported in MBC Clinical Trials

PTs	Number of SAEs	Number of Non-Serious Events
Alveolitis allergic	1	0
Pneumonitis	5	11
ILD	2	3
ARDS	1	0
Pulmonary fibrosis	1	1
Bronchiolitis	0	2

Lung infiltration	0	5
Total	**10**	**22**

ARDS=acute respiratory distress syndrome; ILD=interstitial lung disease; MBC=metastatic breast cancer; PTs=preferred terms; SAEs=serious adverse events.

Source: t_ae_rmp_annex1_sel2_SER_TPL.

Table 13 ILD/ARDS Events Reported in EBC Clinical Trials

PTs	Number of SAEs	Number of Non-Serious Events
Radiation pneumonitis [a]	2	10
Pneumonitis	2	5
Pulmonary fibrosis	1	0
Total	**5**	**15**

ARDS=acute respiratory distress syndrome; EBC=early breast cancer; ILD=interstitial lung disease; PTs=preferred terms; SAEs=serious adverse events.

[a] Adjuvant radiotherapy with trastuzumab emtansine was permitted as part of standard of care treatment in EBC Study BO27938 and thus the majority of patients in the study had concurrent radiation with trastuzumab emtansine.

Source: t_ae_rmp_annex1_sel2_AESER_SE ; l_ae_AESER_SE; l_ae_SE.

Impact on Quality of life:

Some of the most common symptoms of Interstitial lung disease (ILD) may include shortness of breath (especially with exertion), fatigue, weakness or dry cough. If a patient experiences ILD > Grade 1, activities of daily living (ADL) will begin to be limited. It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment.

Risk factors and risk groups:

General risk factors include prior lung disease, pneumonectomy, or abnormal baseline pulmonary physiology. Concomitant or sequential pneumotoxic drugs, or the addition of radiation therapy to the chest may significantly enhance the likelihood of developing adverse pulmonary effects.

Based on the results from the primary analysis of study BO27938 (KATHERINE), there is a small increase in risk of pneumonitis/ radiation pneumonitis associated with concurrent pulmonary radiotherapy and trastuzumab emtansine in EBC patients. However, the majority of pneumonitis/radiation pneumonitis events reported in the study

were Grade 1-2, were manageable and had recovered by the clinical cut-off date of the primary analysis. All three events of Grade 3 severity had also resolved at the clinical cut-off date.

Administration of chemotherapeutic agents to patients who have received radiation therapy in the past may also “recall” a severe skin and/or lung reaction within the previously irradiated area.

Preventability:

Currently there is no known approach to prevention of pulmonary toxicity. Patients with intrinsic lung disease or extensive tumor involvement of the lungs with pre-existing lung injury may be at greater risk for severe pulmonary reactions.

Impact on the benefit-risk balance of the product:

There is no known method to prevent lung toxicity. Patients with lung disease or extensive tumor involvement of the lungs, with pre-existing lung injury may be at greater risk for severe lung reactions. Based on the results from the primary analysis of study BO27938, there is a small increase in the risk of pulmonary toxicity associated with concurrent pulmonary radiotherapy and trastuzumab emtansine in EBC patients; however, the majority of pneumonitis/radiation pneumonitis events in the study were Grade 1-2 and could be managed.

Twenty-four of 1871 patients (1.3%) from MBC clinical trials experienced an event classified as ILD/ARDS, of whom 9/1871 (0.5%) experienced events assessed as serious. Twenty of 740 EBC patients (2.7%) experienced an event classified as ILD/ARDS, of whom 5/740 (0.7%) experienced events assessed as serious.

If a patient experiences ILD > Grade 1, activities of daily living (ADL) will begin to be limited. In patients diagnosed with ILD or pneumonitis, it is recommended that treatment with trastuzumab emtansine be permanently discontinued, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment.

The benefit-risk profile of trastuzumab emtansine remains positive.

Public health impact:

There is no anticipated potential public health impact of this safety concern.

1.2 HEPATIC TOXICITY

MedDRA terms: Cholestasis and jaundice of hepatic origin (Standardized MedDRA Query [SMQ] wide), Liver related investigations, signs and symptoms (SMQ, wide),

Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, wide), Hepatitis, non-infectious (SMQ, wide).

Potential mechanisms: The underlying mechanism by which trastuzumab emtansine affects the liver is unknown. Maytansine, the parent compound of DM1, is known to cause liver toxicity based on non-clinical and clinical data (Issell et al. 1978). Additional information is provided in Module II of this RMP.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Table 14 Characterization of Risk of Hepatic Toxicity

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	568 (30.4%)	277 (37.4%)
95% CI for Incidence Rate (Clopper-Pearson)	(28.28, 32.50)	(33.93, 41.03)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	169 (9.0%)	13 (1.8%)
Grade 3	156 (8.3%)	13 (1.8%)
Grade 4	9 (0.5%)	0
Grade 5	4 (0.2%)	0
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	16 (0.9%)	4 (0.5%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	70 (3.7%)	34 (4.6%)
No. of Patients with at least one AE resulted in Fatal outcome	4 (0.2%)	0

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: `t_ae_12_HTOX_TPL; t_ae_rmp_RMP2_SE.`

Impact on Quality of life:

Hepatic events observed were predominantly reported as laboratory abnormalities, including increases in serum transaminases. Patients are required to undergo frequent monitoring of liver function (prior to receiving each dose) to determine eligibility to continue treatment and to prevent more severe events.

Trastuzumab emtansine doses should be interrupted and modified for MBC patients with transaminase elevations between 5X and up to 20X the upper limit of normal (ULN), and discontinued in patients with transaminase elevations more than 20X the ULN.

For EBC patients, trastuzumab emtansine doses should be interrupted and modified for patients with transaminase elevations between 3X and up to 20X the ULN, and discontinued in patients with transaminase elevations more than 20X the ULN.

Risk factors and risk groups:

Risk factors (in the general population) include age and genetic factors affecting hepatic metabolism of drugs (Bleibel et al. 2007). There are currently no reliable predictors of patients who may or may not be susceptible to hepatotoxicity to trastuzumab emtansine.

Preventability:

Currently there is no known approach of preventing hepatotoxicity. However, the hepatotoxic effects of trastuzumab emtansine may be managed by dose reduction/delay. The MAH includes SmPC recommendations on dose reductions or discontinuation in both MBC and EBC patients for increased transaminases and total bilirubin. The SmPC also advises liver function monitoring prior to initiation of treatment and each dose of trastuzumab emtansine.

Impact on the benefit-risk balance of the product:

The MAH includes SmPC recommendations on dose reductions or discontinuation for increased transaminases and total bilirubin. The SmPC also advises liver function monitoring prior to initiation of treatment and each dose of trastuzumab emtansine.

Hepatic events observed were predominantly reported as laboratory abnormalities, including increases in serum transaminases. About 30.4% of patients from MBC clinical trials experienced some degree of liver toxicity, and 0.2% experienced fatal event. Approximately 37.4% EBC patients experienced an event classified as hepatic toxicity; however, there were no events with a fatal outcome. Although there is no known approach of preventing hepatotoxicity, effects may be managed by dose reduction/delay and discontinued if transaminases are too high.

The benefit-risk profile of trastuzumab emtansine remains positive.

Public health impact:

No potential public health impact of this safety concern.

1.3 NODULAR REGENERATIVE HYPERPLASIA

MedDRA terms: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, wide). Retrieved cases from safety database using the above criteria were reviewed at the case level to identify Nodular regenerative hyperplasia (NRH) diagnoses.

Potential mechanisms: The underlying mechanism by which trastuzumab emtansine affects the liver is unknown.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

- ***Frequency with 95 % CI observed in trastuzumab emtansine clinical program:***

– MBC: 0.37% (no CI available) (7/1871 patients)

– EBC: 0.3% (no CI available) (2/740 patients)

- ***Seriousness/outcomes:***

– **MBC:** Within the pooled MBC studies (N=1871), 50 cases were retrieved per the search criteria, of which 7 cases were confirmed to be NRH. Of the 7 confirmed NRH cases, 2 cases were from TDM4370g/BO21977 (EMILIA), 3 cases from TDM4997g/BO25734 (TH3RESA) and 2 cases from Extension study TDM4529g/BO25430. Of these, one case from Extension study TDM4374g was reported as hepatic cirrhosis with a fatal outcome and was diagnosed as NRH on autopsy.

– **EBC:** Within study BO27938 (KATHERINE) (N=740), 15 cases were retrieved per the search criteria, of which 2 cases were confirmed cases to be NRH. Both events were assessed as Grade 3, serious and related to trastuzumab emtansine by the investigator. The outcome of one event was reported as unresolved and one was resolved as of the clinical cut-off date of the interim analysis.

In addition to the pooled MBC studies and EBC Study BO27938 (KATHERINE), 7 cases of NRH (5 confirmed; 2 unconfirmed based on independent external review) have been identified from other trastuzumab emtansine clinical studies:

– Two cases from MBC study MO28231 (KAMILLA) which reported NRH.

– One case from Chugai-sponsored MBC study TDM4959g/JO22997 reported NRH that could not be confirmed based on independent external review.

– One case from EBC Study BO28408 (KRISTINE; evaluating trastuzumab emtansine plus pertuzumab) which reported NRH.

– Three cases from EBC Study BO28407 (KAITLIN; evaluating trastuzumab emtansine plus pertuzumab), of which one case could not be confirmed based on independent external review.

Of note: Three cases of NRH that were presented in previous EU RMP version 8.1 in this list of 'NRH cases from other trastuzumab emtansine clinical trials' are no longer included for the following reasons:

– Two previously reported cases from MBC study TDM4370g/BO21977- one of which reported blood bilirubin increased and GGT increased and the second of which reported metrorrhagia and catheter site infection - were identified to be in fact one case and is already included in the MBC cases above as part of TDM4370g/BO21977 (EMILIA).

– One case from MBC study TDM4374g of hepatic cirrhosis and NRH diagnosed on autopsy is already included in the MBC cases above as part of Extension study TDM4529g/BO25430.

Impact on Quality of life:

NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver, but with normal transaminases and no manifestations of cirrhosis. Signs and symptoms of portal hypertension may include ascites, hepatic encephalopathy, oesophageal or gastric varices. All of these would require the patient to seek medical attention. Diagnosis of NRH requires histological confirmation. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

Risk factors and risk groups (general population):

The risk of development of NRH and its potential complications increases with age. Sex and ethnicity do not seem to play a role in the development of NRH (Hartleb et al. 2011).

NRH may develop as a result of underlying autoimmune, inflammatory, neoplastic, or idiopathic disease (Hartleb et al. 2011). In an ante-mortem case series, 74% of patients had a coexistent malignant, prothrombotic or rheumatological disease (Morris et al. 2010).

It is hypothesized that immunosuppressive medications may induce NRH by damaging endothelial cells of small hepatic veins (Hartleb et al. 2011).

There are currently no reliable predictors of patients receiving trastuzumab emtansine who may or may not be susceptible to NRH.

Preventability:

Currently there is no known approach of preventing NRH. Proposed labeling for trastuzumab emtansine advises NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography (CT) scan of the liver, but with normal transaminases and no manifestations of cirrhosis. Additionally, labeling notes that upon diagnosis of NRH, trastuzumab emtansine must be permanently discontinued.

Impact on the benefit-risk balance of the product:

NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Kadcyla® SmPC states that diagnosis of NRH can be confirmed only by histopathology and upon diagnosis, trastuzumab emtansine must be permanently discontinued.

There were 7 confirmed cases of NRH from pooled MBC clinical trials (N=1871), including 1 case reporting a fatal outcome and 2 confirmed cases from the EBC Study

BO27938 (KATHERINE) (N=740). Additional 7 cases of NRH (5 confirmed; 2 unconfirmed based on independent external review) have been identified from other trastuzumab emtansine clinical studies.

This is considered as a rare event and benefit-risk profile of trastuzumab emtansine remains positive.

Public health impact:

No potential public health impact of this safety concern.

1.4 INFUSION-RELATED REACTION

MedDRA terms: IRR/Hypersensitivity (Type 1) AEGT Terms. All terms on Day 1 only, except for Infusion-related reaction and Cytokine release syndrome (without time restriction); Allergic oedema, Anaphylactic reaction, Anaphylactoid reaction, Anaphylactoid shock, Anaphylactic transfusion reaction, Angioedema, Bronchospasm, chills, Circulatory collapse, Circumoral oedema, Conjunctival oedema, Corneal oedema, Drug Hypersensitivity, Dyspnoea, Epiglottic oedema, Eye oedema, eye swelling, eyelid oedema, face oedema, face swelling, First use syndrome, flushing, Gingival oedema, Gleich's syndrome, Hereditary angioedema, Hypersensitivity, hypotension, Idiopathic angioedema, Idiopathic urticarial, Intestinal angioedema, Kounis syndrome, Laryngeal oedema, Laryngotracheal oedema, Limbal swelling, Lip oedema, lip swelling, mouth swelling, Oculorespiratory syndrome, Oedema mouth, Oropharyngeal swelling, Palatal oedema, Palatal swelling, Periorbital oedema, Pharyngeal oedema, Pyrexia, Scleral oedema, Shock, Swelling face, Swollen tongue, Tachycardia, Tongue oedema, Tracheal oedema, Type I hypersensitivity, Urticaria, Urticaria cholinergic, Urticaria chronic, Urticaria popular, Wheezing.

Potential mechanisms: The potential mechanisms of infusion-related reactions to monoclonal antibodies have not yet been established, however, Calogiuri et al (Calogiuri et al. 2008) hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions (immediate and delayed hypersensitivity); Gamma-type reactions (over-reactions or depression of the immune functions like the immunodeficit, autoimmune or allergic phenomena); but that other mechanisms such as release of cytokines, might be also involved. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap (Lenz et al. 2007).

Evidence source(s) and strength of evidence:

– MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.

– EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Two analyses were performed in this category: the overall "IRR/Hypersensitivity (Type1)" category (Table 15) and the subgroup "IRR/Hypersensitivity Symptoms" category (Table 16), which includes a narrower group of preferred terms (tachycardia, pyrexia, chills, dyspnea, wheezing, flushing, hypotension and bronchospasm), all also included in the "IRR/Hypersensitivity (Type 1)" category. Both categories include events that occurred only on Day 1 of infusion.

Table 15 Characterization of Risk of Infusion-Related Reactions: Type 1 AEGT terms

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	412 (22%)	57 (7.7%)
95% CI for Incidence Rate (Clopper-Pearson)	(20.16, 23.97)	(5.89, 9.86)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	9 (0.5%)	1 (0.1%)
Grade 3	8 (0.4%)	1 (0.1%)
Grade 4	1 (0.1%)	0
Grade 5	0	0
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	16 (0.9%)	2 (0.3%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	3 (0.2%)	2 (0.3%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0

AE=adverse event; AEGT=Adverse Event Group Term; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: `t_ae_12_IRR_TPL; t_ae_rmp_RMP4_SE.`

Table 16 Characterization of Risk of Infusion-Related Reaction Symptoms: Tachycardia, Pyrexia, Chills, Dyspnea, Wheezing, Flushing, Hypotension, and Bronchospasm (on the Day of Infusion)

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	320 (17.1%)	42 (5.7%)
95% CI for Incidence Rate (Clopper-Pearson)	(15.42, 18.89)	(4.12, 7.59)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	2 (0.1%)	0
Grade 3	2 (0.1%)	0
Grade 4	0	0
Grade 5	0	0
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	3 (0.2%)	1 (0.1%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	0	1 (0.1%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0
No. of Patients with at least one AE Recovered/Resolved	284 (15.2%)	42 (5.7%)

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: t_ae_12_IRRHS_TPL; t_ae_rmp_RMP5_SE.

Impact on Quality of life:

As with any monoclonal antibody, infusion-related reactions may occur in patients receiving trastuzumab emtansine. Therefore, trastuzumab emtansine should only be prescribed by a physician and administered as an intravenous infusion under the supervision of a healthcare professional who is experienced in the treatment of cancer patients (prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available). Patients should be closely observed during the infusions, especially the first infusion, and for at least 30 minutes after infusion. The initial dose of trastuzumab emtansine should be administered as a 90-minute IV infusion.

In the clinical program to date, IRRs have usually been mild to moderate in intensity and have been managed with symptomatic treatment.

Risk factors and risk groups (general population):

There are currently no reliable predictors of patients who may or may not be susceptible to infusion-related reactions to trastuzumab emtansine. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions on the day of or the day after a trastuzumab emtansine infusion. Additionally, patients with a history of infusion reaction to trastuzumab may be at greater risk of a severe reaction due to the trastuzumab component of trastuzumab emtansine. However, patients with severe infusion-related reactions to trastuzumab were excluded from the trastuzumab emtansine clinical studies and therefore data regarding this risk are not available.

Preventability:

Similarly, as with all other antibodies, infusion-related reactions to trastuzumab emtansine cannot be reliably predicted or prevented; however, patients who have had severe IRRs to prior treatment with trastuzumab have a greater risk and are not recommended to receive treatment with trastuzumab emtansine.

Impact on the benefit-risk balance of the product:

Infusion-related reactions, characterized by one or more of the following symptoms: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were mild or moderate. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated.

Additionally, healthcare providers are advised that patients should be observed for hypersensitivity reactions, especially during the first infusion, and that medications and equipment to treat such reactions should be available for immediate use.

Benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

No public health impact is anticipated in view of the population treated and the limitations placed upon administration of trastuzumab emtansine by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-health care professionals is not anticipated.

1.5 HYPERSENSITIVITY

MedDRA terms: Anaphylactic reaction (SMQ narrow), Angioedema (SMQ narrow), Hypersensitivity (PT), and Drug Hypersensitivity (PT)

Potential mechanisms: Hypersensitivity reactions / anaphylaxis are known to generally occur after administration of monoclonal antibodies. Data on the potential mechanisms of hypersensitivity reactions overlap with those of infusion-related reactions.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Table 17 Characterization of Risk of Hypersensitivity

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	110 (5.9%)	29 (3.9%)
95% CI for Incidence Rate (Clopper-Pearson)	(4.86, 7.04)	(2.64, 5.58)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	2 (0.1%)	4 (0.5%)
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	5 (0.3%)	4 (0.5%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	1 (0.1%)	1 (0.1%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0
No. of Patients with at least one AE Recovered/ Resolved	93 (5.0%)	29 (3.9%)

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: `t_ae_12_HS2_TPL; t_ae_rmp_RMP6_SE.`

Impact on Quality of life:

As with any medicinal product, hypersensitivity may occur in patients receiving trastuzumab emtansine. Therefore, trastuzumab emtansine should only be prescribed by a physician and administered as an intravenous infusion under the supervision of a healthcare professional who is experienced in the treatment of cancer patients (prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available). Patients should be closely observed during the infusions, and for at least 30 minutes after infusion. The symptoms may vary

greatly depending on the patient. In the case of a known hypersensitivity, trastuzumab emtansine should be permanently discontinued in which case no further impact on the patient's quality of life (QoL) would occur after resolution of the hypersensitivity reaction.

Risk factors and risk groups:

General factors that increase the likelihood of experiencing type I hypersensitivity reactions include repeated exposure to agent, a history of drug hypersensitivity, and use of the IV route (Kang et al. 2007). Epidemiological data on the risk factors associated with hypersensitivity to trastuzumab emtansine are discussed under infusion-related reactions.

Preventability:

Prevention of anaphylactic/ hypersensitivity reactions to monoclonal antibodies is not possible: these reactions are unpredictable and can occur at any time despite preventive measures. However, patients who have had severe hypersensitivity to prior treatment with trastuzumab have a greater risk and are not recommended to receive treatment with trastuzumab emtansine.

Impact on the benefit-risk balance of the product:

Patients should be observed closely for hypersensitivity reactions, especially during the first infusion. Hypersensitivity, including serious anaphylactic-like reactions, has been observed in clinical trials with treatment of trastuzumab emtansine. Symptoms may include flushing, chills, fever, dyspnoea, hypotension, tachycardia, wheezing, bronchospasm and vary greatly depending on the patient. In the case of a known hypersensitivity, trastuzumab emtansine should be permanently discontinued in which case no further impact on the patient's QoL would occur after resolution of the hypersensitivity reaction.

Benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

No public health impact is anticipated in view of the population treated and the limitations placed upon administration of trastuzumab emtansine by virtue of warnings and precautions included in labeling, and its formulation. Use outside of controlled environments by non-Health Care professionals is not anticipated.

1.6 LEFT VENTRICULAR DYSFUNCTION

MedDRA terms: Kadcyla Specific AEGT - Cardiac dysfunction

Potential mechanisms: Trastuzumab blocks ErbB-2, a receptor tyrosine kinase and co-receptor for other members of the ErbB and epidermal growth factor families, which is

over-expressed on the surface of many malignant cells (Pugatsch et al. 2006). Additionally, ErbB2 is thought to participate in an important pathway for growth, repair, and survival of adult cardiomyocytes as part of a signaling network (Schneider et al. 2002). However, the molecular mechanisms of cardiotoxicity associated with trastuzumab are not fully understood.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Table 18 Characterization of risk of left ventricular dysfunction

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	53 (2.8%)	25 (3.4%)
95% CI for Incidence Rate (Clopper-Pearson)	(2.13, 3.69)	(2.20, 4.95)
Overall number of events		
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	8 (0.4%)	5 (0.7%)
Grade 3	8 (0.4%)	5 (0.7%)
Grade 4	0	0
Grade 5	0	0
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	2 (0.1%)	2 (0.3%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	7 (0.4%)	11 (1.5%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: t_ae_12_CARD_TPL; t_ae_rmp_RMP7_SE.

Impact on Quality of life:

The majority of cardiac events were asymptomatic. LVEF < 40% has been observed and therefore symptomatic congestive heart failure (CHF) is a potential risk. Symptoms may include shortness of breath at rest, chest pain, peripheral oedema, or tachycardia.

For MBC patients: Trastuzumab emtansine should be discontinued in patients with symptomatic CHF and temporarily withheld in patients whose LVEF is between 40%–45% and decreased ≥10% points from baseline, until clarification of LVEF change is obtained. Trastuzumab emtansine should be permanently discontinued in MBC patients whose LVEF has been confirmed to have decreased below 40% and in patients with confirmed LVEF between 40–45% that has not recovered more than 10% points from baseline.

For EBC patients: Trastuzumab emtansine should be discontinued in patients with symptomatic CHF and temporarily withheld in patients whose LVEF is between 45–50% and decreased ≥10% points from baseline, until clarification of LVEF change is obtained. Trastuzumab emtansine should be permanently discontinued in EBC patients whose LVEF has been confirmed to have decreased below 45% and in patients with confirmed LVEF between 45–50% that has not recovered more than 10% points from baseline.

Patients will have to undergo monitoring of cardiac function in order to prevent a symptomatic cardiac event. ECHO/MUGA is recommended at regular intervals such as every three months during treatment.

Risk factors and risk groups:

Previous anthracycline therapy, prior or concurrent exposure to taxanes, patients over the age of 50 years, prior or concurrent anti-hypertensive medication use and low LVEF levels prior to or following the use of paclitaxel.

Preventability:

In contrast to anthracycline-induced cardiac toxicity, trastuzumab-related cardiac dysfunction does not appear to increase with cumulative dose or to be associated with ultrastructural changes in the myocardium and is generally reversible. Risk factors that might predict for cardiac dysfunction with ErbB2- targeted therapy are actively under investigation and will aid in the identification of at-risk populations and in the development of strategies for risk minimization in the future (Perez et al. 2008).

Due to the low incidence of cardiac events, it is not possible to identify with certainty a population of patients who will develop CHF during or following trastuzumab emtansine therapy.

Previous anthracycline use is also a useful indicator of patients at risk. However, evidence from clinical trials suggests that severe cardiotoxicity is rare. In the SmPC, the MAH recommends frequent cardiac monitoring of left ventricular function.

Impact on the benefit-risk balance of the product:

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF $\leq$ 40% has been observed in patients treated with trastuzumab emtansine and therefore symptomatic CHF is a potential risk. Standard cardiac function testing (ECHO or MUGA scanning) should be performed prior to initiation and at regular intervals (e.g., every 3 months) during treatment with trastuzumab emtansine. Treatment with trastuzumab emtansine has not been studied in interventional clinical trials in patients with LVEF $<$ 50% prior to initiation of treatment.

In severe cases, this can cause shortness of breath even at rest, chest pain, swollen ankles or arms, and a sensation of rapid or irregular heartbeats. HER2-directed drugs are known to be associated with left ventricular dysfunction. Other risk factors include prior chemotherapy with taxanes or anthracyclines, being more than 50 years of age, hypertension requiring treatment, and low heart function. Up to 1 in 10 patients receiving trastuzumab emtansine may experience some degree of heart dysfunction.

No patients died as a result of an event of cardiac toxicity. Benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

There is no anticipated potential public health impact of this safety concern.

1.7 THROMBOCYTOPENIA

MedDRA terms: Haematopoietic thrombocytopenia (SMQ, Narrow)

Potential mechanisms: Potential mechanisms for thrombocytopenia observed in patients are not known. However, in vitro mechanistic studies in hematopoietic stem cells, megakaryocytes, and platelets suggest that trastuzumab emtansine does not have a direct effect on platelet function but likely impairs megakaryocyte and platelet production in bone marrow.

The uptake of DM1 conjugated antibodies into megakaryocytes is antigen independent and partially Fc mediated, and the subsequent intracellular release of DM1 appears to result in a reduction of the stem cell population. These in vitro mechanistic studies support the hypothesis that the thrombocytopenia observed in patients may be a consequence of impaired platelet production from megakaryocytes in the bone marrow.

To further assess whether FcγIIa and β1-tubulin receptors may play a role in the ability of megakaryocytes/platelets to bind and internalize trastuzumab emtansine and explain ethnicity differences, the polymorphism status (SNP data) was specifically studied in patients. However, data are limited for definitive conclusions and differential mechanisms across ethnicity remain unknown.

Evidence source(s) and strength of evidence:

- MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Table 19 Characterization of Risk of Thrombocytopenia

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	466 (24.9%)	212 (28.6%)
95% CI for Incidence Rate (Clopper-Pearson)	(22.96, 26.93)	(25.41, 32.05)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	163 (8.7%)	42 (5.7%)
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	12 (0.6%)	10 (1.4%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	49 (2.6%)	31 (4.2%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0
No. of Patients with at least one AE Recovered/Resolved	315 (16.8%)	196 (26.5%)

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: t_ae_12_THR_TPL; t_ae_rmp_RMP8_SE.

Impact on Quality of life:

Patients will require monitoring of platelets prior to each dose of trastuzumab emtansine. Symptoms of thrombocytopenia commonly include epistaxis or gingival bleeding, however, these events did not require treatment when encountered in the clinical trial population. As severe events are uncommon, the impact on quality of life is limited in the majority of patients. Treatment with trastuzumab emtansine should be withheld from patients with Grade 3 or Grade 4 thrombocytopenia, and not reinstated until the platelet count improves to 75,000/mm^3 or higher (Grade 1 or better).

Risk factors and risk groups:

Radiation therapy and certain chemotherapy medications can damage the bone marrow, lowering its production of platelets, and lead to thrombocytopenia. Patients receiving a combination of radiation therapy and chemotherapy are at greater risk for thrombocytopenia.

It was noted in study TDM4370g/BO21977 (EMILIA) that Asian patients had a lower baseline platelet count than non-Asian patients and Asian patients had a higher incidence of Grade 3 or Grade 4 thrombocytopenia, as well as a slightly higher incidence of hemorrhagic adverse events (AEs). However, the frequency of severe hemorrhage

was similar among Asian and non-Asian patients. A higher incidence of Grade ≥3 AEs of platelet count decreased was also reported among Asian patients compared with white patients in EBC Study BO27938 (KATHERINE). The significance of these data is not known.

Preventability:

Currently there is no known approach of preventing thrombocytopenia. However, the platelet effects of trastuzumab emtansine may be managed by dose reduction/delay.

Impact on the benefit-risk balance of the product:

Thrombocytopenia or decreased platelet counts were reported in 24.9% of MBC patients and 28.6% EBC patients in clinical studies with trastuzumab emtansine. In both indications, it was the most common adverse reaction leading to treatment discontinuation (2.6% in MBC population; 4.2% in EBC population).

The majority of the patients had Grade 1 or 2 events (≥ 50,000/mm^3), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (≥ 75,000/mm^3) by the next scheduled dose. In clinical studies, the incidence and severity of thrombocytopenia were higher in Asian patients. Risk factors include radiation therapy and some forms of chemotherapy.

Benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

No potential public health impact of this safety concern.

1.8 PERIPHERAL NEUROPATHY

MedDRA terms: Peripheral Neuropathy (SMQ, wide)

Potential mechanisms: Microtubules play a key role in both the structure and the function of neurons; therefore, microtubule inhibitor therapy is generally associated with some form of neuropathy (Swain et al. 2003). Although the precise mechanisms of neurotoxicity associated with microtubule inhibitors including maytansine derivatives have not been fully defined, preclinical physiologic and histopathologic studies indicate that the pathogenesis of microtubule inhibitor-associated neuropathy is principally a consequence of the interruption of axonal transport within neurons (Meller et al. 1992).

Evidence source(s) and strength of evidence:

– MBC: Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g,

TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.

– EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Table 20 Characterization of Risk of Peripheral Neuropathy

Risk parameter	MBC (N=1871)	EBC (N=740)
Frequency:		
Number of Patients with Adverse Events	542 (29.0%)	237 (32.0%)
95% CI for Incidence Rate (Clopper-Pearson)	(26.92, 31.08)	(28.68, 35.52)
Severity and nature of risk:		
No. of Patients with at least one Grade 3 or above AE	35 (1.9%)	12 (1.6%)
Grade 3	34 (1.8%)	12 (1.6%)
Grade 4	1 (0.1)	0
Grade 5	0	0
Seriousness/Outcomes:		
No. of Patients with at least one Serious AE	3 (0.2%)	4 (0.5%)
No. of Patients with at least one AE leading to Trastuzumab Emtansine discontinuation	10 (0.5%)	15 (2.0%)
No. of Patients with at least one AE resulted in Fatal outcome	0	0

AE=adverse event; EBC=early breast cancer; MBC=metastatic breast cancer.

Source: t_ae_12_PNEU_TPL; t_ae_rmp_RMP9_SE.

Impact on Quality of life:

Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. The most common symptoms of peripheral neuropathy include parasthesia or hypoaesthesia. If a patient experiences symptoms > Grade 1, activities of daily living (ADL) will begin to be limited. Treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤Grade 2.

Risk factors and risk groups:

Chemotherapeutic agents that target microtubules (e.g., taxanes, vinca alkaloids) are recognized to cause peripheral neuropathy; the degree and type of peripheral neuropathy depends on the chemotherapy regimen, cumulative dose, administrative schedule, route of administration and presence of pre-existing risk factors (e.g. diabetes mellitus and concurrent or prior use of neurotoxic drugs) (Nurgalieva et al. 2010).

In a large population-based study of chemotherapy-induced peripheral neuropathy in the US, a total of 65,316 BC, 9242 ovarian cancer and 86,278 non-small cell lung cancer patients from 1991-2002 were identified in the Surveillance, Epidemiology and End Results (SEER) cancer registry. Patients treated with taxanes were 2 times more likely to develop peripheral neuropathy compared to those not receiving chemotherapy (adjusted hazard ratio [HR]=2.22; 95% CI: 1.85-2.66), while patients treated with a platinum-taxane combination were 3 times more likely to develop peripheral neuropathy (adjusted HR=3.33; 95% CI: 2.05-5.05) (Nurgalieva et al. 2010).

Preventability:

Currently there is no known approach of preventing peripheral neuropathy. The MAH recommends in labeling that patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity and that treatment should be temporarily discontinued in patients who experience Grade 3 or 4 peripheral neuropathy until symptoms improve to ≤Grade 2.

The neuropathy induced by microtubule inhibitor therapy is best managed with dose adjustments and/or treatment delay. The reversibility of ixabepilone (a microtubule inhibitor) -associated peripheral neuropathy, both in patients whose dose was reduced and those who required permanent discontinuation, contrasts somewhat with clinical experience using other microtubule-targeting agents. For example, neurotoxicity has been reported to worsen, rather than resolve, with early-genera-tion vinca alkaloids and docetaxel (Swain et al. 2003). The reversibility of chemotherapy-induced peripheral neuropathy is increasingly becoming important, as active chemotherapies prolong survival and the number of long-term cancer survivors increases steadily. Although there are few long-term studies, it must be assumed that chemotherapy-induced peripheral neuropathy is not always completely reversible (Wolfgang et al. 2012).

Impact on the benefit-risk balance of the product:

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. 3/1871 (0.2%) MBC patients and 4/740 (0.5%) EBC patients from clinical trials experienced serious AEs; 1/1871 (0.1%) in MBC patient and 0/740 (0%) in EBC patients had Grade 4 peripheral neuropathy. No patients died as a result of an event of peripheral neuropathy.

Patients should be examined for signs of peripheral neuropathy prior to each dose of trastuzumab emtansine. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. The most common symptoms of peripheral neuropathy include paresthesia or hypoesthesia.

Benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

There is no potential public health impact of this safety concern.

2. INFORMATION ON IMPORTANT POTENTIAL RISKS

2.1 FETAL HARM

MedDRA terms: SMQ Pregnancy and Neonatal Topics

Potential mechanisms: Although not completely known, the effects of trastuzumab emtansine on reproductive organs in rats and monkeys may be consistent with the mechanism of action of DM1 (i.e., microtubule inhibition), on rapidly dividing cells, which would be expected to be translatable to humans. The embryo-fetal effects observed with pertuzumab and trastuzumab are consistent with the role HER-family members play in the development and differentiation of ectodermal/epithelial tissues, including that of renal tissue (Bader et al.2007).

Evidence source(s) and strength of evidence:

- Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Frequency with 95 % CI observed in trastuzumab emtansine clinical program:

Not applicable

Severity and nature of risk:

Not applicable

Seriousness/outcomes:

Cumulatively from 19 January 2006 through 21 February 2024 a total of 43 cases were retrieved in Global Safety Database.

Impact on Quality of life:

No events have been observed; therefore, impact on quality of life is not assessed.

Risk factors and risk groups:

Oligohydramnios:

Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive BC is the mid-50s, at least half the patients likely to receive treatment are unlikely to become pregnant on the basis of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Teratogenicity:

Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of fetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy (Gwyn et al. 2005).

Preventability:

Women of childbearing potential

Labeling states that patients should be advised to use highly effective contraception during treatment with trastuzumab emtansine and for at least 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception.

Impact on the benefit-risk balance of the product:

Fetal harm is a potential risk based on the effects of the components of trastuzumab emtansine.

A Global Enhancement PV Pregnancy Program is in place to confirm the incidence and characterize any events that may occur and present in the periodic safety update report

(PSUR) for 10 years. After closure of this program, the MAH will continue to collect information on trastuzumab emtansine-exposed pregnancies as part of routine PV activities.

Benefit-risk profile of trastuzumab emtansine remains positive.

Interval and cumulative data of the pregnancy outcome (Overall Exposure, Exposure by Parents [mother and farther], Exposure by Source) is present in Annex 7 of the RMP.

Public health impact:

No potential public health impact of this safety concern.

2.2 MEDICATION ERROR

MedDRA terms: HLGT Medication Errors

Potential mechanisms: Medication errors are usually attributed to human error.

Evidence source(s) and strength of evidence:

- Pooled data of 1871 patients from the following 9 MBC studies: TDM4788g/BO22589, TDM4997g/BO25734, TDM4370g/BO21977, TDM4374g, TDM4258g, TDM4688g, TDM3569g, TDM4529g/BO25430, and TDM4450g/BO21976.
- EBC: Data of 740 patients from single pivotal study BO27938.

Characterization of the risk:

Frequency with 95 % CI observed in trastuzumab emtansine clinical program:

- MBC: 0.4% (0.15%, 0.77%) (7/1871 patients).
- EBC: 0.1% (1/740 patients).

Severity and nature of risk:

- MBC: One event (1/7) was reported as Grade 3 in severity.

Seriousness/outcomes:

Seven instances of medication error with trastuzumab emtansine have occurred in the MBC clinical trial setting (total 1871 patients). Of these cases, one was associated with a serious adverse event (sudden death). This case describes a patient who was inadvertently given an accidental overdose of 6mg/kg of trastuzumab emtansine due to confusion with trastuzumab. The patient experienced Grade 2 thrombocytopenia, which

subsequently resolved. The patient died suddenly 19 days after the medication error, which was assessed by the investigator as unrelated to medication error.

One medication error case was reported in the EBC Study BO27938 (KATHERINE).

Impact on Quality of life:

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is trastuzumab emtansine and not another trastuzumab-containing medicine, such as trastuzumab or trastuzumab deruxtecan. Trastuzumab emtansine should only be prescribed by a physician and administered under the supervision of a healthcare professional who are experienced in the treatment of cancer patients (prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available). In the few cases of medication error to date, events of either thrombocytopenia without hemorrhage or asymptomatic increases in transaminases have been observed. A single case of sudden death after medication error has been reported to date; however, after analysis of this case by the MAH, a causal relationship to the medication error was considered unlikely.

Risk factors and risk groups:

Not applicable

Preventability:

The commercial packaging of trastuzumab-containing Roche medicines has been designed to minimize potential medication errors, by distinguishing among two strengths of trastuzumab emtansine (Kadcyla), and intravenous or subcutaneous formulations of trastuzumab (Herceptin).

The MAH has created educational materials for healthcare professionals who are expected to prescribe, prepare, or administer Kadcyla (trastuzumab emtansine) to inform about the risk of confusion between Kadcyla (trastuzumab emtansine) and other trastuzumab-containing medicines, such as trastuzumab or trastuzumab deruxtecan and also suggest measures to avoid errors. Educational materials also highlight differences in branding and appearance in packaging between Roche medicines containing trastuzumab - Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab).

The differences between the various presentations are summarized in the table below.

Table 21 Packaging Detail for Kadcyla® and Herceptin®

	Kadcyla®			Herceptin®	
	100 mg	160 mg		150 mg	600 mg
Product Color (Vertical strip left of product name)	Light Yellow	Light Yellow		Dark Orange	Dark Orange
Strength Bar (also on vial label)	**100 mg** on White bar	**160 mg** on Purple bar		**150 mg** on Red bar	**600 mg/5 ml** on Light Blue bar
Vial Size	15 ml	20 ml		15 ml	6 ml
Vial Flip Cap	White	Purple		Red	Blue
Vial Label	White with yellow background behind the invented name and strength	White with yellow background behind the invented name and strength		White	White

The Kadcyla (trastuzumab emtansine) vial labels and cartons highlight the difference between Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab) by using bolded font for the international non-proprietary name (INN).

In addition to the distinctive packaging for each product and strength, statements are included in the EU SmPC to further minimize the potential for medication errors.

Impact on the benefit-risk balance of the product:

The distinctive packaging that is summarized above, as well as the precautionary statements included in the SmPC, will minimize potential medication errors.

The benefit-risk profile for trastuzumab emtansine remains positive.

Public health impact:

No potential public health impact of this safety concern.

SVII.3.2. Presentation of the Missing Information

3. INFORMATION ON MISSING INFORMATION:

3.1 USE IN PATIENTS WITH HEPATIC IMPAIRMENT

Evidence source:

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. Serious liver and bile disorders have been observed in patients treated with trastuzumab emtansine in clinical studies.

Study BO25499 investigated the safety and efficacy of trastuzumab emtansine in patients with mild to moderate hepatic impairment. No adjustment to the starting dose is required for patients with mild or moderate liver impairment.

Trastuzumab emtansine has not been studied in patients serum transaminases >2.5 × ULN or total bilirubin >1.5×ULN prior to initiation of treatment. trastuzumab emtansine should be permanently discontinued in patients who have serum transaminase levels >3×ULN and concomitant total bilirubin levels >2×ULN.

Trastuzumab emtansine was not studied in patients with severe liver impairment. Treatment of patients with any liver impairment should be undertaken with caution due to known liver toxicity observed with trastuzumab emtansine.

3.2 USE IN PATIENTS WITH LVEF <50%

Evidence source:

BO39807, a secondary data use non-interventional post-authorization safety study (NI-PASS) of patients with a diagnosis of MBC with a documented latest LVEF reported between 40% and 49% within 60 days prior to Kadcyla initiation were identified and followed-up during routine clinical practice had been completed.

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF < 40% has been observed in patients treated with trastuzumab emtansine, and therefore symptomatic congestive heart failure (CHF) is a potential risk. No available data on treatment with trastuzumab emtansine in patients with LVEF <50% prior to initiation of treatment has been reported to date in clinical trials.

The completion of BO39807, a secondary data use non-interventional post-authorization safety study (NI-PASS) constitutes the largest cohort of Kadcyla-treated patients with MBC and low LVEF. These results describe the very small proportion of patients (1.6%) initiating Kadcyla with an LVEF greater or equal to 40% and lower than 50% at treatment initiation. A small number of these patients (N=7, 21.9%) experienced events of LVEF drop of >10% and/or CHF. Patients with low LVEF appear to be monitored for such events while being treated with Kadcyla in routine clinical practice in the United States.

In the context of the cardiovascular morbidity of these patients, initiation of Kadcyla does not constitute an unacceptable cardiac risk. The decision for physicians to prescribe Kadcyla in patients with low LVEF should be considered in the context of the risk for cardiovascular events and availability of alternative anticancer therapies, and cardiac function should be monitored at regular intervals during treatment.

3.3 USE IN PREGNANT WOMEN

Evidence source:

There are no clinical studies of trastuzumab emtansine in pregnant women. No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. Trastuzumab, a component of trastuzumab emtansine, can cause fetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule inhibiting cytotoxic component of trastuzumab emtansine, is expected to be teratogenic and potentially embryotoxic.

Contraception in males and females

Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. Male patients or their female partners should also use effective contraception.

Administration of trastuzumab emtansine to pregnant women is not recommended. Women who become pregnant must contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended.

3.4 USE IN LACTATING WOMEN

Evidence source:

Lactating women were excluded from all clinical trials. Therefore, no information is available from clinical trial program. It is not known whether trastuzumab emtansine is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants from trastuzumab emtansine, women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 22 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• ILD/ARDS • Hepatic Toxicity • Nodular regenerative hyperplasia • Infusion-related reaction • Hypersensitivity • Left ventricular dysfunction • Thrombocytopenia • Peripheral neuropathy
Important potential risks	• Fetal harm • Medication error
Missing information	• Use in patients with hepatic impairment • Use in patients with LVEF <50% • Use in pregnant women • Use in lactating women

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted follow-up with the use of guided questionnaires (see Annex 4) for:

- Hepatic toxicity
- Nodular regenerative hyperplasia
- Use in pregnant women

Other forms of routine pharmacovigilance activities

Continue to monitor as AE of special interest per protocols (Hy's Law lab criteria) for the safety concern of hepatotoxicity.

Periodic review for the following safety concerns:

- ILD/ARDS
- Hepatic toxicity
- Nodular regenerative hyperplasia
- Left ventricular dysfunction
- Infusion-related reaction
- Hypersensitivity
- Thrombocytopenia (including presentation of demographic data as available)
- Peripheral neuropathy
- Fetal harm
- Medication error
- Use in patients with LVEF <50%
- Use in patients with hepatic impairment
- Use in elderly patients (≥ 75 years)
- Use in lactating women
- Clinical impact of anti-drug antibodies

Cumulative review of AEs in pregnant patients and of pregnancies exposed to trastuzumab emtansine:

- Use in pregnant women

Enhanced Pharmacovigilance Pregnancy Program for:

- Fetal harm
- Use in pregnant women

III.2 Additional Pharmacovigilance Activities

Routine pharmacovigilance activities are considered by the MAH/Applicant to be sufficient to obtain and analyze relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of trastuzumab emtansine.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 23 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				
NA	NA	NA	NA	
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	
Category 3 - Required additional pharmacovigilance activities				
NA	NA	NA	NA	NA

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Not applicable.

Table 24 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorization				
None				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

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

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 25 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Identified Risks	
Interstitial lung disease/Acute Respiratory Distress syndrome (ILD/ARDS)	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥Grade 3 or for Grade 2 not responding to standard treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product characteristics (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.

Safety concern	Routine risk minimization activities
Hepatic Toxicity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.2 (Pharmacokinetic properties) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × Upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Nodular regenerative hyperplasia (NRH)	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects: Other side effects include: Uncommon **Routine risk minimization activities recommending specific clinical measures to address the risk:** Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be

Safety concern	Routine risk minimization activities
	permanently discontinued. This has been adequately captured in EU SmPC Section 4.4 **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Infusion-related reaction	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.7 (Effects on ability to drive and use machines) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions, driving and using machinery Section 3 How you are given Kadcyla Section 4 Possible side effects: Common (infusion-related reactions) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.

Safety concern	Routine risk minimization activities
Hypersensitivity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Left ventricular dysfunction	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been

Safety concern	Routine risk minimization activities
	adequately captured in Section 4.4 of EU SmPC. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2).**Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Thrombocytopenia	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. See Section 4.4 EU SmPC **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Peripheral neuropathy	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Potential Risks	
Fetal harm	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) Section 5.3 (Preclinical safety data) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Medication error	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.6 (Special precautions for disposal and other handling) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 5 How to store Kadcyla Section 6 Contents of the pack and other information

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing medicine (e.g. trastuzumab or trastuzumab deruxtecan). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Missing Information	
Use in patients with hepatic impairment	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.

Safety concern	Routine risk minimization activities
Use in patients with left ventricular ejection fraction (LVEF) <50%	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of EU SmPC. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). Based on an observational study, MBC patients with LVEF of 40-49% at baseline comprise less than 2% of patients treated with Kadcyla. Events of LVEF drop of >10% from baseline and/or CHF were observed in these patients; most of these patients had other cardiovascular risk factors. Cardiac function in these patients should be closely monitored. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Use in pregnant women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for

Safety concern	Routine risk minimization activities
	at least 7 months after treatment has concluded. Male patients or their female partners should also use effective contraception. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.
Use in lactating women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women should discontinue nursing prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Trastuzumab emtansine is subject to restricted medical prescription.

V.2. Additional Risk Minimization Measures

Table 26 Additional Risk Minimization Measures

Additional Risk Minimization Measure	Educational materials Safety concern: Medication error
Objectives	Ensure awareness of the potential for medication error
Rationale for the additional risk minimization activity	*Explanatory brochure on medication errors* Ensure awareness of the potential for medication error between Kadcyla (trastuzumab emtansine) and another trastuzumab-containing medicine (e.g., trastuzumab or trastuzumab deruxtecan), provide mitigation measures and also highlight the differences among them in the packaging of the Roche trastuzumab-containing medicines - Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab). *Kadcyla SmPC* The summary of product characteristic (SmPC) is included in the educational materials with the brochure to facilitate distribution
Target audience and planned distribution path	Health care providers
Plans for evaluating the effectiveness of the interventions and criteria for success	*How effectiveness of risk minimization measures for the safety concern will be measured:* Assess awareness of the potential for medication errors based on review of medication error cases reported to the safety database. *Criteria for judging the success of the proposed risk minimization measures:* SmPC recommendations regarding medication errors are adhered to

V.3 Summary of Risk Minimization Measures

Table 27 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Interstitial lung disease/Acute Respiratory Distress Syndrome (ILD/ARDS)	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥Grade 3 or for Grade 2 not responding to standard treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristic (EU SmPC).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Hepatic toxicity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.2 (Pharmacokinetic properties) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Guided questionnaires **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Nodular regenerative hyperplasia (NRH)	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects: Other side effects include: Uncommon **Routine risk minimization activities recommending specific clinical measures to address the risk:** Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued. This has been adequately captured in EU SmPC Section 4.4 **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Guided questionnaires **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-related reaction	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.7 Effects on ability to drive and use machines Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions, driving and using machinery Section 3 How you are given Kadcyla Section 4 Possible side effects: Common (Infusion-Related Reactions) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hypersensitivity	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Left ventricular dysfunction	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Thrombocytopenia	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. See Section 4.4 EU SmPC **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None
Peripheral neuropathy	**Routine risk communication:** **SmPC:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Fetal harm	**Routine risk communication:** **SmPC:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Global Enhanced Pharmacovigilance (PV) pregnancy program **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.6 (Fertility, pregnancy and lactation) Section 5.3 (Preclinical safety data) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Medication error	**Routine risk communication:** **SmPC:** Section 4.2 (Posology and method of administration)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Patient Information Leaflet: Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 5 How to store Kadcyla Section 6 Contents of the pack and other information **Routine risk minimization activities recommending specific clinical measures to address the risk:** In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing medicine, like trastuzumab or trastuzumab deruxtecan. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** Educational materials for health care providers.	
Use in patients with hepatic impairment	**Routine risk communication:** **SmPC:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of EU SmPC. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in patients with left ventricular ejection fraction (LVEF) <50%	**Routine risk communication:** **SmPC:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). This has been adequately captured in Section 4.4 of EU SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Based on an observational study, MBC patients with LVEF of 40-49% at baseline comprise less than 2% of patients treated with Kadcyla. Events of LVEF drop of >10% from baseline and/or CHF were observed in these patients; most of these patients had other cardiovascular risk factors. Cardiac function in these patients, should be closely monitored. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Use in pregnant women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab emtansine and for at least 7 months after treatment has concluded. Male patients or their female partners should also use effective contraception. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Global Enhanced Pharmacovigilance (PV) pregnancy program **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	
Use in lactating women	**Routine risk communication:** **SmPC:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Trastuzumab emtansine is subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** None

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR KADCYLA (TRASTUZUMAB EMTANSINE)

This is a summary of the risk management plan (RMP) for Kadcyla. The RMP details important risks of Kadcyla, how these risks can be minimized, and how more information will be obtained about Kadcyla's risks and uncertainties (missing information).

Kadcyla's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kadcyla should be used.

This summary of the RMP for Kadcyla 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 Kadcyla's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Kadcyla is authorized for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. It contains Trastuzumab Emtansine as the active substance and it is given by intravenous infusion.

Kadcyla is also authorized for treatment in patients with HER2-positive early breast cancer with residual disease in the breast and/or lymph nodes, after pre-operative treatment.

Further information about the evaluation of Kadcyla benefits can be found in Kadcyla's EPAR, including in its plain-language summary, available on the European Medicines Agency (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 Kadcyla, together with measures to minimize such risks and the proposed studies for learning more about Kadcyla's risks, are outlined below.

Measures to minimize 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 authorized 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 (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Kadcyla, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, 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 Kadcyla is not yet available, it is listed under 'missing information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Kadcyla are risks that need special risk management activities to further investigate or minimize 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 Kadcyla. 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Interstitial lung disease/Acute Respiratory Distress Syndrome • Hepatic Toxicity • Nodular regenerative hyperplasia • Infusion-related reaction • Hypersensitivity • Left ventricular dysfunction • Thrombocytopenia • Peripheral neuropathy
Important potential risks	• Fetal harm • Medication error
Missing information	• Use in patients with hepatic impairment • Use in patients with LVEF <50% • Use in pregnant women • Use in lactating women

II.B Summary of Important Risks

Important identified risk	
Interstitial lung disease/Acute Respiratory Distress Syndrome	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	General risk factors include prior lung disease, pneumonectomy, or abnormal baseline pulmonary physiology. Concomitant or sequential pneumotoxic drugs, or the addition of radiation therapy to the chest may significantly enhance the likelihood of developing adverse pulmonary effects. Based on the results from the primary analysis of study BO27938 (KATHERINE), there is a small increase in risk of pneumonitis/ radiation pneumonitis associated with concurrent pulmonary radiotherapy and trastuzumab emtansine in EBC patients. However, the majority of pneumonitis/radiation pneumonitis events reported in the study were Grade 1-2, were manageable and had recovered by the clinical cut-off date of the primary analysis. Administration of chemotherapeutic agents to patients who have received radiation therapy in the past may also “recall” a severe skin and/or lung reaction within the previously irradiated area.

Important identified risk	
Risk minimization measures	**Routine risk communication:** Summary of Product Characteristic (SmPC)**:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with Interstitial lung disease (ILD) or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for ≥Grade 3 or for Grade 2 not responding to standard treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristic (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status**:** Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk	
Hepatic Toxicity	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Risk factors (in the general population) include age and genetic factors affecting hepatic metabolism of drugs (Bleibel et al. 2007). There are currently no reliable predictors of patients who may or may not be susceptible to hepatotoxicity to trastuzumab emtansine.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.2 (Pharmacokinetic properties) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristic (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None

Important identified risk	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Nodular regenerative hyperplasia (NRH)	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	The risk of development of NRH and its potential complications increases with age. Sex and ethnicity do not seem to play a role in the development of NRH (Hartleb et al. 2011). NRH may develop as a result of underlying autoimmune, inflammatory, neoplastic, or idiopathic disease (Hartleb et al. 2011). In an ante-mortem case series, 74% of patients had a coexistent malignant, prothrombotic or rheumatological disease (Morris et al. 2010). It is hypothesized that immunosuppressive medications may induce NRH by damaging endothelial cells of small hepatic veins (Hartleb et al. 2011). There are currently no reliable predictors of patients receiving trastuzumab emtansine who may or may not be susceptible to NRH.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects: Other side effects include: Uncommon **Routine risk minimization activities recommending specific clinical measures to address the risk:** Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued. This has been adequately captured in European Union Summary of Product Characteristics (EU SmPC) Section 4.4

Important identified risk	
	Other risk minimization measures beyond the Product Information: Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Infusion-related reaction	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to infusion-related reactions to trastuzumab emtansine. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions on the day of or the day after a trastuzumab emtansine infusion. Additionally, patients with a history of infusion reaction to trastuzumab may be at greater risk of a severe reaction due to the trastuzumab component of trastuzumab emtansine. However, patients with severe infusion-related reactions to trastuzumab were excluded from the trastuzumab emtansine clinical studies and therefore data regarding this risk are not available.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.7 Effects on ability to drive and use machines Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions, driving and using machinery Section 3 How you are given Kadcyla Section 4 Possible side effects: Common (infusion-related reactions)

Important identified risk	
	Routine risk minimization activities recommending specific clinical measures to address the risk: The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status**:** Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Important identified risk	
Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Previous anthracycline therapy, prior or concurrent exposure to taxanes, patients over the age of 50 years, prior or concurrent anti-hypertensive medication use and low LVEF levels prior to or following the use of paclitaxel.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects

Important identified risk	
	Routine risk minimization activities recommending specific clinical measures to address the risk: Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk	
Hypersensitivity	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	General factors that increase the likelihood of experiencing type I hypersensitivity reactions include repeated exposure to agent, a history of drug hypersensitivity, and use of the IV route (Kang and Saif. 2007). Epidemiological data on the risk factors associated with hypersensitivity to trastuzumab emtansine are discussed under infusion-related reactions.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops infusion-related symptoms (see sections 4.4 and 4.8 of European Union Summary of Product Characteristics (EU SmPC). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk	
Thrombocytopenia	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Radiation therapy and certain chemotherapy medications can damage the bone marrow, lowering its production of platelets, and lead to thrombocytopenia. Patients receiving a combination of radiation therapy and chemotherapy are at greater risk for thrombocytopenia. It was noted in study TDM4370g/BO21977 (EMILIA) that Asian patients had a lower baseline platelet count than non-Asian patients. Asian patients had a higher incidence of Grade 3 or Grade 4 thrombocytopenia, as well as a slightly higher incidence of hemorrhagic AEs. However, the frequency of severe hemorrhage was similar among Asian and non-Asian patients. A higher incidence of Grade ≥3 AEs of platelet count decreased was also reported among Asian patients compared with white patients in EBC Study BO27938 (KATHERINE). The significance of these data is not known.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. See Section 4.4 European Union Summary of Product Characteristics (EU SmPC) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription.

Important identified risk	
	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Peripheral neuropathy	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Chemotherapeutic agents that target microtubules (e.g., taxanes, vinca alkaloids) are recognized to cause peripheral neuropathy; the degree and type of peripheral neuropathy depends on the chemotherapy regimen, cumulative dose, administrative schedule, route of administration and presence of pre-existing risk factors (e.g. diabetes mellitus and concurrent or prior use of neurotoxic drugs) (Nurgalieva et al. 2010). In a large population-based study of chemotherapy-induced peripheral neuropathy in the US, a total of 65,316 breast cancer, 9242 ovarian cancer and 86,278 non-small cell lung cancer patients from 1991-2002 were identified in the Surveillance, Epidemiology and End Results (SEER) cancer registry. Patients treated with taxanes were 2 times more likely to develop peripheral neuropathy compared to those not receiving chemotherapy (adjusted HR=2.22; 95% CI: 1.85-2.66), while patients treated with a platinum-taxane combination were 3 times more likely to develop peripheral neuropathy (adjusted HR=3.33; 95% CI: 2.05-5.05). (Nurgalieva et al. 2010).

Important identified risk	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Fetal harm	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	<u>Oligohydramnios:</u> Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with metastatic breast cancer (MBC) make pregnancies less likely to occur.

Important identified risk	
	Teratogenicity: Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of fetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy (Gwyn et al. 2005).
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.6 (Fertility, pregnancy and lactation) Section 5.3 (Preclinical safety data) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk:** Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 7 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Medication error	
Evidence for linking the risk to the medicine	Randomized clinical trial data and published literature.
Risk factors and risk groups	Not applicable

Important identified risk	
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.6 (Special precautions for disposal and other handling) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 5 How to store Kadcyla Section 6 Contents of the pack and other information **Routine risk minimization activities recommending specific clinical measures to address the risk:** In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing medicine, like trastuzumab or trastuzumab deruxtecan. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** Educational materials for health care providers.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information	
Use in patients with hepatic impairment	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 3 How you are given Kadcyla Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Liver function should be monitored prior to initiation of treatment and each dose. Treatment in patients with serum transaminases > 3 × upper limit of normal (ULN) and concomitant total bilirubin > 2 × ULN should be permanently discontinued. This has been adequately captured in Section 4.4 of European Union Summary of Product Characteristics (EU SmPC). **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information	
Use in patients with LVEF <50%	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Standard cardiac function testing should be performed prior to initiation and at regular intervals during treatment. This has been adequately captured in Section 4.4 of EU SmPC. The dose should be delayed or treatment discontinued as necessary in cases of left ventricular dysfunction (see Section 4.2). **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information	
Use in pregnant women	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk**: Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine. Male patients or their female partners should also use effective contraception. If a pregnant woman is treated with trastuzumab emtansine, close monitoring by a multidisciplinary team is recommended. **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information	
Use in lactating women	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 4.6 (Fertility, pregnancy and lactation) **Patient Information Leaflet:** Section 2 What you need to know before you are given Kadcyla: Warnings and Precautions: Pregnancy **Routine risk minimization activities recommending specific clinical measures to address the risk**: Women should discontinue breast feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast feeding 7 months following the last dose of trastuzumab emtansine. **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Kadcyla is subject to restricted medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 STUDIES WHICH ARE CONDITIONS OF THE MARKETING AUTHORIZATION

None

II.C.2 OTHER STUDIES IN POST-AUTHORIZATION DEVELOPMENT PLAN

None.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Following follow-up forms have been included:

- Guided Questionnaire for Hepatic Disorder and Toxicity
- Guided Questionnaire for Pregnancy-related Adverse Events

Local Data Capture
Version 1.4
Date: 03-Jan-2012
Local Case Number:

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

1. Patient ID: _____

   Study number, if applicable: _____

   Is this a Serious Adverse Event? ☐ Yes ☐ No

   MCN number (unique identifier for SAEs): _____

   Date of Birth: _____

   Age (years): _____

   Gender (sex): ☐ Female ☐ Male

2. ***Relevant Medical History**

☐ History of cholestatic liver disease and/or gallbladder sludge or stones	☐ Liver metastasis. ☐ If YES: is there evidence of progression?	☐ Recent hypotension
☐ Hepatitis history including A, B, C, D and E	☐ Fatty liver or steatohepatitis	☐ Congestive heart failure
☐ Recent exposure to blood products/body fluids/transfusion	☐ Recent intravenous drug abuse	☐ Recent travel to countries with endemic hepatitis
☐ Close contact to a person infected with viral hepatitis	☐ History of alcohol abuse	☐ Exposure to toxic agents including prior chemotherapy

If any item is checked above, please describe relevant clinical details, e.g. onset date, signs and symptoms, laboratory values, duration, diagnosis, treatment and outcomes, if applicable.

Please ensure that ALL Medical History reported above is also reported on the appropriate study Case Report Form (CRF).

3. ***Concomitant medications** Ensure that all medications taken 1 month prior to, or concurrent with T-DM1 have been reported. . Prescription and over-the-counter drugs such as acetaminophen, hormonal treatments, herbal medicines (gingko, etc.) and vitamins should be included.
   Start and stop dates should be specified for each medication.

   Have ALL Concomitant Medications described above been reported on the study CRF?
   ☐ Yes. Please append of eCRF concomitant medication pages.
   ☐ No. If No, please append of eCRF concomitant medication pages, and report all other medications *below*:

Concomitant medication	Indication	Daily dose	Start date	Indicate if ongoing	If stopped, indicate date

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

Concomitant medication	Indication	Daily dose	Start date	Indicate if ongoing	If stopped, indicate date

4. Specifics of the treatment with T-DM1:

***Indication:** _____

Dose/regimen: _____

Start date: _____

Stop date: _____

Was dose adjusted (increased or decreased) during therapy?

☐ Yes ☐ No

If Yes: please specify: _____

5.a List all **signs and symptoms** with onset and resolution dates for each one with special emphasis to the following:

Symptom	Onset date	Resolution date	If persisting, last date
Nausea			
Vomiting			
Malaise			
Reduced appetite			
Tiredness			
Weakness			
Dark urine			
Light colored feces			
Abdominal pain			
Jaundice			
Encephalopathy			
Rash			
Fever			
Eosinophilia			
Other organ involvement			

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

5.b Additional signs and symptoms (e.g. joint pain, pruritus, bleeding complications, ascites, esophageal varices, or other signs of portal hypertension):

6.a ***Laboratory Values Tests** (reference ranges should be provided with each value)
Please specify if not done (ND) in the results section.
No new testing is expected or required.

Have ALL Lab Results been reported on the study CRF?
☐ Yes. Please append copies of the eCRF pages with relevant laboratory results.
☐ No. Please append copies of the eCRF pages with relevant laboratory results, and include other lab results below:

Laboratory test results N: reference ('normal') ranges	**Test results and dates**					
	Baseline	**2nd test**	**3rd test**	**4th test**	**5th test**	**6th test**
Date:						
AST N:						
ALT N:						
Alk Phos N:						
PTT/INR N:						
Factor V N:						
Total Bilirubin N:						
Bilirubin Direct N:						
Bilirubin Indirect N:						
Urobilinogen N:						
GGT (optional) N:						
5'-Nucleotidase N:						

6.b ***Virology Screening Tests** (reference values should be provided with each result)
Please specify if not done (ND) in the results section

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

*Virology screening (specify Ag or Ab types) and immunologic tests		Results
Hepatitis	A	
	B	
	C	
	EBV	
	CMV	
Other (ie; hepatitis delta,hepatitis E, etc)		
Hepatitis Vaccination Status		
Antimitochondrial antibody (AMA)		
Antinuclear antibody (ANA)		
Anti-smooth-muscle antibody (ASM)		
Antineutrophil cytoplasmic antibody (ANCA)		
Anti-liver/kidney microsomal antibody (anti-LKM)		
Other (specify)		

7.a Other laboratory values:
Please specify if not done (ND) in the results section

Laboratory test (N: reference ('normal') ranges)	Baseline	During treatment	After drug discontinuation
Date:			
LDH N:			
Globulin N:			
Protein electrophoresis N:			
Fibrinogen N:			
Coagulation N:			
Blood ammonia N:			

7.b Specify any blood count abnormalities (such as eosinophilia, anemia, thrombocytopenia, etc)

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

8.a Was an ultrasound (or other **imaging investigations**) of the hepatic region performed? Specify imaging date and findings in the table below.

Type of Test	Date	Results
Ultrasound		
Doppler ultrasound (to assess blood flow and blood pressure)		
CT scan		
MRI		
Liver biopsy		
Others (specify)		

8.b Was a ***Liver biopsy** performed?

☐ No
☐ Yes If Yes:

☐ Copy of the pathology report available – please attach
List liver biopsy findings (biopsy type, date, results):

9. Form completed by: _____
Date: _____
Phone: _____
Fax: _____

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

T-DM1
GUIDED QUESTIONNAIRE FOR HEPATIC DISORDER AND TOXICITY

E-mail: _____

N.B Questions marked with an *asterisk are of particular interest.
Please try to obtain as many answers to the questions as possible.

Guided Questionnaire
Pregnancy-Related Adverse Events

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Other Patient Identifiers	
Patient Gender:	❑ M ❑ F		

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Herceptin in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Herceptin, while for Perjeta, Pertuzumab+Trastuzumab FDC SC and Kadcyla, oligohydramnios has been classified as an important potential risk.

By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.

Reporter Information	
Name of reporter completing this form ***(if other than addressee, please provide contact information below)*:**	
Health Care Provider? ❑ Yes ❑ No - Please Specify:	
Phone number:	Fax number:
Email address:	

☐ Drug: **Herceptin** Lot Number(s):_____
☐ Drug: **Perjeta** Lot Number(s):_____
☐ Drug: **Kadcyla** Lot Number(s):_____
☐ Drug: **Pertuzumab + Trastuzumab FDC SC** Lot Number(s):_____

Maternal Information

	Selected Medical History		Comment
☐	None	☐ Unknown	
☐	Hypertension		
☐	Diabetes; if yes, please, specify type		
☐	Seizure disorders		
☐	Thyroid disorder		
☐	Smoking / use of alcohol; specify		
☐	Family history of diabetes mellitus		
☐	Family history of congenital renal anomalies; if yes, please specify		
☐	Other; specify		

	Selected Obstetric History (*previous pregnancies*)		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Gestational hypertension/preeclampsia/eclampsia		
☐	Gestational diabetes		
☐	Spontaneous or induced abortions; if yes and known, please specify cause		
☐	Oligohydramnios		
☐	History of other pregnancy complications; specify		

Guided Questionnaire
Pregnancy-Related Adverse Events

☐	Other; specify		
	Fetal Abnormalities in Previous Pregnancies		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Delayed renal development		
☐	Death in utero; if yes/known, specify reason		
☐	Birth defects; if yes, specify		
☐	Family history of birth defects; if yes, specify		
☐	Other; specify		

Current Pregnancy

Pre-pregnancy weight and height	Weight:	Height:
Blood pressure prior to conception	Date:	BP:

Prenatal Imaging and Aneuploidy Screening/testing (e.g., ultrasound, amniocentesis, etc.)
Was a prenatal test performed? ☐ Yes ☐ No

If yes, Prenatal Test Type	Date	Indication for test	Was a defect noted?	Specify

Ultrasound Assessment Log

Date	Gestational Age	Amniotic Fluid (AF) Measurement	Provider's Assessment of AF	Estimated Fetal Weight	Reported Percentile Growth	Provider's Assessment of Growth
	_____ weeks	AF Index _____ cm Maximum Vertical Pocket _____ cm Other _____ ☐ AF not measured	1 Normal 2 Abnormal 3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal development 7 Other: _____ 8 Not assessed	_____ grams ☐ Not estimated	_____ ☐ Not reported ☐ Growth not measured	☐ Normal ☐ Abnormal ☐ IUGR* (< 10%ile) ☐ Severe IUGR (< 3%ile) ☐ Large for Gestational Age (> 90%ile) ☐ Growth not measured

* IUGR=Intrauterine growth retardation

Guided Questionnaire
Pregnancy-Related Adverse Events

Concomitant Medications, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy:				
Product Name	**Indication**	**Total daily dose**	**Start date**	**Stop date/Ongoing**

	Maternal Medical Conditions During Current Pregnancy *Please check all that apply and provide detailed information on pregnancy-related complications on last page*			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ Preeclampsia superimposed on chronic hypertension	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Gestational Diabetes	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Spontaneous or induced abortions; if yes/known, specify cause	Pathology results:	Start date / Gestational age	Contributing factors
☐	Chronic leakage of amniotic fluid	Start date / Gestational age		Contributing factors
☐	Other; specify	Pathology results:	Start date / Gestational age	Contributing factors
	Fetal Conditions During Current Pregnancy *Please check all that apply and provide detailed information on fetal complications on last page*			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contributing factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date / Gest. age	Specify

Guided Questionnaire
Pregnancy-Related Adverse Events

☐	Post-maturity syndrome	Evidence:	Start date / Gestational age	Contributing factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date / Gestational age	Contributing factors
☐	Other; specify			

Infant information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps / vacuum ☐ Cesarean section	Date	
Gestational age at birth		Apgar score	

Please check all that apply and provide detailed information on complications in infants on last page

	Date of Assessment			Contributing factors
☐	Birth outcome	☐ Live birth ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional significance to the child	Specify	
		☐ Minor malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify	
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify	
☐	Abnormal renal function	☐ Proteinuria ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

Guided Questionnaire
Pregnancy-Related Adverse Events

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: ..... Tel. No.: .....

Contact name for further information on pregnancy and/or on the infant:

Function ..... Tel. No.: .....

Contact Address: ..... Fax No.: .....

..... Email: .....

.....

Guided Questionnaire
Pregnancy-Related Adverse Events

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

EDUCATIONAL MATERIALS FOR HEALTHCARE PROFESSIONALS REGARDING THE RISK OF MEDICATION ERROR

The HCP information shall contain the following key messages:

1. Kadcyla is different from other trastuzumab-containing medicines such as Herceptin (trastuzumab) or Enhertu (trastuzumab deruxtecan), with different active substances never to be used interchangeably.
2. Kadcyla is NOT a generic version of Herceptin and has different properties, indications and dose.
3. Kadcyla is an antibody-drug conjugate containing humanized anti-HER2 IgG1 antibody trastuzumab and DM1, a microtubule-inhibitory maytansinoid.
4. Do not substitute or combine Kadcyla with other trastuzumab-containing medicines such as Herceptin (trastuzumab) or Enhertu (trastuzumab deruxtecan).
5. Do not administer Kadcyla in combination with chemotherapy.
6. Do not administer Kadcyla at doses greater than 3.6 mg/kg once every 3 weeks.
7. If a prescription for Kadcyla is written electronically, it is important to ensure that the medication prescribed is trastuzumab emtansine and not another trastuzumab-containing medicine, such as Herceptin (trastuzumab) or Enhertu (trastuzumab deruxtecan).
8. Both the invented name Kadcyla and its full non-proprietary name (trastuzumab emtansine) should be used and confirmed when prescribing, preparing the infusion solution and administering Kadcyla to patients. It must be verified that the non-proprietary name is trastuzumab emtansine.
9. In order to prevent medication errors it is important to review the Summary of Product Characteristics and to check the outer carton and vial labels to ensure that the medicinal product being prepared and administered is Kadcyla and not another trastuzumab-containing medicine, such as Herceptin (trastuzumab) or Enhertu (trastuzumab deruxtecan).
10. A description of the key differences between Roche products Kadcyla, Herceptin and Herceptin SC in relation to indication, dose, administration and packaging differences.