12.5 VI.2 ELEMENTS FOR A PUBLIC SUMMARY

12.5.1 VI.2.1 Overview of disease epidemiology

Breast cancer affects 10–12% of women globally, and is more common among older people. Some cancer cells have proteins on their cell surface called HER2. These proteins can receive chemical signals that stimulate growth. Cancers with such cell surface proteins are called HER2-positive. About 20% of breast cancers are HER2-positive.

About 264,000 new cases of HER2-positive breast cancer occur each year globally. In about 5% of these cases, the cancer is found to have metastasized (spread to distant parts of the patient's body). Cancer that has spread to adjacent organs of the patient's body is called "locally advanced." HER2-positive breast cancers can be more aggressive than other breast cancers.

There is no single treatment for HER2-positive metastatic breast cancer. Guidelines for treatment recommend early administration of anti-HER2 medicine to patients with this disease. Three other HER2-specific medicines are approved in the EU: trastuzumab (Herceptin), pertuzumab (Perjeta), and lapatinib (Tyverb).

12.5.2 VI.2.2 Summary of treatment benefits

The primary study to support the use of trastuzumab emtansine (Kadcyla™) in treatment of HER2-positive metastatic breast cancer was called the EMILIA study (also called TDM TDM4370g/BO21977). This study included 991 patients who had incurable HER2-positive locally advanced breast cancer or metastatic breast cancer that could not be treated with surgery, and who had received prior treatment with trastuzumab and a taxane chemotherapy drug. The patients were randomly assigned to treatment with either Kadcyla™ (495 patients) or with a chemotherapy regimen that included the drugs lapatinib and capecitabine (496 patients).

The EMILIA study measured how long it took for the cancer to begin spreading in half of the patients of each group (called progression free survival). Among Kadcyla-treated patients, this time was 9.6 months, while among the lapatinib plus capecitabine-treated patients, it was 6.4 months. After a later analysis, overall survival was also significantly improved in patients receiving trastuzumab emtansine, with a 31.8% reduction in the risk of death in patients who received trastuzumab emtansine compared with lapatinib and capecitabine. The median duration of survival was 25.1 months in patients treated with lapatinib plus capecitabine, compared with 30.9 months in patients treated with trastuzumab emtansine. Study TDM4370g/BO21977 is still ongoing.

12.5.3 VI.2.3 Unknowns relating to treatment benefits

In EMILIA, treatment benefit was seen with Kadcyla, regardless of patient age, race, severity of disease, or prior treatment. In patients 75 or older, lapatinib plus capecitabine seemed to provide more benefit than Kadcyla, but no firm conclusions could be drawn because of the low number of such patients.

12.5.4 VI.2.4 Summary of safety concerns

Table 91 Summary of Safety Concerns

Risk	What is known	Preventability
Important identified risk		
Lung Inflammation (ILD/ARDS)	ILD/ARDS is an inflammation of lung tissue causing breathing problems such as shortness of breath (either at rest or while performing normal activity), coughing, or coughing spells with a dry cough. Risk factors for such inflammations include prior lung conditions, radiation therapy, or chemotherapy. About 1% of patients in the clinical studies experienced such events after treatment with Kadcyla™, and one patient died as a result of the event.	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. Doctors are warned in the Kadcyla™ prescribing information that serious lung problems may occur in patients taking Kadcyla™. Doctors are recommended to stop Kadcyla™ treatment in patients who have interstitial lung disease or pneumonitis.
Liver damage (hepatic toxicity)	This risk refers to liver problems affecting how well the liver works, caused by inflammation or injury to cells in the liver. Inflamed or injured liver cells may leak higher than normal amounts of certain substances (liver enzymes) into the bloodstream. This can be measured in blood tests of liver enzymes. In most cases, during Kadcyla™ treatment, liver enzyme levels increase mildly and for a short period of time and do not cause any symptoms. Rarely, severe liver damage may occur and symptoms may include jaundice (skin and whites of eyes get yellow). About 32% of patients experienced some degree of liver toxicity, and 0.8% experienced a life-threatening or fatal event. There are currently no reliable predictors of patients who may be susceptible to	There is no known method of preventing liver toxicity. However, the liver toxicity effects of Kadcyla™ may be reduced by either lowering the dose or delaying the dose. Doctors are warned in the Kadcyla™ label that liver problems may occur in patients taking Kadcyla™. They are advised to check patient blood tests for liver enzyme levels before starting Kadcyla™, and before each infusion. It is recommended that Kadcyla™ dose should be decreased, and treatment should be interrupted or completely stopped, if a patient's blood test results show that liver enzymes are too high.

Risk	What is known	Preventability
	hepatotoxicity to trastuzumab emtansine, although age and genetics are known risk factors	
Nodular growth of liver cells (nodular regenerative hyperplasia)	This condition is a liver abnormality that occurs rarely in patients receiving Kadcyla™ , leading to symptoms over time, such as a bloated sensation in the belly or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the esophagus or rectum. NRH may develop as a result of underlying autoimmune, inflammatory, or cancerous disease, or for no understood cause. The only reliable way to identify NRH is by direct examination of liver tissue, usually obtained by placing a needle through the skin of the abdomen and directly into the liver itself. Five patients have been confirmed to have NRH across all clinical studies of Kadcyla™ in any type of cancer.	There is no known method of preventing nodular regenerative hyperplasia. Doctors are advised that nodular regenerative hyperplasia should be considered in all patients with symptoms of increased blood pressure in the liver blood vessels, but with normal liver enzymes (transaminase levels) and no signs of final stage of liver disease (cirrhosis). Kadcyla™ must be discontinued upon diagnosis of nodular regenerative hyperplasia.
Heart muscle weakness (left ventricular dysfunction)	This risk refers to weakness of the heart muscle leading to problems with blood circulation. 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 one in 10 patients receiving Kadcyla™ may experience some degree of heart dysfunction. In clinical trials of	Doctors are warned in the Kadcyla™ label that heart muscle weakness may occur in patients taking Kadcyla™ . They are advised to have heart tests done on patients to check heart muscle strength before starting Kadcyla™ and at regular intervals during treatment. It is recommended that Kadcyla™ treatment should be interrupted or completely stopped if a heart test shows that the patient's heart is not functioning normally.

Risk	What is known	Preventability
	Kadcyla™ , 19 of 882 patients experienced such events (about 2.2%).	
Reaction to Kadcyla infusion (infusion related reaction)	Kadcyla™ can cause infusion-related reactions. The symptoms of these reactions may occur while Kadcyla™ is being given into the vein [an infusion] or later on the same day of drug administration. The symptoms of this reaction may include flushing, shivering, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of the face or tongue, or trouble swallowing.	Doctors are warned in the Kadcyla™ label that patients may have severe infusion- related reactions. The label also advises on the situations in which Kadcyla™ should be interrupted or stopped as a result of an allergic reaction.
Allergic reactions to Kadcyla	Kadcyla™ can cause allergic reactions. The symptoms of these reactions may occur while Kadcyla™ is being given into the vein [an infusion] or later on the same day of drug administration. The symptoms of this reaction may include flushing, shivering, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of the face or tongue, or trouble swallowing.	Doctors are warned in the Kadcyla™ label that patients may have severe allergic reactions. The label also advises on the situations in which Kadcyla™ should be interrupted or stopped as a result of an allergic reaction

Risk	What is known	Preventability
Decreased blood platelets (thrombocytopenia)	This risk refers to abnormally low levels of platelets in the blood. Platelets help blood to clot. Patients with thrombocytopenia may experience unexpected bleeding (for example bleeding from mucosal membranes, such as the mouth, or nose bleeds) or bleeding for longer than normal. Risk factors include radiation therapy and some forms of chemotherapy. About 31% of patients treated with Kadcyla™ developed an event of thrombocytopenia. Severe decreases in the number of platelets were not associated with higher grades of bleeding.	Doctors are warned in the Kadcyla™ label that patients' platelet levels may decrease. They are advised to obtain blood test results before each dose of Kadcyla™ . It is recommended that Kadcyla™ treatment should be decreased or interrupted if a patient's platelet counts decrease below a certain level and that treatment should not be resumed until the platelet counts improve.
Nerve damage to hands and feet (peripheral neuropathy)	Peripheral neuropathy is a form of nerve damage affecting the hands and feet. The nerve damage varies from mild tingling and altered sensation to irreversible disabling damage in the most severe cases. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy. Risk factors include chemotherapy. Two hundred forty one patients (about 27% of patients treated with Kadcyla™ in the clinical trial population) experienced a degree of peripheral neuropathy.	Doctors are advised in the Kadcyla™ label that treatment with Kadcyla™ should be temporarily discontinued or decreased in patients experiencing significant peripheral neuropathy until symptoms resolve or improved. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity

Table 92 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in pregnant women	There are no clinical studies with Kadcyla™ in pregnant women. Trastuzumab, which is a component of Kadcyla™ , can cause harm or death to a fetus. Animal studies of medicines like DM1, the other component of Kadcyla™ , show that such medicines can cause birth defects and/or the death of a fetus. Kadcyla™ should not be given to pregnant women. Women who become pregnant must immediately contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Kadcyla™ , close monitoring by a team of doctors is recommended.
Decreased fertility	Infertility is common in adult cancer survivors, and is associated with radiotherapy and chemotherapy. Amenorrhoea (ceasing of the female period) has been observed in one patient of 882 in the clinical trial population treated with Kadcyla™
Medication error	Six patients in clinical trials have been treated accidentally with the wrong medicine, either Kadcyla™ , HERCEPTIN or PERJETA. Commercial (non-trial) packaging for Kadcyla™ has been designed to be clearly different from that for HERCEPTIN (trastuzumab). Additionally, the two strengths of Kadcyla™ have different colored markings on the packaging to prevent situations in which patients may receive the wrong medicine or wrong dose by accident. Also, healthcare professionals receive materials to explain why it is important to ensure that the correct medicine is being given.

Table 93 Important missing information

Risk	What is known
Use in patients with existing liver damage (use in patients with hepatic impairment)	Serious liver and bile disorders have been observed in patients treated with Kadcyla™ in clinical studies. Safety and effectiveness of Kadcyla™ have not been studied in patients with pre-existing liver damage. No study of Kadcyla™ has been completed in patients with liver damage; however, study BO25499 is presently ongoing in patients with mild to moderate hepatic impairment (see Table 63 and Table 64 for details of this study).
Use in patients with severe kidney damage (use in patients with severe renal impairment)	Kadcyla™ has been studied in patients with mild or moderate kidney damage. Results from these studies showed that Kadcyla is removed from the body in patients with mild or moderate kidney damage in a similar way as in other patient populations. Therefore, no adjustment to the starting dose is necessary in these patients. There are no data with Kadcyla™ in patients with severe kidney damage, and therefore no dosage recommendations can be made for this subgroup.
Use in patients with heart failure (use in patients with left ventricular ejection fraction [LVEF] less than 50%)	Treatment with Kadcyla™ has not been studied in patients whose hearts do not function well.
Use in elderly patients aged 75 years or more	There are insufficient data to establish the safety and efficacy of Kadcyla™ in patients aged 75 years or more. No dose adjustment of Kadcyla™ is required in patients aged 65 years or more.
Use in pregnant women	There are no clinical studies with Kadcyla™ in pregnant women. Trastuzumab, which is a component of Kadcyla™ , can cause harm or death to a fetus. Animal studies of medicines like DM1, the other component of Kadcyla™ , show that such medicines can cause birth defects and/or the death of a fetus. Kadcyla™ should not be given to pregnant women. Women who become pregnant must immediately contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Kadcyla™ , close monitoring by a team of doctors is recommended. Women of childbearing potential should use effective contraception while receiving Kadcyla and for 6 months following the last dose of Kadcyla. Male patients or their female partners should also use effective contraception.
Use in breast-feeding women	It is not known whether Kadcyla™ is excreted in human milk. Women should discontinue breast-feeding before starting Kadcyla™ treatment because many medicinal products are known to appear in human milk and can cause serious problems in infants feeding on breast milk. Women may begin breast-feeding 6 months after finishing treatment.

Risk	What is known
Use in male patients	The vast majority of patients in clinical studies were women and it has not yet been possible to study whether Kadcyla™ is distributed and eliminated differently in the bodies of men and women.
Possibility of developing antibodies against Kadcyla™	Some patients in clinical trials have been shown to produce antibodies against Kadcyla™ . Such antibodies could potentially reduce the effectiveness of the treatment. However, insufficient information is currently available to allow a full understanding of this safety concern.
Treatment of patients whose cancer is not reliably tested as being HER2 positive	All patients in clinical trials have had HER2-positive cancer, identified by reliable tests. Treatment of other cancer patients has not been studied.
The frequency and type of heart problems that might occur in patients who have previously received treatment with Herceptin or Perjeta	It is known that this class of medicines may cause heart damage. Patients with heart problems were excluded from clinical trials for their safety. Information on heart side effects will be examined for patients who have previously received treatment with the related medicines Herceptin or Perjeta.

12.5.5 VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Kadcyla can be found on Kadcyla's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Kadcyla's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risk:

Medication errors

Healthcare professional educational material
Objective and rationale Healthcare professionals to understand the potential risk of medication error between Kadcyla (trastuzumab emtansine) and Herceptin® (trastuzumab), and are aware of the differences in the packaging, preparation and administration of the two products.
This HCP educational material shall consist of the following: • an explanatory brochure describing the differences between Kadcyla and Herceptin as well as the differences in their packaging, to help healthcare providers avoid medication errors between Kadycla and Herceptin; and • the SmPC.

12.5.6 VI.2.6 Planned post authorisation development plan

Table 94 List of studies in post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
BO25499 A Phase I, open-label, parallel group, pharmacokinetic study of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer and normal or reduced hepatic function	Primary To assess the PK profiles of trastuzumab emtansine and relevant catabolites, after an IV infusion of a 3.6 mg/kg dose given on a Q3W schedule in patients with HER2-postive MBC who have mild or moderate hepatic impairment. Secondary To investigate the safety and tolerability of trastuzumab emtansine in patients with mild or moderate hepatic impairment and compare these results with those in patients with normal hepatic function. Exploratory To investigate the efficacy of trastuzumab emtansine in HER2-postive MBC patients with mild or moderate hepatic impairment	• Hepatic toxicity • Nodular regenerative hyperplasia • Severe hepatotoxicity (severe DILI [Hy's Law cases]) • Use in patients with hepatic impairment	Study ongoing	• Primary analysis Q2 2014 • Primary CSR Q3 2014 • Follow-up analysis Q3 2014 • Follow-up CSR Q2 2015

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
TDM4874g/BO22857 A multicenter, multinational Phase II study to assess the clinical safety and feasibility of trastuzumab emtansine sequentially with anthracycline-based chemotherapy, as adjuvant or neoadjuvant therapy for patients with early stage HER2 – positive breast cancer	<u>Primary</u> • To evaluate the rate of prespecified cardiac events following initiation of trastuzumab emtansine treatment after completion of anthracycline-containing chemotherapy • To evaluate the safety profile of trastuzumab emtansine <u>Secondary</u> • To evaluate the safety and feasibility of trastuzumab emtansine when given with concurrent radiotherapy • To evaluate the feasibility of the planned duration (up to 17 cycles) of treatment with trastuzumab emtansine • To assess the pathological CR (pCR) rate in patients treated with trastuzumab emtansine -containing neoadjuvant therapy • To assess the efficacy of trastuzumab emtansine in the adjuvant setting in patients with HER-2/neu overexpressed/amplified EBC as measured by	Left ventricular dysfunction	Study ongoing	• Study end June 2013 • Final report May 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
	disease-free survival (DFS) rate at 12 months for all patients who were treated with protocol treatment (trastuzumab emtansine or AC/FEC) • To assess the efficacy of trastuzumab emtansine in the neoadjuvant setting as measured by DFS for all patients who are treated with protocol treatment (trastuzumab emtansine following AC/FEC) and receive surgery; in addition, DFS rate at 12 months will be calculated separately for patients who achieve a pCR and for patients who do not achieve a pCR. <u>Exploratory</u> • To explore biomarkers (proBNP [brain natriuretic peptide], BNP, troponin I) as prognostic markers for cardiac toxicity For patients receiving neoadjuvant treatment: (optional) • Correlation of trastuzumab emtansine efficacy (as			

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
	measured by pathological response) with biomarkers in tumor tissue			
H4621g (MotHER) An observational study of preganancy and pregnancy outcomes in women with breast cancer treated with Herceptin or Pejeta in combination with Herceptin during pregnancy or within 6 months prior to conception	Primary objectives are to describe adverse pregnancy complications such as • oligohydramnios; • pregnancy outcomes such as live births, stillbirths, and abortions; • fetal/infant outcomes such as major malformations, deformations, and disruptions; and • fetal or infant functional deficits among children of women with breast cancer following treatment with trastuzumab (either in combination with chemotherapies or as a single agent), pertuzumab plus trastuzumab, or trastuzumab emtansine during pregnancy or within 6 months prior to conception.	Fetal harm Use in pregnant women	Ongoing	• Protocol revision to include trastuzumab emtansine May 2013 • Annual interim reports May 2014 through May 2022 • Study end May 2023 • Final report May 2024
TDM4370g/BO21977 (EMILIA)	<u>Primary Objectives:</u> • To compare efficacy of T-DM1 versus capecitabine plus lapatinib in patients with HER2-positive, unresectable, locally	Safety in Elderly Patients	Ongoing	• Study end May 2014 • Clinical study report November

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
	advanced breast cancer or MBC as measured by PFS on the basis of an independent review of tumor assessments • To compare the efficacy of T-DM1 versus capecitabine plus lapatinib in patients with HER2-positive, unresectable, locally advanced breast cancer or MBC as measured by overall survival (OS) and to assess landmark (1-year and 2-year) survival rates within each treatment group, as appropriate • To assess safety of T-DM1 relative to the safety of capecitabine plus lapatinib			2014
TDM4788g/BO22589 (MARIANNE)	<u>Primary Objectives:</u> • To compare the efficacy of the combination of T-DM1 plus pertuzumab and/or T-DM1 plus pertuzumab-placebo versus trastuzumab plus docetaxel/paclitaxel in patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer patients, based on	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Ongoing	• Primary Analysis Q3 2014 • Primary Clinical Study Report (CSR) Q1 2015 • Study end April 2016 • Final report April 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
	tumor assessments reviewed by an independent review facility (IRF). • To compare the safety of the combination of T-DM1 plus pertuzumab and T-DM1 plus pertuzumab-placebo versus trastuzumab plus docetaxel or paclitaxel in the aforementioned patient population. • To provide a post-hoc analysis of safety data from patients who had previous exposure to trastuzumab.			
TDM4997g/BO25734 (TH3RESA)	To evaluate the efficacy of trastuzumab emtansine compared with treatment of physician's choice in patients with HER2-positive MBC who have progression after at least two regimens of HER2-directed therapy, including receipt of both trastuzumab and lapatinib, in the metastatic or unresectable locally advanced/recurrent setting, as measured by PFS and OS.	Left Ventricular Dysfunction Safety in Elderly Patients	Ongoing	• Primary Analysis June 2013 • Primary CSR July 2014 • Final Analysis August 2015 • Final CSR August 2016

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
MO28231 (KAMILLA)	Primary objective To evaluate the safety and tolerability of trastuzumab emtansine. Secondary Objectives • Progression Free Survival (PFS) • Overall survival (OS) • Overall response rate (ORR) • Clinical Benefit Rate (CBR) • Duration of Response (DoR) • Time to Response (TTR) Pharmacoeconomics Outcome Objective • Health Resource Utilization	Left Ventricular Dysfunction Safety in Elderly Patients Use of a non-validated HER2 test	Planned	• Final Analysis Q4 2016 • Final CSR Q4 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
BO27938 (KATHERINE)	Objectives • To compare invasive disease-free survival in patients with residual invasive breast cancer after treatment with preoperative chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the 2 treatment arms The secondary efficacy objective for this study is as follows: • To compare cardiac safety and overall safety between the 2 treatment arms	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Ongoing	• Study start April 2013 • Primary Analysis Q3 2018 • Primary CSR Q4 2018 • Final Analysis Q2 2023 • Final CSR Q3 2023
BO28407 (KAITLIN; planned)	<u>EBC – Adjuvant</u> TBD	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Planned	• TBD
BO28408 (KRISTINE; planned)	<u>EBC – Neoadjuvant</u> TBD	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Planned	• TBD

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned/started)	Date for submission of interim or final reports (planned or actual)
YO28405	Primary Objectives: • To compare efficacy of trastuzumab emtansine versus trastuzumab + docetaxel in patients with HER2-positive progressive or recurrent, unresectable, locally advanced, and/or metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy for MBC. • To compare safety of trastuzumab emtansine versus the trastuzumab + docetaxel	Safety in Elderly Patients	Planned	
CAPA impact assessment	Pharmacovigilance	any signal or changes in incidence/severity of AEs	Ongoing	• February 2014 and monthly updates

12.5.6.1 Studies which are a condition of the marketing authorisation

None of the studies above is a condition of the marketing authorisation.

12.5.7 VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable: no Risk Management Plan has yet been approved.