Summary of Product Characteristics for pharmaceutical product

1. Name of the medicinal product:

Kadcyla 100 mg powder for concentrate for solution for infusion.
Kadcyla 160 mg powder for concentrate for solution for infusion.

2. Qualitative and quantitative composition

Kadcyla 100 mg powder for concentrate for solution for infusion
One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab emtansine. After reconstitution one vial of 5 mL solution contains 20 mg/mL of trastuzumab emtansine (see section 6.6).

Kadcyla 160 mg powder for concentrate for solution for infusion
One vial of powder for concentrate for solution for infusion contains 160 mg of trastuzumab emtansine. After reconstitution one vial of 8 mL solution contains 20 mg/mL of trastuzumab emtansine (see section 6.6).
Trastuzumab emtansine is an antibody-drug conjugate that contains trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture, covalently linked to DM1, a microtubule inhibitor, via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for concentrate for solution for infusion.
White to off-white lyophilised powder.

4. Clinical particulars

4.1 Therapeutic indications

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.
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.

4.1 Posology and method of administration

Kadcyla 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 (i.e. prepared to manage allergic/anaphylactic infusion reactions and in an environment where full resuscitation facilities are immediately available (see section 4.4)).

Patients treated with trastuzumab emtansine should have HER2 positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a CE-marked In Vitro Diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2-status should be assessed by an alternate validated test.

In order to prevent medicinal product 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 product (e.g. trastuzumab or trastuzumab deruxtecan).

Posology

The recommended dose of trastuzumab emtansine is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle).

The initial dose should be administered as a 90 minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration. Cases of delayed epidermal injury or necrosis following extravasation have been observed in the post-marketing setting (see section 4.4 and 4.8).

If the prior infusion was well tolerated, subsequent doses of trastuzumab emtansine may be administered as 30 minute infusions. Patients should be observed during the infusion and for at least 30 minutes after infusion.

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.

Duration of treatment

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.

Dose modification

Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine as per guidelines provided in text and Tables 1 and 2.

Trastuzumab emtansine dose should not be re-escalated after a dose reduction is made.

Table 1 Dose reduction schedule

Dose reduction schedule (Starting dose is 3.6 mg/kg)	**Dose to be administered**
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

able 2 Dose Modification Guidelines

Dose Modifications for Patients with EBC		
Adverse reaction	**Severity**	**Treatment modification**
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to < 75,000/mm^3)	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time < 25,000/mm^3	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level.
Increased Alanine Transaminase (ALT)	Grade 2-3 (> 3.0 to ≤ 20× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue trastuzumab emtansine
Increased Aspartate Transaminase (AST)	Grade 2 (> 3.0 to ≤ 5× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (> 5 to ≤ 20× ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (> 20 × ULN at any time)	Discontinue trastuzumab emtansine
Hyperbilirubinemia	TBILI > 1.0 to ≤ 2.0× the ULN on day of scheduled treatment	Do not administer trastuzumab emtansine until total bilirubin recovers to ≤ 1.0× ULN, and then reduce one dose level
	TBILI > 2× ULN at any time	Discontinue trastuzumab emtansine
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication

Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue trastuzumab emtansine
Peripheral Neuropathy	Grade 3-4	Do not administer trastuzumab emtansine until resolution ≤ Grade 2
Left Ventricular Dysfunction	LVEF < 45%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with trastuzumab emtansine
Heart Failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue trastuzumab emtansine
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue trastuzumab emtansine
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue trastuzumab emtansine if not resolving with standard treatment
	Grade 3-4	Discontinue trastuzumab emtansine
Dose Modifications for Patients with MBC		
Adverse reaction	**Severity**	**Treatment modification**
Thrombocytopenia	Grade 3 (25,000 to < 50,000/mm^3)	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level
	Grade 4 (< 25,000/mm^3)	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then reduce one dose level
Increased Transaminase (AST/ALT)	Grade 2 (> 2.5 to ≤ 5× the ULN)	Treat at the same dose level
	Grade 3 (> 5 to ≤ 20× the ULN)	Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level
	Grade 4 (> 20× the ULN)	Discontinue trastuzumab emtansine
Hyperbilirubinemia	Grade 2 (> 1.5 to ≤ 3× the ULN)	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.
	Grade 3 (> 3 to ≤ 10× the ULN)	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.
	Grade 4 (> 10× the ULN)	Discontinue trastuzumab emtansine
Drug Induced Liver Injury (DILI)	Serum transaminases > 3 x ULN and concomitant total bilirubin > 2× ULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation

		of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue trastuzumab emtansine
Left Ventricular Dysfunction	Symptomatic CHF	Discontinue trastuzumab emtansine
	LVEF <40%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, discontinue trastuzumab emtansine
	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue trastuzumab emtansine.
	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
	LVEF > 45%	Continue treatment with trastuzumab emtansine.
Peripheral Neuropathy	Grade 3-4	Do not administer trastuzumab emtansine until resolution ≤Grade 2
Pulmonary Toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue trastuzumab emtansine

ALT = alanine transaminase; AST = aspartate transaminase, CHF = congestive heart failure, LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction, TBILI = Total Bilirubin, ULN = upper limit of normal

* Prior to starting trastuzumab emtansine treatment.

Delayed or missed dose

If a planned dose is missed, it should be administered as soon as possible; without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The next dose should be administered in accordance with the dosing recommendations above.

Peripheral neuropathy

Trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. At retreatment a dose reduction may be considered according to the dose reduction schedule (see Table 1).

Special populations

Elderly patients

No dose adjustment is required in patients aged ≥ 65 years. There are insufficient data to establish the safety and efficacy in patients ≥ 75 years due to limited data in this subgroup. However, for patients ≥65 years, subgroup analysis of 345 patients from study MO28231 shows a tendency of higher incidences of grade 3, 4 and 5 AE's, SAE's and AE's

leading to drug discontinuation/interruption, but with a similar incidence of AEs of grade 3 and above classified as drug related.

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine (see sections 5.1 and 5.2).

Renal impairment

No adjustment to the starting dose is needed in patients with mild or moderate renal impairment (see section 5.2). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data and therefore patients with severe renal impairment should be monitored carefully.

Hepatic impairment

No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment. Trastuzumab emtansine has not been studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with trastuzumab emtansine (see section 4.4 and 5.2).

Paediatric population

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of breast cancer.

Method of administration

Kadcyla is for intravenous use. Trastuzumab emtansine must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.2 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.3 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

In order to prevent medicinal product 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 product (e.g. trastuzumab or trastuzumab deruxtecan).

Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was commonly reported with trastuzumab emtansine and was the most common adverse reaction leading to treatment discontinuation, dose reduction, and dose interruption (see section 4.8). In clinical studies, the incidence and severity of thrombocytopenia were higher in Asian patients (see section 4.8).

It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Patients with thrombocytopenia (≤ 100,000/mm^3) and patients on anti-coagulant treatment (e.g. warfarin, heparin, low molecular weight heparins) should be monitored closely while on trastuzumab emtansine treatment. Trastuzumab emtansine has not been studied in patients with platelet counts ≤ 100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (< 50,000/mm^3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥ 75,000/mm^3) (see section 4.2).

Haemorrhage

Cases of haemorrhagic events, including central nervous system, respiratory and gastrointestinal haemorrhage, have been reported with trastuzumab emtansine treatment. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1-4 transaminitis), has been observed during treatment with trastuzumab emtansine in clinical studies (see section 4.8). Transaminase elevations were generally transient with peak elevation at day 8 after administration of therapy and subsequent recovery to Grade 1 or less prior to the next cycle. A cumulative effect on transaminases has also been observed (the proportion of patients with Grade 1-2 ALT/AST abnormalities increases with successive cycles).

Patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the cases (see section 4.8).

Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some with a fatal outcome due to drug-induced liver injury have been observed in patients treated with trastuzumab emtansine. Observed cases may have been confounded by comorbidities and/or concomitant medicinal products with known hepatotoxic potential.

Liver function should be monitored prior to initiation of treatment and each dose. Patients with baseline elevation of ALT (e.g. due to liver metastases) may be predisposed to liver injury with a higher risk of a Grade 3-5 hepatic event or liver function test increase. Dose reductions or discontinuation for increased serum transaminases and total bilirubin are specified in section 4.2.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine. NRH is a rare liver condition characterised by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can be confirmed only by histopathology. 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 other manifestations of cirrhosis. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

Trastuzumab emtansine has not been studied in patients with serum transaminases > 2.5 × ULN or total bilirubin > 1.5 × ULN prior to initiation of treatment. Treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN should be permanently discontinued. Treatment of patients with hepatic impairment should be undertaken with caution (see sections 4.2 and 5.2).

Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical studies with trastuzumab emtansine. MBC patients with Grade ≥ 3 and EBC patients with Grade ≥ 2 peripheral neuropathy at baseline were excluded from clinical studies. 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. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

Left ventricular dysfunction

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with trastuzumab emtansine, and therefore symptomatic congestive heart failure (CHF) is a potential risk (see section 4.8). General risk factors for a cardiac event and those identified in adjuvant breast cancer studies with trastuzumab therapy include advancing age (> 50 years), low baseline LVEF values (< 55%), low LVEF levels prior to or following the use of paclitaxel in the adjuvant setting, prior or concomitant use of antihypertensive medicinal products, previous therapy with an anthracycline and high BMI (> 25 kg/m^2).

Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed prior to initiation of treatment and also at regular intervals (e.g. every three months) during treatment. The dosing should be delayed, or treatment discontinued as necessary in cases of left ventricular dysfunction (see section 4.2).

In clinical studies, patients had a LVEF ≥ 50% at baseline. Patients with a history of congestive heart failure (CHF), serious cardiac arrhythmia requiring treatment, history of myocardial infarction or unstable angina within 6 months of randomization, or current dyspnoea at rest due to advanced malignancy were excluded from clinical studies.

Events of LVEF drop of >10% from baseline and/or CHF were observed in an observational study (BO39807) of MBC patients with baseline LVEF of 40-49% in a real world setting. The decision to administer trastuzumab emtansine in MBC patients with low LVEF must be made only after careful benefit risk assessment and cardiac function should be closely monitored in these patients (see section 4.8).

Pulmonary toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical studies with trastuzumab emtansine (see section 4.8). Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates.

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 (see section 4.2).

Patients with dyspnoea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events.

Infusion-related reactions

Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR); treatment is not recommended for these patients. Patients should be observed closely for infusion-related reactions, especially during the first infusion.

Infusion-related reactions (due to cytokine release), characterized by one or more of the following symptoms have been reported: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia. In general, these symptoms were not severe (see section 4.8). In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Treatment should be interrupted in patients with a severe IRR until signs and

symptoms resolve. Consideration for re-treatment should be based on clinical assessment of the severity of the reaction. Treatment must be permanently discontinued in the event of a life threatening infusion-related reaction (see section 4.2).

Hypersensitivity reactions

Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients.

Patients should be observed closely for hypersensitivity/allergic reactions, which may have the same clinical presentation as an IRR. Serious, anaphylactic reactions have been observed in clinical studies with trastuzumab emtansine. Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

Injection-site reactions

Extravasation of trastuzumab emtansine during intravenous injection may produce local pain**.** Exceptionally, cases of severe tissue lesions and epidermal necrosis may occur. If extravasation occurs, the infusion should be terminated immediately and the patient should be examined regularly as necrosis may occur within days to weeks after infusion.

Sodium content in excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

4.4 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

In vitro metabolism studies in human liver microsomes suggest that DM1, a component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and, to a lesser extent, by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with trastuzumab emtansine should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medicinal product with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying trastuzumab emtansine treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives

of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and trastuzumab emtansine treatment cannot be delayed, patients should be closely monitored for adverse reactions.

4.5 Fertility, pregnancy, and lactation

Contraception in males and females

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.

Pregnancy

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 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 (see section 5.3).

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

Breast-feeding

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, women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment.

Fertility

No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine.

4.6 Effects on ability to drive and use machines.

Trastuzumab emtansine has minor influence on the ability to drive and use machines.

The significance of reported adverse reactions such as fatigue, headache, dizziness and blurred vision on the ability to drive or use machines is unknown. Patients experiencing infusion-related reactions

(flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia) should be advised not to drive and use machines until symptoms abate.

4.7 Undesirable effects

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Summary of the safety profile

The safety of trastuzumab emtansine has been evaluated in 2,611 breast cancer patients in clinical studies. In this patient population:

• the most common serious ADRs (> 0.5% of patients) were haemorrhage, pyrexia, thrombocytopenia, dyspnoea, abdominal pain, musculoskeletal pain, and vomiting.

• the most common adverse drug reactions (ADRs) (≥25%) with trastuzumab emtansine were nausea, fatigue, musculoskeletal pain, haemorrhage, headache, transaminases increased, thrombocytopenia, and peripheral neuropathy. The majority of ADRs reported were of Grade 1 or 2 severity.

• the most common National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3 ADRs (> 2%) were thrombocytopenia, increased transaminases, anaemia, neutropenia, fatigue and hypokalaemia.

Tabulated list of adverse reactions

The ADRs in 2,611 patients treated with trastuzumab emtansine are presented in Table 3. The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and SOC, adverse reactions are presented in order of decreasing seriousness. ADRs were reported using NCI-CTCAE for assessment of toxicity.

Table 3 Tabulated list of ADRs in patients treated with trastuzumab emtansine in clinical trials

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia, Anaemia	Neutropenia, Leucopoenia	
Immune system disorders		Drug hypersensitivity	
Metabolism and nutrition disorders		Hypokalaemia	

Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral, Headache	Dizziness, Dysgeusia, Memory impairment	
Eye disorders		Dry eye, Conjunctivitis, Vision blurred, Lacrimation increased	
Cardiac disorders		Left ventricular dysfunction	
Vascular disorders	Haemorrhage	Hypertension	
Respiratory, thoracic and mediastinal disorders	Epistaxis, Cough, Dyspnoea		Pneumonitis (ILD)
Gastrointestinal disorders	Stomatitis, Diarrhoea, Vomiting, Nausea, Constipation, Dry mouth, Abdominal pain	Dyspepsia, Gingival bleeding	
Hepatobiliary disorders	Transaminases increased	Blood alkaline phosphatase increased, Blood bilirubin increased	Hepatotoxicity, Hepatic failure, Nodular regenerative hyperplasia, Portal hypertension
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia, Nail disorder, Palmar-plantar erythrodysaesthesia syndrome, Urticaria	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Arthralgia, Myalgia		
General disorders and administration site conditions	Fatigue, Pyrexia, Asthenia	Peripheral oedema, Chills	Injection site extravasation
Injury, poisoning and procedural complications		Infusion-related reactions	Radiation pneumonitis

Table 3 shows pooled data from the overall treatment period in the MBC studies (N= 1871; median number of cycles of trastuzumab emtansine was 10) and in KATHERINE (N=740; median number of cycles was 14).

Description of selected adverse reactions

Thrombocytopenia

Thrombocytopenia or decreased platelet counts were reported in 24.9% of patients in MBC clinical studies with trastuzumab emtansine and was the most common adverse reaction leading to treatment discontinuation (2.6%). Thrombocytopenia was reported in 28.5% of patients in EBC clinical studies with trastuzumab emtansine and was the most common reported adverse reaction for all grades and grades ≥ 3, as well as the most common adverse reaction leading to treatment discontinuation (4.2%), dose interruptions, and dose reductions. 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. Independent of race, the incidence of Grade 3 or 4 events (< 50,000/mm^3) was 8.7% in patients with MBC treated with trastuzumab emtansine and 5.7% in

patients with EBC. For dose modifications for thrombocytopenia, see sections 4.2 and 4.4.

Haemorrhage

Haemorrhagic events were reported in 34.8% of patients in MBC clinical trials with trastuzumab emtansine and the incidence of severe haemorrhagic events (Grade ≥3) occurred in 2.2%. Haemorrhagic events were reported in 29% of patients with EBC and the incidence of severe haemorrhagic events (Grade ≥3) was 0.4%, including one Grade 5 event. In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors. Cases of bleeding events with a fatal outcome have been observed in both MBC and EBC.

Transaminases increased (AST/ALT)

Increase in serum transaminases (Grade 1-4) has been observed during treatment with trastuzumab emtansine in clinical studies (see section 4.4). Transaminase elevations were generally transient. A cumulative effect of trastuzumab emtansine on transaminases has been observed, and generally recovered when treatment was discontinued. Increased transaminases were reported in 24.2% of patients in MBC clinical studies. Grade 3 or 4 increased AST and ALT were reported in 4.2% and 2.7% of patients with MBC respectively and usually occurred in the early treatment cycles (1-6). Increased transaminases were reported in 32.4% of patients with EBC. Grade 3 and 4 increased transaminases were reported in 1.5% of patients with EBC. In general, the Grade ≥ 3 hepatic events were not associated with poor clinical outcome; subsequent follow-up values tended to show improvement to ranges allowing the patient to remain on study and continue to receive study treatment at the same or reduced dose. No relationship was observed between trastuzumab emtansine exposure (AUC), trastuzumab emtansine maximum serum concentration (C_{max}), total trastuzumab exposure (AUC), or C_{max} of DM1 and increases in transaminase. For dose modifications in the event of increased transaminases, see sections 4.2 and 4.4.

Left ventricular dysfunction

Left ventricular dysfunction was reported in 2.2% of patients in MBC clinical studies with trastuzumab emtansine. The majority of events were asymptomatic Grade 1 or 2 decrease in LVEF. Grade 3 or 4 events were reported in 0.4% of patients with MBC. In an observational study (BO39807), approximately 22% (7 out of 32) of MBC patients initiating trastuzumab emtansine with LVEF of 40-49% at baseline, experienced a LVEF drop of >10% from baseline and/or CHF; most of these patients had other cardiovascular risk factors. Left ventricular dysfunction occurred in 3.0% of patients with EBC, with Grade 3 or 4 in 0.5% of patients. For dose modifications in the event of LVEF decrease, see Table 2 in section 4.2 and section 4.4.

Peripheral neuropathy

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of trastuzumab emtansine. In patients with MBC,

the overall incidence of peripheral neuropathy was 29.0% and 8.6% for Grade ≥ 2. In patients with EBC, the overall incidence was 32.3% and 10.3% for Grade ≥ 2.

Infusion-related reactions

Infusion-related reactions are characterised by one or more of the following symptoms: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia. Infusion-related reactions were reported in 4.0% of patients in MBC clinical studies with trastuzumab emtansine, with six Grade 3 and no Grade 4 events reported. Infusion-related reactions were reported in 1.6% of patients with EBC, with no Grade 3 or 4 events reported. Infusion-related reactions resolved over the course of several hours to a day after the infusion was terminated. No dose relationship was observed in clinical studies. For dose modifications in the event of infusion-related reactions, see sections 4.2 and 4.4.

Hypersensitivity reactions

Hypersensitivity was reported in 2.6% of patients in MBC clinical studies with trastuzumab emtansine, with one Grade 3 and one Grade 4 events reported. Hypersensitivity was reported in 2.7% of patients with EBC, with Grade 3 or 4 in 0.4% of patients. Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. For dose modifications in the event of hypersensitivity reactions, see sections 4.2 and 4.4.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to trastuzumab emtansine. A total of 1243 patients from seven clinical studies were tested at multiple time points for anti-drug antibody (ADA) responses to trastuzumab emtansine. Following trastuzumab emtansine dosing, 5.1% (63/1243) of patients tested positive for anti-trastuzumab emtansine antibodies at one or more post-dose time points. In the Phase I and Phase II studies, 6.4% (24/376) of patients tested positive for anti- trastuzumab emtansine antibodies. In the EMILIA study (TDM4370g/BO21977), 5.2% (24/466) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 13 were also positive for neutralizing antibodies. In the KATHERINE (BO27938) study, 3.7% (15/401) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 5 were also positive for neutralizing antibodies. Due to the low incidence of ADA, conclusions cannot be made on the impact of anti- trastuzumab emtansine antibodies on the pharmacokinetics, safety, and efficacy of trastuzumab emtansine.

Extravasation

Reactions secondary to extravasation have been observed in clinical studies with trastuzumab emtansine. These reactions were usually mild or moderate and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. In the post-marketing setting, cases of epidermal injury or necrosis following extravasation have been exceptionally observed within days

to weeks after infusion. Specific treatment for trastuzumab emtansine extravasation is unknown at this time (see section 4.4).

Laboratory abnormalities

Tables 4 and 5 displays laboratory abnormalities observed in patients treated with trastuzumab emtansine in clinical study TDM4370g/BO21977/EMILIA and study BO27938/KATHERINE.

Table 4 Laboratory abnormalities observed in patients treated with trastuzumab emtansine in study TDM4370g/BO21977/EMILIA

	Trastuzumab emtansine (N=490)		
Parameter	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hepatic			
Increased bilirubin	21	< 1	0
Increased AST	98	8	< 1
Increased ALT	82	5	< 1
Haematologic			
Decreased platelet count	85	14	3
Decreased haemoglobin	63	5	1
Decreased neutrophils	41	4	< 1
Potassium			
Decreased potassium	35	3	< 1

Table 5 Laboratory abnormalities observed in patients treated with trastuzumab emtansine in study BO27938/KATHERINE

	Trastuzumab emtansine (N=740)		
Parameter	**All Grade %**	**Grade 3 (%)**	**Grade 4 (%)**
Hepatic			
Increased bilirubin	11	0	0
Increased AST	79	<1	0
Increased ALT	55	<1	0
Haematologic			
Decreased platelet count	51	4	2
Decreased haemoglobin	31	1	0
Decreased neutrophils	24	1	0
Potassium			
Decreased potassium	26	2	<1

4.8 Overdose

There is no known antidote for trastuzumab emtansine overdose. In case of overdose, the patient should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted. Cases of overdose have been reported with trastuzumab emtansine treatment, most associated with thrombocytopenia, and there was one death. In the fatal case, the patient incorrectly received trastuzumab emtansine 6 mg/kg and died approximately 3 weeks

following the overdose; a causal relationship to trastuzumab emtansine was not established.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, HER2 inhibitors, ATC code: L01FD03

Mechanism of action

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.

Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

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 Fcγ 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.

Clinical efficacy

Early Breast Cancer

BO27938 (KATHERINE)

BO27938 (KATHERINE) was a randomized, multicenter, open-label trial of 1486 patients with HER2-positive, early breast cancer with residual invasive tumor (patients who had not achieved pathological complete response (pCR))

in the breast and/or axillary lymph nodes following completion of preoperative systemic therapy that included chemotherapy and HER2-targeted therapy. Patients may have received more than one HER2-targeted therapy. Patients received radiotherapy and/or hormonal therapy concurrent with study treatment as per local guidelines. Breast tumor samples were required to show HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥ 2.0 determined at a central laboratory. Patients were randomized (1:1) to receive trastuzumab or trastuzumab emtansine. Randomization was stratified by clinical stage at presentation (operable vs. inoperable), hormone receptor status, preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluated after preoperative therapy.

Trastuzumab emtansine was given intravenously at 3.6 mg/kg on Day 1 of a 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg on Day 1 of a 21-day cycle. Patients were treated with trastuzumab emtansine or trastuzumab for a total of 14 cycles unless there was recurrence of disease, withdrawal of consent, or unacceptable toxicity, whichever occurred first. Patients who discontinued trastuzumab emtansine could complete the duration of their intended study treatment up to 14 cycles of HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion.

The primary efficacy endpoint of the study was Invasive Disease-Free Survival (IDFS). IDFS was defined as the time from the date of randomization to first occurrence of ipsilateral invasive breast tumor recurrence, ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Additional endpoints included IDFS including second primary non-breast cancer, disease-free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI).

Patient demographics and baseline tumor characteristics were balanced between treatment arms. The median age was approximately 49 years (range 23-80 years), 72.8% were White, 8.7% were Asian and 2.7% were Black or African American. All but 5 patients were women; 3 men were included in the trastuzumab arm and 2 in the trastuzumab emtansine arm. 22.5 percent of patients were enrolled in North America, 54.2% in Europe and 23.3% throughout the rest of the world. Tumor prognostic characteristics including hormone receptor status (positive: 72.3%, negative: 27.7%), clinical stage at presentation (inoperable: 25.3%, operable: 74.8%) and pathological nodal status after preoperative therapy (node positive: 46.4%, node negative or not evaluated: 53.6%) were similar in the study arms.

The majority of the patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen.19.5% percent of patients received another HER2-targeted agent in addition to trastuzumab as a component of neoadjuvant therapy; 93.8% of these patients received pertuzumab. All of the patients had received taxanes as part of neoadjuvant chemotherapy.

A clinically meaningful and statistically significant improvement in IDFS was observed in patients who received trastuzumab emtansine compared with trastuzumab (HR = 0.50, 95% CI [0.39, 0.64], p <0.0001. Estimates of 3 years IDFS rates were 88.3% vs. 77.0% in trastuzumab emtansine vs. trastuzumab arms, respectively. See Table 6 and Figure 1.

Table 6 Summary of efficacy from study BO27938 (KATHERINE)

	Trastuzumab N = 743	**Trastuzumab Emtansine N = 743**
Primary Endpoint		
Invasive Disease-Free Survival (IDFS)		
Number (%) of patients with event	165 (22.2%)	91 (12.2%)
HR [95% CI]	0.50 [0.39, 0.64]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2],% [95% CI]	77.02 [73.78, 80.26]	88.27 [85.81, 90.72]
Secondary Endpoints[1]		
Overall Survival (OS)		
Number (%) of patients with event	56 (7.5%)	42 (5.7%)
HR [95% CI]	0.70 [0.47, 1.05]	
p-value (Log-Rank test, unstratified)	0.0848	
5 year survival rate[2],% [95% CI]	86.8 [80.95, 92.63]	92.1 [89.44, 94.74]
IDFS including second primary non-breast cancer[3]		
Number (%) of patients with event	167 (22.5%)	95 (12.8%)
HR [95% CI]	0.51 [0.40, 0.66]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2],% [95% CI]	76.9 [73.65, 80.14]	87.7 [85.18, 90.18]
Disease-Free Survival (DFS)[3]		
Number (%) of patients with event	167 (22.5%)	98 (13.2%)
HR [95% CI]	0.53 [0.41, 0.68]	
p-value (Log-Rank test, unstratified)	<0.0001	
3 year event-free rate[2],% [95% CI]	76.9 [73.65, 80.14]	87.41 [84.88, 89.93]
Distant recurrence-free interval (DRFI)[3]		
Number (%) of patients with event	121 (16.3%)	78 (10.5%)
HR [95% CI]	0.60 [0.45, 0.79]	
p-value (Log-Rank test, unstratified)	0.0003	
3 year event-free rate[2],% [95% CI]	83.0 [80.10, 85.92]	89.7 [87.37, 92.01]

Data from first interim analysis 25 July 2018

Key to abbreviations (Table6): HR: Hazard Ratio; CI: Confidence Intervals,

1. Hierarchical testing applied for IDFS and OS

2. 3-year event-free rate and 5-year survival rate derived from Kaplan-Meier estimates

3. These secondary endpoints were not adjusted for multiplicity

Figure 1 Kaplan-Meier Curve of Invasive Disease-Free Survival in KATHERINE

In KATHERINE, consistent treatment benefit of trastuzumab emtansine for IDFS was seen in all the pre-specified subgroups evaluated, supporting the overall result.

Metastatic Breast Cancer

TDM4370g/BO21977(EMILIA)

A Phase III, randomised, multicentre, international, open-label clinical study was conducted in patients with HER2-positive unresectable locally advanced breast cancer (LABC) or MBC who had received prior taxane and trastuzumab-based therapy, including patients who received prior therapy with trastuzumab and a taxane in the adjuvant setting and who relapsed during or within six months of completing adjuvant therapy. Only patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 were eligible. Prior to enrolment, breast tumour samples were required to be centrally confirmed for HER2-positive status defined as a score of 3 + by IHC or gene amplification by ISH. Baseline patient and tumour characteristics were well balanced between treatment groups. Patients with treated brain metastases were eligible for enrollment if they did not require therapy to control symptoms. For patients randomised to trastuzumab emtansine, the median age was 53 years, most patients were female (99.8%), the majority were Caucasian (72%), and 57% had oestrogen-receptor and/or progesterone-receptor positive disease. The study compared the safety and efficacy of trastuzumab emtansine with that of lapatinib plus capecitabine. A total of 991 patients were randomised to trastuzumab emtansine or lapatinib plus capecitabine as follows:

• Trastuzumab emtansine arm: trastuzumab emtansine 3.6 mg/kg intravenously over 30-90 minutes on Day 1 of a 21-day cycle

• Control arm (lapatinib plus capecitabine): lapatinib 1250 mg/day orally once per day of a 21-day cycle plus capecitabine 1000 mg/m^2 orally twice daily on Days 1-14 of a 21-day cycle

The co-primary efficacy endpoints of the study were progression-free survival (PFS) as assessed by an independent review committee (IRC) and overall survival (OS) (see Table 7 and Figures 2 to 3).

Time to symptom progression, as defined by a 5-point decrease in the score derived from the Trials Outcome Index-Breast (TOI-B) subscale of the Functional Assessment of Cancer Therapy-Breast Quality of Life (FACT-B QoL) questionnaire was also assessed during the clinical study. A change of 5 points in the TOI-B is considered clinically significant. Kadcyla delayed patient-reported time to symptom progression for 7.1 months compared with 4.6 months for the control arm (Hazard Ratio 0.796 (0.667, 0.951); p-value 0.0121). The data are from an open-label study and no firm conclusions can be drawn.

Table 7 Summary of efficacy from study TDM4370g/BO21977 (EMILIA)

	Lapatinib + Capecitabine n = 496	**Trastuzumab emtansine n = 495**
Primary endpoints		
IRC-assessed progression-free survival (PFS)		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard ratio (stratified*)	0.650	
95% CI for Hazard ratio	(0.549, 0.771)	
p-value (Log-rank test, stratified*)	< 0.0001	
Overall Survival (OS)**		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard ratio (stratified*)	0.682	
95% CI for Hazard ratio	(0.548, 0.849)	
p-value (Log-rank test*)	0.0006	
Key secondary endpoints		
Investigator-assessed PFS		
Number (%) of patients with event	335 (67.5%)	287 (58.0%)
Median duration of PFS (months)	5.8	9.4
Hazard ratio (95% CI)	0.658 (0.560, 0.774)	
p-value (Log-rank test*)	<0.0001	
Objective response rate (ORR)		
Patients with measurable disease	389	397
Number of patients with OR (%)	120 (30.8%)	173 (43.6%)
Difference (95% CI)	12.7% (6.0, 19.4)	
p-value (Mantel-Haenszel chi-squared test*)	0.0002	
Duration of objective response (months)		
Number of patients with OR	120	173
Median 95% CI	6.5 (5.5, 7.2)	12.6 (8.4, 20.8)

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; OR: objective response; IRC: independent review committee; HR: hazard ratios; CI: confidence interval

* Stratified by: world region (United States, Western Europe, other), number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0-1 *vs.* > 1), and visceral *vs.* non-visceral disease.

** The interim analysis for OS was conducted when 331 events were observed. Since the efficacy boundary was crossed at this analysis, this is considered the definitive analysis.

A treatment benefit was seen in the subgroup of patients who had relapsed within 6 months of completing adjuvant treatment and had not received any prior systemic anti-cancer therapy in the metastatic setting (n=118); hazard ratios for PFS and OS were 0.51 (95% CI: 0.30, 0.85) and 0.61 (95% CI: 0.32,

1.16), respectively. The median PFS and OS for the trastuzumab emtansine group were 10.8 months and not reached, respectively, compared with 5.7 months and 27.9 months, respectively, for the lapatinib plus capecitabine group.

Figure 2 Kaplan-Meier curve of IRC-assessed progression-free survival

Figure 3 Kaplan-Meier curve of overall survival

In study TDM4370g/BO21977, consistent treatment benefit of trastuzumab emtansine was seen in the majority of pre-specified subgroups evaluated, supporting the robustness of the overall result. In the subgroup of patients with hormone receptor-negative disease (n=426), the hazard ratios for PFS and OS were 0.56 (95% CI: 0.44, 0.72) and 0.75 (95% CI: 0.54, 1.03), respectively. In the subgroup of patients with hormone receptor-positive disease (n=545), the hazard ratios for PFS and OS were 0.72 (95% CI: 0.58, 0.91) and 0.62 (95% CI: 0.46, 0.85), respectively.

In the subgroup of patients with non-measurable disease (n=205), based on IRC assessments, the hazard ratios for PFS and OS were 0.91 (95% CI: 0.59, 1.42) and 0.96 (95% CI: 0.54, 1.68), respectively. In patients ≥ 65 years old (n=138 across both treatment arms) the hazard ratios for progression-free survival (PFS) and Overall Survival (OS) were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. In patients 65 to 74 years old (n=113), based on IRC assessments, the hazard ratios for PFS and OS were 0.88 (95% CI: 0.53, 1.45) and 0.74 (95% CI: 0.37, 1.47), respectively. For patients 75 years or above, based on IRC assessments, the hazard ratios for PFS and OS were 3.51 (95% CI: 1.22, 10.13) and 3.45 (95% CI: 0.94, 12.65), respectively. The subgroup of patients 75 years or above did not demonstrate a benefit for PFS or OS, but was too small (n=25) to draw any definitive conclusions.

In the descriptive follow-up overall survival analysis, the hazard ratio was 0.75 (95% CI 0.64, 0.88). The median duration of overall survival was 29.9 months in the trastuzumab emtansine arm compared with 25.9 months in the lapatinib plus capecitabine arm. At the time of the descriptive follow-up overall survival analysis, a total of 27.4% of the patients had crossed over from the lapatinib plus capecitabine arm to the trastuzumab emtansine arm. In a sensitivity analysis censoring patients at the time of cross-over, the hazard ratio was 0.69 (95% CI 0.59, 0.82). The results of this descriptive follow-up analysis are consistent with the confirmatory OS analysis.

TDM4450g

A randomised, multicentre, open-label phase II study evaluated the effects of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with HER2-positive MBC who had not received prior chemotherapy for metastatic disease. Patients were randomised to receive trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks (n = 67) or trastuzumab 8 mg/kg

intravenous loading dose followed by 6 mg/kg intravenously every 3 weeks plus docetaxel 75-100 mg/m^2 intravenously every 3 weeks (n = 70).

The primary endpoint was investigator assessed Progression-Free Survival (PFS). The median PFS was 9.2 months in the trastuzumab plus docetaxel arm and 14.2 months in the trastuzumab emtansine arm (hazard ratio, 0.59; p = 0.035), with a median follow-up of approximately 14 months in both arms. The objective response rate (ORR) was 58.0% with trastuzumab plus docetaxel and 64.2% with trastuzumab emtansine. The median duration of response was not reached with trastuzumab emtansine *vs.* 9.5 months in the control arm.

TDM4374g

A Phase II, single-arm, open-label study evaluated the effects of trastuzumab emtansine in patients with HER2-positive incurable, LABC or MBC. All patients were previously treated with HER2-directed therapies (trastuzumab and lapatinib), and chemotherapy (anthracycline, taxane, and capecitabine) in the neoadjuvant, adjuvant, locally advanced, or metastatic setting. The median number of anti-cancer agents that patients had received in any setting was 8.5 (range, 5-19) and in the metastatic setting was 7.0 (range, 3-17), including all agents intended for the treatment of breast cancer.

Patients (n = 110) received 3.6 mg/kg of trastuzumab emtansine intravenously every 3 weeks until disease progression or unacceptable toxicity.

The key efficacy analyses were ORR based on independent radiologic review and duration of objective response. The ORR was 32.7% (95% CI: 24.1, 42.1), n = 36 responders, by both IRC and investigator review. The median duration of response by IRC was not reached (95% CI, 4.6 months to not estimable).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with trastuzumab emtansine in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

Pharmacokinetic properties

The population pharmacokinetic analysis suggested no difference in trastuzumab emtansine exposure based on disease status (adjuvant vs. metastatic setting).

Absorption

Trastuzumab emtansine is administered intravenously. There have been no studies performed with other routes of administration.

Distribution

Patients in Study TDM4370g/BO21977 and Study BO29738 who received 3.6 mg/kg of trastuzumab emtansine intravenously every 3 weeks had a mean Cycle 1 maximum serum concentration (C_{max}) of trastuzumab emtansine of 83.4 (± 16.5) µg/mL and 72.6 (± 24.3) µg/mL, respectively. Based on

population PK analysis, following intravenous administration, the central volume of distribution of trastuzumab emtansine was (3.13 L) and approximated that of plasma volume.

Biotransformation (trastuzumab emtansine and DM1)

Trastuzumab emtansine is expected to undergo deconjugation and catabolism by means of proteolysis in cellular lysosomes.

In vitro metabolism studies in human liver microsomes suggest that DM1, a small molecule component of trastuzumab emtansine, is metabolised mainly by CYP3A4 and to a lesser extent by CYP3A5. DM1 did not inhibit major CYP450 enzymes in vitro. In human plasma, trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels. *In vitro,* DM1 was a substrate of P-glycoprotein (P-gp).

Elimination

Based on population pharmacokinetic (PK) analysis, following intravenous administration of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer, the clearance of trastuzumab emtansine was 0.68 L/day and the elimination half-life ($t_{1/2}$) was approximately 4 days. No accumulation of trastuzumab emtansine was observed after repeated dosing of intravenous infusion every 3 weeks.

Based on population PK analysis, body weight, albumin, sum of longest diameter of target lesions by Response Evaluation Criteria In Solid Tumors (RECIST), HER2 shed extracellular domain (ECD), baseline trastuzumab concentrations, and aspartate aminotransferase (AST) were identified as statistically significant covariates for trastuzumab emtansine PK parameters. However, the magnitude of effect of these covariates on trastuzumab emtansine exposure suggests that these covariates are unlikely to have any clinically meaningful effect on trastuzumab emtansine exposure. In addition, exploratory analysis showed that the impact of covariates (i.e., renal function, race and age) on the pharmacokinetics of total trastuzumab and DM1 was limited and was not clinically relevant. In nonclinical studies, trastuzumab emtansine catabolites including DM1, Lys-MCC-DM1, and MCC-DM1 are mainly excreted in the bile with minimal elimination in urine.

Linearity/non-linearity

Trastuzumab emtansine when administered intravenously every 3 weeks exhibited linear PK across doses ranging from 2.4 to 4.8 mg/kg; patients who received doses less than or equal to 1.2 mg/kg had faster clearance.

Elderly patients

The population PK analysis showed that age did not affect the PK of trastuzumab emtansine. No significant difference was observed in the PK of trastuzumab emtansine among patients < 65 years (n = 577), patients between 65-75 years (n = 78) and patients > 75 years (n = 16).

Renal impairment

No formal PK study has been conducted in patients with renal impairment. The population PK analysis showed that creatinine clearance does not affect the PK of trastuzumab emtansine. Pharmacokinetics of trastuzumab emtansine in patients with mild (creatinine clearance CLcr 60 to 89 mL/min, n = 254) or moderate (CLcr 30 to 59 mL/min, n = 53) renal impairment were similar to those in patients with normal renal function (CLcr ≥ 90 mL/min, n = 361). Pharmacokinetic data in patients with severe renal impairment (CLcr 15 to 29 mL/min) are limited (n = 1), therefore no dosage recommendations can be made.

Hepatic impairment

The liver is a primary organ for eliminating DM1 and DM1-containing catabolites. The pharmacokinetics of trastuzumab emtansine and DM1-containing catabolites were evaluated after the administration of 3.6 mg/kg of trastuzumab emtansine to metastatic HER2+ breast cancer patients with normal hepatic function (n=10), mild (Child-Pugh A; n=10) and moderate (Child-Pugh B; n=8) hepatic impairment.

- Plasma concentrations of DM1 and DM1-containing catabolites (Lys-MCC-DM1 and MCC-DM1) were low and comparable between patients with and without hepatic impairment.

- Systemic exposures (AUC) of trastuzumab emtansine at Cycle 1 in patients with mild and moderate hepatic impairment were approximately 38% and 67% lower than that of patients with normal hepatic function, respectively. Trastuzumab emtansine exposure (AUC) at Cycle 3 after repeated dosing in patients with mild or moderate hepatic dysfunction was within the range observed in patients with normal hepatic function.

No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe hepatic impairment (Child-Pugh class C).

Other special populations

The population PK analysis showed that race did not appear to influence the PK of trastuzumab emtansine. Because most of the patients in trastuzumab emtansine clinical studies were females, the effect of gender on the PK of trastuzumab emtansine was not formally evaluated.

5.2 Preclinical safety data

Animal toxicology and/or pharmacology

Administration of trastuzumab emtansine was well tolerated in rats and monkeys at doses up to 20 and 10 mg/kg, respectively, corresponding to 2040 µg DM1/m^2 in both species, which is approximately equivalent to the clinical dose of trastuzumab emtansine in patients. In the GLP toxicity studies, with

the exception of irreversible peripheral axonal toxicity (observed only in monkeys at ≥ 10 mg/kg) and reproductive organ toxicity (observed only in rats at 60 mg/kg), partially or completely reversible dose dependent toxicities were identified in both animal models. Principal toxicities included liver (liver enzyme elevations) at ≥ 20 mg/kg and ≥ 10 mg/kg, bone marrow (reduced platelet and white blood cell count)/hematologic at ≥ 20 mg/kg and ≥ 10 mg/kg, and lymphoid organs at ≥ 20 mg/kg and ≥ 3 mg/kg, in rat and monkey, respectively.

Mutagenicity

DM1 was aneugenic or clastogenic in an *in vivo* single-dose rat bone marrow micronucleus assay at exposures that were comparable to mean maximum concentrations of DM1 measured in humans administered trastuzumab emtansine. DM1 was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Impairment of fertility and teratogenicity

No fertility studies in animals have been performed to evaluate the effect of trastuzumab emtansine. However, based on results from general animal toxicity studies, adverse effects on fertility can be expected.

Dedicated embryo-foetal development studies have not been conducted in animals with trastuzumab emtansine. Developmental toxicity of trastuzumab has been identified in the clinical setting although it was not predicted in the non-clinical program. In addition, developmental toxicity of maytansine has been identified in non-clinical studies which suggests that DM1, the microtubule-inhibiting cytotoxic maytansinoid component of trastuzumab emtansine, will be similarly teratogenic and potentially embryotoxic.

6 Pharmaceutical particulars

6.2 List of excipients

Succinic acid

Sodium hydroxide

Sucrose

Polysorbate 20

6.3 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned in section 6.6.

(5%) solution should not be used for reconstitution or dilution since it causes aggregation of the protein.

6.4 Shelf life

Unopened vial

4 years.

Reconstituted solution

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 24 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, the reconstituted vials can be stored for up to 24 hours at 2°C to 8°C, provided it was reconstituted under controlled and validated aseptic conditions, and must be discarded thereafter.

Diluted solution

The reconstituted Kadcyla solution diluted in infusion bags containing sodium chloride 9 mg/mL (0.9%) solution for infusion, or sodium chloride 4.5 mg/mL (0.45%) solution for infusion, is stable for up to 24 hours at 2°C to 8°C, provided it was prepared under controlled and validated aseptic conditions. Particulates may be observed on storage if diluted in 0.9% sodium chloride (see section 6.6).

6.5 Special precautions for storage:

Store in a refrigerator (2°C – 8°C).
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.6 Nature and contents of container

Kadcyla 100 mg powder for concentrate for solution for infusion
Kadcyla is provided in 15 mL (100 mg) Type 1 glass vial closed with a grey-butyl rubber stopper coated with fluoro-resin laminate, and sealed with an aluminium seal with a white plastic flip-off cap.
Pack of 1 vial.

Kadcyla 160 mg powder for concentrate for solution for infusion
Kadcyla is provided in 20 mL (160 mg) Type 1 glass vial closed with a grey-butyl rubber stopper coated with fluoro resin laminate, and sealed with an aluminium seal with a purple plastic flip-off cap.
Pack of 1 vial.

6.7 Special precautions for disposal and other handling:

Appropriate aseptic technique should be used. Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used. The reconstituted Kadcyla solution should be diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin infusion bags.

The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required for the infusion when the concentrate for infusion is diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion.

In order to prevent medicinal product errors it is important to check the vial labels to ensure that the medicinal product being prepared is Kadcyla (trastuzumab emtansine) and not another trastuzumab-containing product (e.g. trastuzumab or trastuzumab deruxtecan).

Instructions for reconstitution

• 100 mg trastuzumab emtansine vial: Using a sterile syringe, slowly inject 5 mL of sterile water for injection into the vial.
• 160 mg trastuzumab emtansine vial: Using a sterile syringe, slowly inject 8 mL of sterile water for injection into the vial.
• Swirl the vial gently until completely dissolved. Do not shake.

Reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. The reconstituted solution should be free of visible particulates, clear to slightly opalescent. The colour of the reconstituted solution should be colourless to pale brown. Do not use if the reconstituted solution contains visible particulates, or is cloudy or discoloured.

Instructions for dilution

Determine the volume of the reconstituted solution required based on a dose of 3.6 mg trastuzumab emtansine/kg body weight (see section 4.2):

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of sodium chloride 4.5 mg/mL (0.45%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion. Glucose (5%) solution should not be used (see section 6.2). Sodium chloride 4.5 mg/mL (0.45%) solution for infusion may be used without a polyethersulfone (PES) 0.20 or 0.22-µm in-line filter. If sodium chloride 9 mg/mL (0.9%) solution for infusion is used for infusion, a 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required. Once the infusion is prepared it should be administered immediately. Do not freeze or shake the infusion during storage.

Disposal

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Roche Products Limited

6 Falcon Way, Shire Park

Welwyn Garden City

AL7 1TW

United Kingdom

Manufacturing site address:
Roche Pharma AG Emil-Barell-Strasse
1 D-79639 Grenzach-Wyhlen
Germany

8 Marketing authorization number
CTD9715

9 Date of first registration
22/03/ 2022

10. Date of revision of the text:
29/03/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable