19 September 2013
EMA/749228/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kadcyla

International non-proprietary name: Trastuzumab emtansine

Procedure No. EMEA/H/C/002389/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Kadcyla
Applicant:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW UNITED KINGDOM
Active substance:	Trastuzumab emtansine
International Nonproprietary Name:	Trastuzumab emtansine
Pharmaco-therapeutic group (ATC Code):	Antineoplastic Agents, monoclonal antibodies (L01XC14)
Therapeutic indication:	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.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strengths:	100 mg and 160 mg
Route of administration:	Intravenous infusion
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

AE	adverse event
ATA	anti-therapeutic antibody
CBR	clinical benefit rate
CI	confidence interval
CEP17	chromosome 17 centromeric probe
CHF	congestive heart failure
CNS	central nervous system
CR	complete response
CSR	clinical study report
CT	computed tomography
DAS	Diarrhea Assessment Scale
iDMC	independent data monitoring committee
DOR	duration of response
ECD	extracellular domain
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
FACT-B	Functional Assessment of Cancer Therapy-Breast
FISH	fluorescence in situ hybridisation
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
IRC	independent review committee
IRR	infusion-related reaction
LABC	locally advanced breast cancer
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NR	not reached
ORR	overall response rate
OS	overall survival
PD	disease progression
PFS	progression-free survival
PK	pharmacokinetic
PPK	population pharmacokinetic
PR	partial response
PRO	patient-reported outcomes
PS	performance status
RECIST	Response Evaluation Criteria in Solid Tumors
(q)RT-PCR	(quantitative) reverse transcriptase polymerase chain reaction
q3w	every 3 weeks
qw	every week
SAE	serious adverse event
SD	stable disease
T-DM1	trastuzumab-MCC-DM1
TSP	time to symptom progression
TOI-PFB	Trial Outcome Index-Physical Functional Breast
TTF	time to treatment failure

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd submitted on 30 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kadcyla, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that trastuzumab emtansine was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/973755/2011; CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active substance status

The applicant requested the active substance trastuzumab emtansine contained in the above medicinal product to be considered as a new active substance in comparison to the known trastuzumab previously authorised in the Union as Herceptin® and claimed that trastuzumab emtansine differs significantly in properties with regard to safety and efficacy from the already authorised substance. Please refer to section 2.2.1.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 November 2009, 16 December 2010, 23 June 2011, 21 July 2011, 20 October 2011, 17 November 2011 and 15 March 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Lonza Ltd.
Lonzastrasse
CH-3930 Visp
Switzerland

Manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Ersbøll Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 30 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 December 2012.
- PRAC advice was given on 10 January 2013.
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to

the List of Questions to all CHMP members on 28 May 2013.

- PRAC advice was given on 13 June 2013.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 29 August 2013.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Kadcyla.

2. Scientific discussion

2.1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, accounting for 23% (1.38 million) of all new cancer cases and 14% of the cancer deaths in females in 2011 (Jemal, Bray et al. 2011). In developed countries, the majority of cases are diagnosed when the disease is confined to the breast or has spread only to regional lymph nodes and can be treated with curative intent; however 25%-40% of such patients will develop metastatic disease (Guarneri and Conte 2009). For metastatic breast cancer (MBC) overall, the median survival time for patients with metastatic tumors at first diagnosis is approximately 24 months, and only 18%-23% of patients (in the US and Europe) will live at least 5 years after diagnosis of MBC (Sant, Allemani et al. 2003; Howlader, Noone et al. 2011).

MBC remains incurable, and an estimated 450,000 patients globally die from breast cancer per annum (Ferlay, Shin et al. 2010). Of these, approximately 15%-20% (60,000~90,000) are likely to be due to HER2-positive disease. Amplification of human epidermal growth factor receptor 2 (HER2) is associated with shortened survival (Slamon, Clark et al. 1987; Slamon, Leyland-Jones et al. 2001).

Trastuzumab plus a taxane is approved in the first-line setting for MBC in HER2-positive patients based on data from patients who had not been previously treated with trastuzumab (Slamon, Leyland-Jones et al. 2001; Marty, Cognetti et al. 2005). The currently approved combination regimen for the treatment of HER2-positive MBC in second-line treatment is lapatinib plus capecitabine (Cameron, Casey et al. 2008).

Trastuzumab emtansine (also known as T-DM1) is a novel antibody–drug conjugate (ADC) that contains the humanized anti-HER2 IgG1 antibody trastuzumab and DM1, a microtubule-inhibitory maytansinoid, linked through a thioether bond. Trastuzumab emtansine retains the mechanisms of action of both trastuzumab and DM1. It binds to HER2, and triggers the same

anti-tumor activities as trastuzumab, including suppression of HER2 signaling pathways, HER2 ECD shedding, and mediation of antibody-dependent cell-mediated cytotoxicity (ADCC). Trastuzumab emtansine is then internalized and degraded to release DM1-containing cytotoxic components which cause inhibition of cell division and cell growth, and eventually cell death. The targeted delivery of DM1 is expected to improve the therapeutic window compared with the unconjugated molecule.

This application is seeking approval for the use of trastuzumab emtansine for the following indication:

"Trastuzumab emtansine, as a single agent, is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane."

The recommended dose of trastuzumab emtansine (see SmPC section 4.2) is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). Patients should be treated until disease progression or unacceptable toxicity. 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 (see SmPC section 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 SmPC sections 4.4 and 4.8). Trastuzumab emtansine should be discontinued in case of life-threatening infusion reactions. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment should be available for immediate use (see section SmPC 4.4). 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. Methods of administration are described in the SmPC (see sections 4.2 and 6.6). Trastuzumab emtansine is contraindicated in case of hypersensitivity to the active substance or to any of the excipients (see SmPC section 6.1).

2.2. Quality aspects

2.2.1. Introduction

A number of Scientific Advices have been given to Trastuzumab emtansine by National Agencies as well as CHMP. Two Advices in relation to Quality have been given in November 2009 (DK and PT) and in June 2011 (follow-up (DE and BE)).

Trastuzumab emtansine consists of the antibody trastuzumab conjugated to the cytotoxic drug DM1. The DM1 is linked to the lysidne residues on the antibody via the heterobifunctional reagent *trans*-succinimidyl 4-(*N*-maleimidomethyl)cyclohexane- 1-carboxylate (SMCC).

The finished product is presented as a powder for concentrate for solution for infusion containing 100 mg or 160 mg of trastuzumab emtansine as active substance.

Other ingredients are: succinic acid, sodium hydroxide, sucrose and polysorbate 20.

The product is available in Type I glass vial closed with a grey-butyl rubber stopper coated with fluoro-resin laminate, and sealed with an aluminium seal with a white or purple plastic flip-off cap.

The final dosage form is a lyophilised Drug Product that is reconstituted for intravenous administration.

Trastuzumab

Trastuzumab, consists of a consensus human IgG1 kappa framework and complementarity determining regions derived from the murine anti-HER2 monoclonal antibody 4D5. Trastuzumab is a well characterized recombinant monoclonal antibody expressed in Chinese Hamster Ovary (CHO) cells and purified using an approved manufacturing process as described in the Herceptin marketing application.

DM1

Information on the sources of the starting material maytansinol (MayOH), a semisynthetic fermentation product, has been provided by the applicant. Declarations concerning the use of materials of animal origin in the synthesis of the starting material MayOHhas been provided .

SMCC Linker

The linker denoted SMCC is a commercially available reagent that is chemically synthesised.. Adequate specification limits have been set .

Trastuzumab emtansine

Trastuzumab emtansine is manufactured by Lonza, Visp, Switzerland. Production of trastuzumab emtansine occurs in two major steps, a modification reaction step (addition of SMCC linker to trastuzumab) and a conjugation reaction step (addition of DM1 to SMCC linkers).

2.2.2. Active Substance

Nomenclature, structure and general properties

Nomenclature:

The product name and INN is the following: Trastuzumab emtansine

The chemical Name is the following: Immunoglobulin G1, anti-(human receptor tyrosine-protein kinase erbB-2 (EC 2.7.10.1, p185erbB2, MLN 19 or CD340)); humanized mouse monoclonal rhuMab HER2γ1 heavy chain (223-214')-disulfide with humanized mouse monoclonal rhuMab HER2 κlight chain, dimer (229-229'':232-232'')-bisdisulfide dimer; conjugated on an average of 3

to 4 lysyl, to maytansinoid DM1 via a succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) linker.

CAS Registry Number: 1018448-65-1

Structure:

Trastuzumab emtansine is an antibody-drug conjugate that contains the humanized anti-HER2 IgG1, trastuzumab, linked to the microtubule-inhibitory maytansinoid, DM1, via a thioether bond. The drug is linked to antibody lysine residues using the heterobifunctional reagent, SMCC.

General properties:

Trastuzumab emtansine exhibits potent in vitro cytotoxic activity against a number of cultured cell lines that over-express *p185*HER2. In addition, trastuzumab emtansine is effective in several murine models of HER2-positive breast cancer, including ones that do not respond to unconjugated trastuzumab. Although the primary mechanism of action of trastuzumab emtansine is distinct from that of unconjugated trastuzumab, the two molecules are similar with respect to a number of biological activities including binding to recombinant HER2 ECD, C1q, and the neonatal Fc receptor (FcRn). Trastuzumab emtansine also showed similar binding to FcγRI and moderately increased (2- to 3-fold) binding to FcγRIIa and IIb, compared with unconjugated trastuzumab. Additionally, trastuzumab emtansine showed similar FcγRIIIa binding activity and antibody-dependent cell-mediated cytotoxicity to unconjugated trastuzumab.

New Active substance status:

Trastuzumab emtansine, is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory product DM1 (a maytansine derivative) with the stable thioether MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate) linker.

Trastuzumab emtansine is produced from two intermediates (DM1 and trastuzumab) and a starting material (SMCC), each of which is tested and released using methods and specifications appropriate to its molecular type (small molecule or protein). The resulting antibody conjugate product exhibits a unique and specific set of product characteristics, distinct from the intermediates used in its production.

Manufacture

The drug substance manufacturer is the following:

Trastuzumab Emtansine Drug Substance Bulk Manufacturer and Responsibilities:

Manufacturer	Responsibilities
Lonza Ltd CH-3930 Visp, Switzerland	Manufacture Batch release testing Stability testing

Manufacturing Process Characterisation and Validation

Process characterisation and validation studies for trastuzumab emtansine Drug Substance were conducted by a Quality by Design (QbD) approach to define the commercial process parameters, including the proven acceptable ranges (PARs) and multivariate acceptable ranges (MARs). These were defined by process characterisation studies performed throughout development.

Throughout the development history of trastuzumab emtansine from Phase I process through the commercial process several process improvements have been implemented, including changes in scale and manufacturing sites, changes to the manufacturer of the DM1 intermediate, and the change from a liquid to a lyophilised formulation of the drug product.

Characterisation of trastuzumab emtansine

A comprehensive characterisation of trastuzumab emtansine and its product related variants have been presented. The methods used are considered state of the art and capable to elucidate the structural characteristics and physicochemical properties of trastuzumab emtansine.

Control of drug substance

Specification

The trastuzumab emtansine specification is overall considered well justified based on batch release data of a substantial number of batches, manufacture experience and clinical and non-clinical considerations.

The active substance specification contain test for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity and potency

Reference standards of materials

The current trastuzumab emtansine Reference Materialis used to establish the identity, purity, and potency of trastuzumab emtansine in all assays requiring a trastuzumab emtansine Reference Standard to test production batches.

Assays that measure the appearance, identity, purity, strength, potency, and general characteristics of trastuzumab emtansine were used to qualify the primary Reference Standard.

The results of the qualification testing using Drug Substance and Drug Product release testing methods met the acceptance criteria. Extended characterisation testing was also performed to provide detailed physicochemical characterisation using additional analytical analyses not part of routine release testing. From the extended characterisation results, the Reference Standard was shown to have the expected physicochemical properties. The results of release testing and extended characterisation demonstrated its suitability for use as the primary Reference Standard.

Container closure system

Trastuzumab emtansine Drug Substance is stored and transferred in vessels. The vessels protects the Drug Substance from light. The Applicant states that Drug Product release testing provides assurance that changes to the quality of Drug Substance will be detected. Stability studies indicate that there is no significant change in trastuzumab emtansine product quality stored at the recommended temperature of −15°C to −25°C or colder.

Stability

Based on the stability data provided, a shelf life of 36 months (1096 days) at −20°Cis proposed for commercial trastuzumab emtansine Drug Substance.

2.2.3. Finished Medicinal Product

Description of the drug dosage

Trastuzumab emtansine 100 mg and 160 mg vials are the dosage configurations for trastuzumab emtansine. The product is a sterile powder for concentrate for solution for infusion available in 100 mg and 160 mg single-use vials.

Trastuzumab emtansine Drug Product is available in two vial configurations:

- Trastuzumab emtansine 100 mg, provided in a 15 mL vial as a sterile, white to off-white, lyophilized cake intended for reconstitution with 5.0 mL Sterile Water for Injection. Each vial, following reconstitution, is configured to deliver 5.0 mL.

- Trastuzumab emtansine 160 mg, provided in a 20 mL vial as a sterile, white to off-white, lyophilized cake intended for reconstitution with 8.0 mL Sterile Water for Injection. Each vial, following reconstitution, is configured to deliver 8.0 mL.

The presentations have been selected to provide flexible combinations over the likely body weight range of patients while minimising product wastage. These two configurations are dose-proportional and therefore have the same composition and only the filling volumes are different.

After reconstitution, Trastuzumab emtansine Drug Product contains 20 mg/mL trastuzumab emtansine, sodium succinate, sucrose, and polysorbate 20.

Composition

Trastuzumab emtansine 100 mg is provided as a lyophilized formulation, which, upon reconstitution, yields a solution containing 20 mg/mL trastuzumab emtansine, sodium succinate, sucrose, and polysorbate 20.

Trastuzumab emtansine 160 mg is provided as a lyophilized formulation, which, upon reconstitution, yields a solution containing 20 mg/mL trastuzumab emtansine, sodium succinate, sucrose, and polysorbate 20.

Container

Trastuzumab emtansine 100 mg is provided in a single use, 15 mL Type I glass vial while Trastuzumab emtansine 160 mg is provided in a single use, 20 mL Type I glass vial. In both cases, the vial is sealed with a grey-butyl rubber stopper coated with fluoro-resin laminate on the product side. The rubber stopper is sealed with an aluminum seal with a plastic flip-off cap. The seal and cap do not come into contact with the Drug Product.

Pharmaceutical development

The applicant states that acceptable ranges of critical process parameters and formulation components are based on process and product characterization, process validation studies, and/or prior knowledge to ensure a consistent and robust manufacturing process is obtained. This understanding provided the basis for development of the control strategy.

Manufacturers of Trastuzumab Emtansine, 100 mg Sterile, Lyophilized Powder, 20 mg/mL

The production of trastuzumab emtansine 100 mg Drug Product occurs at thefollowing location:

Manufacturer	
DSM, Inc. 5900 Martin Luther King Jr Highway Greenville, North Carolina 27834 USA	

Manufacturers of Trastuzumab Emtansine, 160 mg Sterile, Lyophilized Powder, 20 mg/mL

The production of trastuzumab emtansine 160 mg Drug Product occurs at the following location:

Manufacturer	
DSM, Inc. 5900 Martin Luther King Jr Highway Greenville, North Carolina 27834 USA	

Manufacture of the product

Trastuzumab emtansine is manufactured as a lyophilised Drug Product formulation Drug Product is produced in a 100 mg or 160 mg per vial configuration, and the bulk protein concentration is 20 mg/mL. Drug Product is aseptically filled into a glass vial that is closed with a lyophilisation stopper, and crimped with an aluminium seal fitted with a plastic flip-off cap.

The frozen Drug Substance is thawed, re-circulated until homogeneous, and stored at 2°C–8°C until further processing.

In preparation for filling, Drug Substance is sterile-filtered through a sterile 0.22 µm nominal pore size membrane filter into a filling vessel. Empty vials are subjected to an internal and external cleaning. Stoppers are washed and steam-sterilized

Prior to filling, the sterile-filtered bulk is again filtered through a second sterilised 0.2 µm pore size filling reservoir that feeds the filling needles. The product is filled into depyrogenated USP/Ph. Eur./JP Type I 15 mL or 20 mL glass vials. Filled glass vials are partially stoppered with lyophilisation stoppers during the filling process and automatically conveyed to a tray loader for loading into lyophilisation trays. Prior to the filling operations, the product-contacting parts of the filling machine are sterilized in place.

The contents of the partially stoppered vials are lyophilised and the vials are then fully stoppered by collapsing the lyophiliser shelves.

Upon the completion of the lyophilisation process, vials are unloaded and transferred to the capper. The vials are crimped with sterilized 20 mm aluminum seals fitted with plastic flip-off caps. Following capping, vials are transferred to an exterior vial washer. The exterior vial washer rinses the outside of product vials from the shoulder down with WFI. The vials are then dried with compressed air.

Filled and capped vials are 100% visually inspected by means of manual inspection. After the final vial inspection, the batch is sampled for Drug Product release testing. Before the inspection process, the vials may undergo interim storage at 2°C–8°C. After the inspection process, the vials are quarantined and stored at 2°C–8°C pending release.

Vials are released by the Quality Unit (QU) and delivered at 2°C–8°C by qualified shippers to the labelling facility. When the labelling and packaging operation is completed, the vials and labels are reconciled, and the vials are stored at 2°C–8°C pending final QU release.

For the Drug Product process, several process parameters were evaluated for their criticality with respect to the predetermined quality attributes.

Process validation

Process validation studies for trastuzumab emtansine Drug Product were carried out using the commercial process parameters.

Overall, the approach used to validate the DP production process is adequate as the obtained data demonstrate that the process is under control.

Control of Drug Product

Product quality is tightly controlled based on a thorough understanding of the manufacturing process and a series of in-process controls and release specifications for starting materials, intermediates, and trastuzumab emtansine Drug Substance and Drug Product.

Adventitious agents

Trastuzumab, DM1, and sucrose are the only materials of animal, human, or recombinant origin in the production of trastuzumab emtansine.

Testing to ensure the absence of adventitious agents throughout the Drug substance manufacturing process and final Drug Product is performed.

TSE safety

The applicant has carried out a risk evaluation of trastuzumab emtansine Drug Product with respect to transmissible spongiform encephalopathy (TSE) in accordance with the current revision of the EMA/410/01 *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.

Viral validation

Trastuzumab is a well-characterized recombinant monoclonal antibody product expressed in CHO cells and produced using a manufacturing process already authorised for human use as the active substance of Herceptin®. The virus inactivation/removal studies that were authorised for Herceptin® apply to Kadcyla.

Control of drug product

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: test for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity and potency.

Container closure system

The primary packaging materials used for the manufacture of trastuzumab emtansine Drug Product, powder for concentrate for solution for infusion, consist of 15 mL (100 mg/vial) or 20 mL (160 mg/vial) USP/Ph. Eur/JP Type I glass vial sealed with a 20 mm fluoro-resin laminated, double-vented, grey-butyl rubber lyophilization stopper and crimped with a 20 mm aluminum seal fitted with purple (160 mg) or white (100 mg) flip-off plastic caps.

All primary packaging materials are standard quality, suited for packaging sterile products, and comply with relevant pharmacopoeial requirements.

Stability of the product

The proposed shelf-life for both vial configurations is 36 months at 2-8°C .

Shelf-life of the 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.

Shelf-life of the diluted solution

The reconstituted Kadcyla solution diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin 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.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to submit the results from additional studies to support drug substance stability.

- The applicant is recommended to provide updated data on the stability of drug product vial configuration.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacology studies were conducted in nude mice and the *in* vivo safety pharmacology study was conducted in female cynomolgus monkeys. Pharmacokinetic studies were conducted in mice, rats and cynomolgus monkeys and single- and repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys. The safety pharmacology and pivotal toxicity studies were conducted in accordance with Good Laboratory Practice (GLP).

During the period 2009 to 2012, the applicant consulted the CHMP for advice on 8 occasions. Non-clinical issues were addressed on 3 occasions in relation to cardiotoxicity, reproductive toxicity and environmental risk assessment. The CHMP advices were followed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The *in vitro* pharmacodynamic properties of T-DM1 were compared with unconjugated trastuzumab with respect to:

- Binding activity to HER2 extracellular domain
- Binding activity with Fc gamma (Fcγ) receptors (RIa RIIa, RIIb, RIIIa V158, and RIIIa F158)
- Binding activity with complement C1q
- Induction of antibody-dependent cell-mediated cytotoxicity
- Anti-proliferative activity in a variety of HER2-positive cell lines
- Ability to induce apoptosis in breast cancer cell lines
- The effect on cell-cycle progression
- The effect on PI3 kinase signaling pathway
- The effect on HER2 extracellular domain shedding
- The anti-proliferative effect in trastuzumab resistant cell lines

Trastuzumab and trastuzumab emtansine (T-DM1) bound to the extracellular domain of human HER2 *in vitro* with similar affinity and binding kinetics. Hence, average K_D values were determined to be 1.08 nM for T-DM1 and 1.01 nM for trastuzumab as determined by Surface Plasmon Resonance technology. Trastuzumab and T-DM1 display similar binding affinities for Fcγ receptors.

Comparable binding curves for T-DM1 and trastuzumab were observed in an ELISA assay applying purified human complement C1q (EC_{50} for T-DM1 was 1.4 µg/mL and EC_{50} for trastuzumab was 1.2 µg/mL).

T-DM1 induced a slightly increased antibody-dependent cell-mediated cytotoxicity (ADCC) activity compared with unconjugated trastuzumab. The anti-proliferative activity of T-DM1 and trastuzumab was compared in various breast cancer cell lines expressing different levels of HER2. Cell viability was reduced to a greater extent by T-DM1 than trastuzumab in all HER2 over-expressing breast cancer cell lines (HER2 ≥ 2 +). Moreover, T-DM1 treatment induced a potent anti-proliferative response in cell lines resistant to trastuzumab (KPL-4, HCC1954, BT-474EEI). For the cell lines with normal (MCF7) or no HER2 expression (MDA-MB-468), the cell viability was only affected at high T-DM1 concentrations (10 µg/mL). Trastuzumab displayed no activity in the cell lines with no or normal HER2 expression.

T-DM1 induced caspase-3 and -7 activation (markers of apoptosis) in a dose-dependent manner in the breast cancer cell lines SK-BR-3, BT-474 and KPL-4. Since trastuzumab did not induce caspase-3 and -7 activation, the effect was caused by the DM1 moiety. In addition, exposure of breast cancer cell lines to T-DM1 (≥30 ng/mL) and DM-1 (≥20 nM) resulted in an increase in G2/M phase cells, as would be predicted by an agent that disrupts microtubule function. The arrest of cell division late in the cell cycle (G2/M phase) resulted in the activation of the intrinsic apoptosis pathway and cell death. Trastuzumab, on the other hand, inhibited the growth of breast cancer cell lines by arresting the cells early in the cell cycle (G0/G1 phase).

Maximal inhibition of HER2 extracellular domain shedding into the growth media of BT-474-M1 cells, was 42% with trastuzumab exposure and 43% with T-DM1 exposure. The IC_{50} values for the antibodies were 0.3 µg/mL and 0.184 µg/mL, respectively.

The anti-proliferative activity of T-DM1 was evaluated in HER2-positive cell lines resistant to trastuzumab (non−small cell lung cancer cell line Calu-3, SK-OV-3, gastric carcinoma cell line MKN7, and a cell line established from BT-474 cell, BT-474-EI). A dose-dependent anti-proliferative activity was observed for T-DM1 in all four cell types. In contrast, trastuzumab showed virtually no activity except at high doses in Calu-3 cells.

SK-BR-3 cells were treated with T-DM1 for a variety of time exposures and incubated further in conjugate-free media to investigate whether the cytotoxic effects are long-lived (study 05-1111). After treatment of SK-BR-3 cells with T-DM1 for 10, 30, or 60 minutes, or 72 hours, the media were removed, the cells were washed once, and fresh media (containing no conjugate) added for a total incubation period of 72 hours. At the highest concentration (1 µg/mL) the anti-proliferative activity resulting from a 10-minute exposure was equivalent to the activity of exposure for the full 72 hours.

Similar *in vitro* pharmacodynamic properties were seen for various T-DM1 batches when evaluated with respect to HER2 binding, binding to Fcγ receptors, C1q binding, ADCC and anti-proliferative activity in five breast cancer cell lines.

The majority of the nude mice bearing trastuzumab-resistant BT474EI (HER 2+) breast cancer cell line tumours, experienced complete tumour regression following p.o. administration of weekly or once every three weeks T-DM1 doses ≥10 mg/kg. Moreover, a similar frequency of tumour-bearing mice experienced complete tumour regression following twice weekly administration of 18 mg/kg T-DM1. The anti-tumour efficacy of p.o. T-DM1 was also evaluated in nude mice bearing MMTV-HER2 mammary tumours (HER 2+). When evaluated at doses giving rise to identical total drug exposure during the course of the study, better treatment efficacy

(number of complete MMTV-HER2 tumour responses) was obtained with dosing once every three weeks than with weekly dosing. Still, the tumour regression was transient with detectable tumours returning following a treatment-free period. The tumour response was observed at clinically relevant T-DM1 serum concentration levels (clinical Cmax is 80 µg/mL).

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted.

Safety pharmacology programme

Two studies were submitted:

A Single Dose Intravenous Cardiovascular Safety Pharmacology Study of T-DM1 Administered to Female Cynomolgus Monkeys with a 3 Week Recovery Period

Female cynomolgus monkeys were surgically fitted with a large animal electrocardiogram (ECG) and pressure transmitter. Four animals were allocated to each group, and dosed with either 0, 3, 10 or 30 mg/kg T-DM1 in an iv bolus injection in the saphenous vein on Day 1. The dosing was followed by a 3 week dosing free period. ECG and pressure measurements were recorded twice in the pre-treatment period. On Day 1; at least 60 minutes prior to treatment, and 8 hours after treatment were recorded continuously, followed by 10 minutes every hour for at least 24 hours. On Days 3, 4, 5, 8, 15 and 22 at least 10 minutes of recordings were made around the same time of day as dosing were performed on Day 1. Four hours post dose a statistically significant decrease in the uncorrected QT interval was observed in Group 2 (3 mg/kg T-DM1) and 4 (30 mg/kg T-DM1). However, no effect was observed on the corrected QT interval for these groups at that time point, and a slight (not statistically significant) increase in the heart rate was observed. As no other differences were recorded, this was considered to be unrelated to treatment with T-DM1 by the Study Director.

No statistically significant differences were observed with regards to the heart rate and systolic, diastolic, mean arterial, and pulse pressures (systolic-diastolic). However, the high dose group (30 mg/kg) showed elevated systolic, diastolic, mean and pulse pressure values when compared to the control group from approximately Day 3 and until Day 22 (statistically nonsignificant but n=4/group). During the study period mean exposure levels ranged from 322 µg/mL on Day 2 to 90.9 µg/mL on Day 22.

Intra-thoracic pressure measurements included respiratory rate and a qualitative assessment of respiratory depth. Respiratory parameters were quantified in 1 minute means, at similar time points as specified for the ECG and blood pressure parameters. Not statistically significant differences were observed with respect to the respiratory rate or depth.

Blood samples for anti-drug antibody analysis were taken pre-dose and on Day 22. No anti-drug antibodies were detected in the post dose samples. However, one pre-dose sample from a Group 3 animal was positive. The sensitivity of the assay was such that 8% false positive samples would be detected.

Blood samples for toxicokinetic measurements were sampled pre-dose, on Day 2 and on Day 22. No T-DM1 was detected in the pre-dose samples, or in Group 1 (negative control). Increasing total trastuzumab plasma levels were recorded in Groups 2 (38.4 µg/mL) to 4 (332 µg/mL) on

Day 2, and 1.36 to 90.9 µg/mL respectively on Day 22, proving that the animals had indeed been exposed to the test article, in the appropriate doses.

Effects of DM1 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells

The *in vitro* effects of DM1 on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG) were determined.

DM1 in concentrations of 2.6, 8.8 and 29.5 µM (nominal 3, 10 and 30 µM), was applied to the test system. The lower than expected recovery of DM1 following dose formulation analysis, was determined to be due to adherence of DM1 to plastics and standard glassware. The DM1 solutions were therefore prepared in silanized glassware (to avoid the adherence of DM1 to the glassware) however, when handling the dose formulations during preparation and sampling, non-silanized items such as micropipette tips had to be used. Therefore the measured concentrations of 2.6, 8.8 and 29.5 µM were reported.

DM1 inhibited hERG current by 0.3%, 1.0% and 2.5% in low, medium and high dose levels respectively, versus 0.63% in control (n=3). The positive control (60 nM terfenadine) inhibited hERG potassium current by 82% (n=2).

The IC_{20} and IC_{50} could not be determined, as the high concentration was selected based on maximum solubility. As 29.5 µM DM1 caused only 2.5% inhibition, both IC_{20} and IC_{50} were estimated to be greater than the tested highest dose.

Pharmacodynamic drug interactions

One study has been submitted:

The influence of Trastuzumab on MMTV-HER2 Fo5 Tumour response to T-DM1 conjugates

In this study, the potency of T-DM1, as both the MCC- and SPP- conjugate (un-cleavable and cleavable linker respectively) were investigated in the presence of trastuzumab (Herceptin). The MMTV-HER2 Fo5 tumour model overexpress HER2 (>1,000,000 copies of human HER2 per cell) and does not respond to trastuzumab treatment. Therefore the drug interaction, between T-DM1 and trastuzumab competing for the HER2 antigenic sites can be evaluated. A control antibody (anti-IL8) was also administered, that would have no physiologic effect in the mice, as the target is not expressed in mice. An IV bolus of 15 mg/kg trastuzumab or anti-IL8 was followed 4 hours later (t=0) by either 0 or 10 mg/kg T-MCC-DM1 (T-DM1) or T-SPP-DM1 IV. To ensure that the circulating levels of trastuzumab would stay above 80 µg/mL in the animals receiving trastuzumab, an osmotic pump was inserted, which administered 0.5 mg/kg/day trastuzumab intraperitoneally for approximately 25 days. However, the serum concentrations of trastuzumab only persisted above 80 µg/mL until Day 7, and by Day 10 had dropped to 40.9 µg/mL, and continued to drop until end of study.

The anti-IL8 and trastuzumab monotherapy showed rapid tumour progression and a mean time to tumour doubling of 8 days, and survival time of approximately 10 days. The conjugated antibody therapies, alone and with trastuzumab showed slower mean time to tumour doubling of 12-14 days, and a survival time of up to 20 days or longer.

Total trastuzumab as well as conjugated trastuzumab concentrations were measured with an ELISA assay. Total trastuzumab were generally higher than conjugated trastuzumab following T-

DM1 treatment. Furthermore, conjugated trastuzumab concentrations were higher following treatment with T-DM1 than with T-SPP-DM1, supporting that T-SPP-DM1 de-conjugates due to the cleavable SPP-linker.

2.3.3. Pharmacokinetics

Methods of analysis

The structural complexity of T-DM1 resulted in the development of both enzyme-linked immunosorbent assays (ELISA) in order to quantify T-DM1 and total trastuzumab in serum from rats and cynomolgus and LC-MS/MS assays in order to detect free DM1 in plasma from rats and monkeys. In addition, a method for the determination of antibodies against T-DM1 was validated in cynomolgus monkey serum. The validations of the developed methods of analysis were all conducted according to GLP.

Absorption

T-DM1 is intended for IV administration, and therefore this route of administration was used in the non-clinical studies. The PK of T-DM1 was evaluated in mice, rats and cynomolgus monkeys, whereas the PK of DM1 or MCC-DM1 (DM1 with linker) was characterized in rats or mice.

The pharmacokinetics of T-DM1 in mice was evaluated over a single-dose range of 0.3 to 15 mg/kg, with plasma or serum clearance ranging from approximately 13 to 19.2 mL/day/kg. As was expected in species that do not express the target molecule (human HER2), pharmacokinetics (CL, V1, $T_{½, \beta}$) were similar across all doses. Clearance appeared independent of dose, and was not affected by the presence of HER2-positive tumours. The terminal half-life ($T_{½, \beta}$) was estimated at 4.23-13.1 days, and the volume of distribution was similar to plasma or serum volume (40.5-62.9 mL/kg).

In rats, the pharmacokinetics of T-DM1 was evaluated following single doses ranging from 0.3 to 20 mg/kg. Again, since T-DM1 does not express affinity towards rat HER2, the pharmacokinetic parameters (CL, V1, $T_{½, \beta}$) were similar across all doses. Plasma or serum clearance of T-DM1 ranged from 10.1 to 22.1 mL/day/kg. The terminal half-life of T-DM1 varied from 4.9 to 5.4 days while the volume of distribution ranged from 72.9 to 149 mL/kg. No gender differences in pharmacokinetic parameters were noted rats.

The pharmacokinetics of T-DM1 in cynomolgus monkeys following a single dose was investigated in both male and female monkeys over a dose range of 0.3 to 30 mg/kg. T-DM1 binds to cynomolgus HER2, resulting in some degree of target-mediated clearance. The clearance was fastest at low doses (40.4 mL/day/kg at a dose of 0.3 mg/kg), decreasing to approximately around 16.5 mL/day/kg at 3 mg/kg and 10.1 mL/day/kg at 30 mg/kg. As expected terminal half-life was inversely related to clearance, ranging from approximately 1 day at 0.3 mg/kg to 5.30 days at 30 mg/kg. The volume of distribution appeared to increase with dose, although the increase was not dose proportional. Hence, V_{ss} was 44.2 mL/kg at 0.3 mg/kg and 68.6 mL/kg at 30 mg/kg. No gender differences in pharmacokinetic parameters were noted in monkeys.

Plasma DM1 concentrations, peaked immediately after T-DM1 administration, decreased over time, and were generally proportional to T-DM1 concentrations. This behaviour was not consistent with typical metabolite/catabolite pharmacokinetics. DM1 concentrations in plasma

may be affected by DM1 liberated from T-DM1, during the processing of plasma sampling. Consequently, the measured plasma DM1 concentrations might be higher than the actual concentrations of DM1 that have been released from T-DM1 in vivo.

The pharmacokinetics of DM1 in rodents after DM1 administration, waqs characterized by a large apparent Volume of distribution (> 5,000 mL/kg) and a CL ranging from 25 to 80 mL/min/kg in rats to >200 mL/min/kg, in mice.

Distribution

Radiolabelled T-DM1 and trastuzumab, [^{125}I]-trastuzumab-MCC-DM1, trastuzumab-MCC-[^{3}H]DM1 and [^{3}H]DM1 were used to assess the impact of drug conjugation on trastuzumab and DM1 distribution as well as the potential for accumulation following a single IV dosing in rats. Still, the results should be interpreted with caution since the rat is a pharmacodynamically irrelevant species in the sense that T-DM1 does not bind to rat HER2.

T-DM1 and trastuzumab-related radioactivity was mainly confined to the blood compartment followed by highly perfused organs, e.g., lungs, liver and kidney. When ^{3}H-labelled DM1 was administered, the radioactivity quickly distributed to the tissues with the highest levels of radioactivity being found in the lungs and kidneys, followed by liver spleen and adrenals. Neither T-DM1 nor free DM1 were associated with tissue persistence or accumulation.

When T-DM1 and trastuzumab tissue distribution was compared, a similar pattern of distribution over time was seen, indicating that the antibody component mediates the tissue distribution of T-DM1. However, T-DM1 was cleared faster from tissues than trastuzumab.

Across the concentrations, the protein binding was fairly constant at 97.1%, 91.5% and 92.5% in rat, cynomolgus monkey and human plasma, respectively.

Metabolism

Upon administration, T-DM1 is thought to undergo linker cleavage, in cells or plasma, releasing DM1 or other DM1-containing catabolites. The other process is cellular uptake and catabolism of T-DM1 resulting in amino acids deriving from trastuzumab and DM1-containing catabolic products. Although the linker is designed to be stable under physiological conditions, *in vitro* and *in vivo* data showed that it undergoes cleavage. While no T-DM1 de-conjugation was observed for the first two days following IV administration to rats, by Day 14, only 40% of the total trastuzumab circulating in the plasma was T-DM1. The T-DM1 catabolite Lys-MCC-DM1 was present at the highest concentration in the urine and bile of rats administered T-DM1 followed by MCC-DM1 and DM1. Lys-MCC-DM1 and MCC-DM1 are pharmacodynamically inactive in an *in vitro* assay. DM1 undergoes extensive metabolism in rats hence eleven metabolites were identified in the bile collected from bile duct cannulated rats receiving ^{3}H-labelled DM1. *In vitro* studies applying human liver microsomes and recombinant cytochrome P450 enzymes indicated CYP3A4 and CYP3A5 are responsible for DM1 metabolism.

Excretion

The primary excretion route for T-DM1 in rats was bile (approximately 50% of the administered dose) followed by faeces, whereas only a minor part was excreted in the urine (7-8%). In both urine and faeces the majority of the radioactively labelled DM1 had been de-conjugated from the

trastuzumab moiety. Thogh without any supporting evidence, the potential of DM1 and its catabolites to undergo entero-hepatic recirculation in rats cannot be completely ruled out.

Pharmacokinetic drug interactions

In vitro metabolism studies suggested that DM1 does not induce or inhibit P-450–mediated metabolism at the highest concentration tested (600 ng/mL). DM1 is a weak time-dependent inhibitor of CYP3A4 in vitro. However, the risk of DM1 as a potential time-dependent inhibitor of CYP3A4 in vivo in humans is considered low given the low systemic exposure of DM1.

DM1 appeared to be a substrate but not an inhibitor of P-gp when tested at 0.5 µM in MDCKII-MDR1 cells. Based on *in vitro* data, DM1 does not appear to be a breast cancer resistance protein (BCRP) substrate. The few clinical data available do not indicate that concomitant treatment with OATP 1B1 and 1B3 inhibitors results in pharmacokinetic drug interactions. Regarding the potential interaction with drugs considered *in vivo* inhibitors of the renal transporters OCT2, OAT1, and OAT3, a discussion on data from the University of Washington DDI database has been provided considering cimetidine (OCT2, OAT3), quinidine (OCT2), probenecid (OAT2, OAT3), and diclofenac (OAT3). For all these drugs, a Ki value not lower than 1.3 µM has been reported. Considering the unbound DM1 C_{max} of 0.6 nM, a relevant inhibition of these transporters can be considered very unlikely.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were conducted in rats and Cynomolgus monkeys. The results are summarized in the table below.

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
05-1157 Non-GLP Single dose, Necropsy on Day 12	Sprague Dawley rat 2 F (control) 6 F treated groups	DM1 0, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 mg/kg i.v.	0.2 mg/kg	≥0.1 mg/kg: transient body weight decrease, platelets↓ AST, ALT and GGT↑ NEU↑ LYM and WBC↓ ≥0.4 mg/kg Piloerection, hind-limb paralysis, tremor, lethargy ALP↑ bilirubin↑ Terminated on Days 3 (≥0.6mg/kg))and 4 (0.4 mg/kg) ↑ cells in meta-phase mitosis in epithelial, reticulo-endothelial/ histiocytotic and endothelial cells Necrosis in multiple organs
05-1191 GLP Single dose, Necropsy on Day 3 or 22	Sprague Dawley rat 10 M/F main study (5/5 per scheduled necropsy) 4 M/F TK sampling	DM1 0, 0.05, 0.1, 0.2 mg/kg (0, 300, 600, 1200 µg/m^2) i.v.	DM1 0.2 mg/kg 1200 µg/m^2	Day 3: ≥ 0.05 mg/kg PLT↓ RETIC↓ and LYM↓ (males) Mitoses↑ (several organs and tissues) ≥0.1 mg/kg LYM↓ NEU↑ AST↑ ALT↑ Day 8: ≥ 0.05 mg/kg PLT↑ RETIC↑ RBC↓ HT↓ HB↓ ≥ 0.2 mg/kg NEU↓ ≥ 0.1 mg/kg: 1 premature euthanasia in each group due to inflammation and ulceration of injection site Day 22 necropsy: ≥ 0.2 mg/kg: mitosis↑ (adrenal cortex only)
07-0389 Non-GLP Single dose, Necropsy on Day 12	Sprague Dawley rat 3 F (control) 5 F (treated groups)	Tmab-SMCC-DM1 46 mg/kg (4138 µg/m^2) Also tested 6 other ADC's in this study	T-DM1 46 mg/kg (4138 µg/m^2 DM1)	Transient weight loss Transient changes in (**present at Day 12**): WBC↑ **NEU**↑ **LYM**↑ HB↓ MCV↓ MCH↓ HT↓ **RDW**↑ Plt↓ ALT↑ ALP↑ **AST**↑ ALB↓ tbili↑ GGT↑ **Chol**↑ Organ weights Lung, spleen and liver↑ Thymus↓

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
04-1214-1459 GLP Necropsy on Day 3 or 22	Sprague Dawley rat 10 M/F main study (5/5 per scheduled necropsy) 3 M/F TK sampling	T -DM1 0, 6, 20, 60 mg/kg (0, 612, 2040, 6120 µg/m^2 DM1) i.v.	T -DM1 20 mg/kg (2040 µg/m^2 DM1)	60 mg/kg Animals euthanized as scheduled Day 3, but remaining animals euthanized on Day 5 and 6 Day 3: Clinical pathology ≥ 20 mg/kg ALT↑ ALP↑ globulin↑ AST↑(males) ≥ 60mg/kg AST↑ (females) tbili↑ Glucose↓ Chol↑ Histopathology: ≥6 mg/kg mitosis↑ (general) Liver degeneration/ necrosis ≥ 20 mg/kg Kidney degeneration/necrosis No adverse findings at Day 22 necropsies or histopathology ≥ 6 mg/kg globulin↑ Chol↑ (females) ≥20 mg/kg retic↑ (males)
03-0140-1345 Non-GLP Single dose, Necropsy on Day 5	Sprague Dawley rat 6 F main study groups *TK: 2 F (additional)	Tmab-SSP-DM1 22.3 mg/kg (2410 µg/m^2 DM1) Tmab-SMCC-DM1 10*, 25, 50 mg/kg (960, 2401, 4802 µg/m^2 DM1) Free DM1 0.16* mg/kg (960 µg/m^2 DM1) i.v.	50 mg/kg Tmab-SMCC-DM1 (4802 µg/m^2 DM1)	≥ 50mg/kg: bodyweight↓ GGT↑ AST↑ ALT↑
04-0976-1459 GLP Single dose, Necropsy on Day 3 or 22	Cynomolgus monkey 6 M/F (3/3 per scheduled necropsy)	T-DM1 0, 3, 10, 30 mg/kg (0, 612, 2040, 6120 µg/m^2) i.v.	30 mg/kg T-DM1 (6120 µg/m^2 DM1)	≥ 3 mg/kg **Histopathology:** mitosis↑ (liver, spleen, injection site) ≥ 30 mg/kg: Bodyweight gain↓ AST↑ PLT↓ ALP↑ ALB↓

Tmab: Trastuzumab, Tmab-MCC-DM1/T-DM1: trastuzumab emtansine, DM1: emtansine, ADC: antibody drug conjugate, Plt: platelet count, retic; reticulocyte count, ALB: albumin, ALP: alkaline phosphatase, ALT: alanin aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyltransferase, MCV: mean cell volume, MCH: mean cell haemoglobin, RDW: red blood cell distribution width, LYM: lymphocyte count, NEU: neutrophile count, WBC: white blood cell count, UN: urea nitrogen, tbili: total bilirubin, Chol: cholesterol, SSP: cleavable linker, SMCC/MCC: non-cleavable linker

Repeat dose toxicity

One repeat dose toxicity study was performed in rats, and 4 repeat dose studies were performed with cynomolgyus monkeys. As the rat as a species does not express a target for the antibody moiety of the T-DM1, the observed toxicity in the rat is expected to be non-target specific toxicity.

See below a summary table of the repeat-dose toxicity studies performed:

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
04-0669-1459 Non-GLP Multiple Dosing on Day 1, 8 and 15, followed by a 1 month recovery	Sprague Dawley rat 5 Females/Group	IV T-DM1: 0, 8.88, 22.26 and 44.51 mg/kg (DM1; 714, 1789 and 3579 µg/m^2) PBS vehicle	Dosing on Day 1, 8 and 15, 1 month recovery	T-DM1: 22.26 mg/kg DM1: 1789 µg/m^2)	Mortality: 2 animals in Group 4 (44.51 mg/kg, 4210 µg/m^2)on Day 22 and 24 respectively Group 4 was terminated on Day 24 ≥26.19 mg/kg: **Clinical pathology** WBC↑ AST↑ ALT↑ GGT↑ 52.37 mg/kg: (euthanized on Day 24) Body weight gain↓ **Clinical pathology** bilirubin↑ LDH↑ PLT↓ neutrophils↑ **Histopathology** Extrameddullary hematopoiesis (liver and spleen) Bone marrow hypocellular Mitotic arrested cells (liver)↑
03-0674-1459 Non-GLP DRF study 1 or 2 treatment followed by 14 or 28 day recovery	Cynomolgus monkeys 2 M/F per group	IV T-DM1: 0*, 30*, 47# mg/m^2 (DM1: 0*, 4900*, 7400# µg/m^2) PBS vehicle	2 to 1 dosings with 0*, 30*, 47# mg/m2 T-DM1 *Dosing on Day 1 and 22 #Dosing on Day 22	30*, 47# mg/m^2 T-DM1 *2 dosings 3 weeks apart #1 dosing	All groups (incl control) LDH↑ ≥30 mg/m^2 **Clinical pathology** AST↑ ALT↑ retic↓Lymphocyte↑ **Histopathology** Liver: mitotic arrest↑ apoptosis↑ 47 mg/m^2 **Clinical pathology** Leukocytes↓ Neutrophils↓

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
04-0977-1459 GLP Once every 3 weeks for 4 doses, followed by 3 or 6 weeks recovery	Cynomolgus monkey 7 M/F Group	IV T-DM1: 0, 3, 10, 30 mg/kg (DM1: 0, 612, 2040, 6120 µg/m^2)	Once every 3 weeks for 4 doses, followed by 3 or 6 weeks recovery	3 mg/kg T-DM1 (612 µg/m^2 DM1) (due to non-reversible axonal degeneration in doses ≥10 mg/kg)	≥3 mg/kg **Histopathology** Kuppfer cell hypertrophy Mitotic arrest (several tissues, including injection site)↑ ≥10 mg/kg Clinical pathology NEU↑ (F) FIB↑ (F) AST↑ globulin↑ **Organ weight** Thymus↓ (F) **Histopathology** Axonal degeneration↑ 30 mg/kg **Clinical pathology** RBC↓ HT↓ HB↓ PLT↓ NEU↑ LYM↓ (F) APTT↑ FIB↑ ALT↑ ALP↑ albumin↓ **Organ weight** spleen↑ Thymus↓ M: testes↓ prostate↓ epididymides↓ seminal vesicles↓ **Histopathology** Spleen:Red pulp cellularity↑ lymphoid depletion follicular centers Liver: Multinucleated hepatocytes, hepatocellular vacuolation Recovery: Clinical pathology, except increased globulin and ALT (30 mg/kg) were reversible. Histopathological findings were reversible, except axonal degeneration, which was also observed at 6 weeks recovery and mitotic arrest in the basal epithelium of the tongue (≥ 30mg/kg only).

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
07-0653 GLP Once every 3 weeks for 8 doses, followed by a 6 week recovery phase	Cynomolgus monkeys 6 M/F Group	0, 1, 3, 10 mg/kg T-DM1 (DM1: 0, 232, 695, 2316 µg/m^2)	Dosing on Day: 1, 22, 43, 64, 85, 106, 127, 148 Necropsy Day 155 (3/3) and 190 (3/3)	3 mg/kg T-DM1 (695 µg/m^2 DM1)	≥1 mg/kg: **Histopathology:** Axonal degeneration at recovery necropsy ≥3 mg/kg: **Clinical pathology** AST↑ P↓ (M) **Histopathology** kuppfer cell hypertrophy ≥10 mg/kg: **Clinical pathology** PLT↓ MONO↑ FIB↑ Chol↑ CK↑ **Histopathology** Lacrimal gland; epithelial cell hypertrophy and decrease mucous cells Liver; Mitotic figures↑ hepatocyte and Kuppfer cell hypertrophy
07-0655 Non-GLP 6 Week repeat dose toxicity study followed by 3 weeks recovery T-DM1 And 3 Thio-MAB-toxin conjugates	Cynomolgus monkey 4 F Group	IV T-DM1 And 3 Thio-MAB-toxin conjugates T-DM1: 29 mg/kg¤ DM1: 6000 µg/m^2¤	Dosing on Day 1 and 22 Followed by 3 weeks recovery	<6000 µg/m^2 DM1	AST↑, ALP↑ LDH↑ GGT↑ globulin↑ P↓ albumin↓ **Histopathology** Axonal degeneration↑ Liver: Kuppfer cell hypertrophy and hyperplasia, multinucleated hepatocytes, hemorrhage and congestion, cellular infiltrates in the sinusoids

**Dosing on Day 1 and 22, #Dosing on Day 22, ¤ Dose levels as specified in the TK report for Study No 07-0655, F: females, M: males, LDH: lactate dehydrogenase, ALT: alanine transferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, Chol: Cholesterol, GGT: gamma glutamyl transferase, WBC: white blood cell count, MONO: monocyte count, APTT: activated partial thromboplastin time, FIB: fibrinogen, P: phosphorous, PLT: platelet count*

Genotoxicity

The genotoxicity of DM1 was evaluated in a reverse mutation assay with Salmonella strains as well as an *in vivo* chromosome aberration test performed in rats. See table below summarizing the results obtained in these two studies, as well as the micronucleus evaluation performed as part of the pivotal monkey T-DM1 repeat-dose toxicity study.

Type of test/study ID/GLP	Test system	Concentrations/ Metabolising system	Results
Gene mutations in bacteria Study No 09-2645 GLP	Salmonella strains	1.6, 50, 160, 500, 1600 and 5000 µg/plate DM1 +/- S9	Negative.
Chromosomal aberrations in vivo Study No 09-2726 GLP	Rat, micronuclei in bone marrow	Rat, single dose DM1 0, 0.01, 0.05, 0.1, 0.2 mg/kg	Positive. DM1 increased micronucleus frequency in a dose dependent matter at 0.05, 0.1, and 0.2 mg/kg, demonstrating evidence of aneugenicity and/or clastogenicity. DM1 was cytotoxic to the bone marrow.
Micronucleus Bone Marrow Assay Part of Study No 07-0653 GLP	Cynomolgus Monkey Micronuclei in bone marrow	Monkey, repeat dose TDM1: 0, 1, 3, 10 mg/kg T-DM1 (DM1: 0, 232, 695, 2316 µg/m^2)	Micronuclei frequency in treated groups similar to vehicle control, however, PCE:NCE ratio was decreased in a dose dependent manner in males, suggestive of bone marrow toxicity

PCE; polychromatic erythrocytes, NCE; normochromatic erythrocytes

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive or developmental toxicity studies have been performed with T-DM1 (see discussion on non-clinical aspects).

Toxicokinetic data

See below a summary table of toxicokinetic parameters from the single and repeat-dose-toxicity studies:

Study ID	Daily Dose		DM1: conjugate ratio	Animal AUC_{0-t} (µg*day/ml)		C_0 (µg/ml)		Animal:Human 495(µg*day/ml) Exposure Multiple	
	mg/kg T-DM1	(µg/m^2 DM1)		♂	♀	♂	♀	♂	♀
04-0976-1459 Cynomolgus monkey (GLP) SD	3	612	3.4	292	313	88.0	81.9	-	0.6
	10	2040		1360	1250	280	253	-	2.5
	30	6120		4020 (0-all)	4370	743	697	-	8.8 *
03-0674-1459 Cynomolgus	30	4900 RPT	2.73	8880		879		-	17.9 *

Study ID	Daily Dose		DM1: conjugate ratio	Animal AUC_{0-t} (µg*day/ml)		C_0 (µg/ml)		Animal:Human 495(µg*day/ml) Exposure Multiple	
	mg/kg T-DM1	(µg/m² DM1)		♂	♀	♂	♀	♂	♀
monkey (Non-GLP) SD/RPT #	47	7400 SD		12300 (0-inf)		1640		-	24.8 *
04-0977-1459 Cynomolgus monkeys (GLP) RPT	3	612	3.4	316	338	79.9	78.9	-	0.7 *
	10	2040		1760	1990	264	263	-	4.0
	30	6120		6570 (0-inf)	7670	800	784	-	15.5
07-0653 Cynomolgus monkeys (GLP) RPT	1	232	3.8	34.3	32.4	20.8	23.0	-	0.07
	3	695		158	140	72.6	70.9	-	0.3 *
	10	2316		662 (0-21)	629	184	196	-	1.3
07-0655 Cynomolgus monkey (Non-GLP) RPT	29¤	6000¤	3.4	-	2310 (0-21)	-	700	-	4.7

¤ *As specified in the TK report, SD: Single dose, RPT: Repeat dose * NOAEL for the respective studies. #PBS vehicle, remaining studies: T-DM1 vehicle (lot M3-TOX098, NB55122-75 or 54310-1D)*

Local Tolerance

No dedicated local tolerance studies have been submitted (see discussion on non-clinical aspects).

Other toxicity studies

Anti-Drug-Antibody analysis

See below table summarising the anti-drug-antibody (ADA), also referred to as Anti-Therapeutic Antibody (ATA), analysis performed in cynomolgus monkey studies.

Study No.	Study Title	Trastuzumab Emtansine Dose (mg/kg)	No. of Animals with Positive ATA Response [a]
04-0975-1459	Evaluation of the Pharmacokinetics of PRO132365 (Trastuzumab-SMCC-DM1) following a Single Intravenous Bolus Dose in Cynomolgus Monkeys with Preliminary Tolerability	0.3, 3, 30	2 of 12
04-0976-1459	Single-Dose Intravenous Toxicity Study of Trastuzumab-MCC-DM1 (PRO132365) in Cynomolgus Monkeys with a 3-Week Recovery Period	3, 10, 30	0 of 18
04-0977-1459	Multiple-Dose Intravenous Toxicity Study of Trastuzumab-MCC-DM1 (PRO132365) Administered to Cynomolgus Monkeys Once Every 3 Weeks for 4 Doses, with a 3- or 6-Week Recovery Period	3, 10, 30	0 of 42
04-1031-1605	A Single-Dose Intravenous Cardiovascular Safety Pharmacology Study of Trastuzumab-MCC-DM1 (PRO132365) Administered to Female Cynomolgus Monkeys with a 3-Week Recovery Period	3, 10, 30	0 of 12
05-0848	Single Dose Intravenous Toxicity Study of Trastuzumab-MCC-7% Unconjugated Maytansinoid in CynomolgusDM1 (PRO132365) with 5 Monkeys with a 3-Week Recovery Period	3, 10 ,30	0 of 18
07-0653	An Intravenous Chronic Toxicity Study of Trastuzumab-MCC-DM1 (PRO132365) Administered to Cynomolgus Monkeys Once Every 3 Weeks for 8 Doses, with a 6-Week Recovery Phase	1, 3, 10	4 of 36
07-1474	Pharmacokinetic Comparability of Trastuzumab-MCC-DM1 (50 g EPPS and 150 g EPPS) in Female Cynomolgus Monkeys	10	1 of 26
08-0800	Pharmacokinetic Comparability of Trastuzumab-MCC-DM1 (150 g Sicor DM1 and 1.5 kg Lonza) in Female Cynomolgus Monkeys	10	1 of 26

ATA = anti-therapeutic antibody.

[a] Data for each study are expressed as the number of animals with positive titers post-dose from the total number of animals dosed with trastuzumab emtansine.

Haemolytic potential and blood compatibility

The haemolytic potential and blood compatibility were evaluated in human and cynomolgus monkey blood (Study No 041257-1459). One human volunteer and 3 cynomolgus monkeys were sampled. T-DM1 in 1.25, 2.5 and 5.0 mg/mL were added to the samples, as well as control article, plasma (negative control) and 1% saponin (positive control). Sample and test or control article volume was equal (0.5 mL), therefore the final concentration in whole blood, serum or plasma. No positive or negative controls were used in the blood compatibility assay. T-DM1 did not cause hemolysis in either cynomolgus monkey or human blood and was compatible with cynomolgus monkey and human serum and plasma.

Cross-Reactivity of T-DM1 with human and cynomolgus tissue *in vitro*

This study was performed to compare and characterize the target antigen-specific and non-target binding of T- DM1. Two concentrations of T-DM1 (1.0 and 10 µg/mL) was applied to cryosections from a full panel of human and cynomolgus monkey tissues and immunohistochemically detected with a mouse anti-DM1 secondary antibody followed by a biotinylated anti-mouse IgG tertiary antibody.

Human tissues were collected as surgical or autopsy specimens, and cynomolgus tissues were collected as necropsy specimens from three individuals in both species. Negative controls for

each tissue were generated using Human IgG1κ antibody (isotype control) in place of T-DM1 at the same concentrations defined for the test article (1.0 and 10 µg/mL).

In the cynomolgus monkey tissue, moderate to high levels of background staining in connective tissue were present at both concentration levels for both T-DM1 and control article. The background staining was attributed to the secondary antibody (mouse anti-DM1), and this was confirmed by omitting T-DM1, and the background staining was similar. The presence of this background "noise" made it difficult to assess the presence of T-DM1 specific binding in the interstitial tissue components, however, as this was only the case for the cynomolgus tissue and not the human tissue, the clinical relevance was limited.

The epithelial cells had primarily granular membrane staining with T-DM1, while spindle cells (presumptive nerve sheath/Schwann cells) had primarily cytoplasmic staining. Glial and mononuclear cells had both membrane and cytoplasmic staining. In general, epithelial and glial cell staining was greater in intensity than spindle cell staining. Ductal and apocrine gland epithelium stained with the greatest intensity and squamous epithelium with the least. Basal and basolateral cell surfaces stained more intensely than the apical cell surface.

Epithelial and spindle cells were most frequently positive for T-DM1 binding, however, the monkey samples were less frequently positive compared to the human tissue samples. It was not possible to discern the reasons for these differences between the human and cynomolgus monkey samples, as the monkey samples had a relatively high degree of background staining, especially in the connective tissue, attributed to the secondary antibody (mouse anti-DM1).

The positive spindle cells were often closely associated with peripheral nerve bundles and ganglia (presumptive Schwann cells).

Thrombocytopenia: Mechanism of Action Investigation

Effects of T-DM1 on platelet function and formation from haematopoietic stem cells were evaluated. While T-DM1 did not have a direct effect on the platelet function, it impaired megakaryocyte and platelet production. The findings in this study are consistent with the mechanism of action of DM1 as an inhibitor of tubulin polymerisation, and the critical role of microtubules in megacaryocyte integrity and platelet production. DM1-conjugated antibodies were internalised in a target independent, partially Fc-mediated manner into megakaryocytes and intracellular release of DM1 resulted in a reduction of the precursor megakaryocyte cell population.

2.3.5. Ecotoxicity / environmental risk assessment

T-DM1 is readily degradable (84% in 28 days). Toxicity for algae, planktonic crustaceans (daphnids), fish (guppy) as well as inhibition of aerobic bacterial respiration was evaluated for T-DM1 (according to OECD Nos. 201, 202, 203 semi static and 301 F respectively). The results are summarised below:

Algae (Desmodesmus)	ErC_{50} (72 h) EyC_{50} (72 h)	>100 mg/L ~ 100 mg/L
Planktonic	EC_{50} (48h)	>100 mg/L

crustacians (Daphina magna)	NOEC (48h)	100 mg/L
Fish (Guppy)	LC_{50} (96h) NOEC (96h)	>100 mg/L <100 mg/L

As breast cancer on the whole and HER2-positive breast cancer in particular have lower prevalence than the default Fpen, a refinement based on the use of crude incidence rates reflecting the actual number of cases arising in a specific population with a given age-structure was considered appropriate. The Applicant used the highest reported crude incidence rate instead of the prevalence of breast cancer in Europe, which is 178.9 per 100,000 women (or 0.179%) and occurs in Belgium [International Agency for Research on Cancer online analysis, h*ttp://globocan.iarc.fr/,* accessed April 14th 2011]. Extrapolating to the whole population, assuming 1) that there are 50% each of males and females and 2) that breast cancer incidence in males is only about 1% of that in females and can therefore be neglected, the overall prevalence of breast cancer in the whole European population is at most 0.09%.

In addition, based on recent publications (Jones and Budzar (2009), Koeninki et al (2009), Parise et al (2009), Schmitt (2009), Aitken et al (2010), Davoli et al (2010), Lund et al (2010) and Reichmann et al (2010)) referring to the Europe and USA, there is a consensus that not more than 30% of breast cancer patients are HER2-positive.

When factoring in the incidence of breast cancer in the whole European population as well as the fraction of HER2 positive cancer patients, the refined Fpen based on incidence for the whole theoretical T-DM1 patient group is 0.027% or 0.00027. Based on the Fpen refinement to 0.027% or 0.00027 (above) and on a maximum daily dose (MDD) of 252 mg T-DM1 (assuming a 70 kg body weight) applied only once every three weeks. In well-defined cases the MDD may be divided into the minimum number of days for one treatment period, which for T-DM1 is 21 days. Therefore, the theoretical initial surface water PEC for whole T-DM1 is PECsurfacewater = 1.62 ng T-DM1/l.

In the course of both human metabolism and bacterial degradation in wastewater treatment the major moiety by far (the trastuzumab antibody) will be removed. As MCC-DM1 (along with lys-MCC-DM1) is the compound excreted by patients and released from sewage treatment into the environment, MCC-DM1 should be considered to better represent the environmental fate and effects of T-DM1. Making up just below 2% of the molecular mass of the whole T-DM1 molecule (an average 3.5 MCC-DM1 units are conjugated to one trastuzumab molecule) a realistic PECsurfacewater for MCC-DM1 is 0.0000324 µg MCC-DM1/l or 0.0324 ng MCC-DM1/l. Moreover, based on the logKOW at pH 5, 7 and 9, which is always below 1.5 with a maximum of 1.31 in one measurement at pH 7, MCC-DM1 is not predicted to bioaccumulate.

In addition, both T-DM1 and MCC-DM1 were not inhibitory to the activated sludge bacteria in the respective ready and inherent biodegradation tests at nominal initial concentrations of 20 mg/l respectively 30 mg/l. Back-calculating from the PECsurfacewater of 0.0324 ng MCC-DM1/l by applying the 10-fold default dilution factor results in a PECsewage treatment of 0.324 ng MCC-DM1/l. Comparing this PECsewage treatment with the non-inhibitory concentrations, particularly

the one of MCC-DM1, suggests a margin of safety in the region of 106 for the compartment wastewater treatment, hence there is no evidence for risk to sewage treatment.

A summary of the main study results for T-DM1 is shown in the below table.

Summary of main study results

Substance (INN / Invented Name): T-DM1			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	1.31 pH7.0	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.31 pH7.0	not B
	BCF		
Persistence	DT50 or ready biodegradability	60% of ThOD in a 10-d window (OECD301F)	not P
Toxicity	NOEC or CMR	Not definitive	Not known
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00162	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			No

2.3.6. Discussion on non-clinical aspects

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). 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, 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.

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/m2 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 (see SmPC section 5.3). In view of these results, the highest non-severely toxic dose (HNSTD) in cynomolgus monkeys was 10 mg/kg for four injections every 3 weeks which was below the no observable adverse effect level in that species and below one-tenth of the severely toxic dose in rats, this information was used to determine a Phase I starting dose in humans.

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 (see SmPC section 5.3).

Dedicated fertility studies have not been conducted with trastuzumab emtansine. However, based on results from general animal toxicity studies, adverse effects on fertility can be expected (see SmPC section 5.3).

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 (see SmPC section 5.3).

The antibody-drug-conjugate T-DM1 is metabolised in the body, and the antibody moiety (trastuzumab) will not reach the environment. On the other hand, the drug part of the conjugate will reach the environment, and therefore the partition coefficient between octanol and water (logKow) was determined for both the intact antibody-drug-conjugate and the metabolite MCC-DM1. For both T-DM1 and also SMCC-DM1 (the excreted metabolite) $PECsurfacewate_r$ value is below the action limit of 0.01μg/L and is not a PBT substance as logKow does not exceed 4.5.

As the PECsurfacewater for both T-DM1 and MCC-DM1have been determined to be smaller than the 0.01 μg/L threshold as well as the logKow for MCC-DM1was smaller than the 4.5 limit, there is no need for any further studies on environmental safety.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC section 6.6).

2.3.7. Conclusion on the non-clinical aspects

Based on the nonclinical safety data trastuzumab emtansine has been adequately characterised in terms of its pharmacodynamic activity, pharmacokinetic properties and safety profile.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Number	Study Design and Patient Population	Dose	Primary Endpoints	Scope of Safety Data Collection	No. of Patients in Analyses	Data Cut-off Date
Pivotal Phase III Study						
TDM4370g/ BO21977 [a] (Phase III)	Study Design: A randomized, multicenter, Phase III open-label study of the efficacy and safety of trastuzumab emtansine vs. lapatinib + capecitabine Population: Patients with incurable LABC or MBC whose tumors are positive for HER2 overexpression and have previously received trastuzumab and a taxane.	Trastuzumab emtansine 3.6 mg/kg q3w until disease progression or unmanageable toxicity Or Lapatinib 1250 mg/day continual dosing Capecitabine 2000 mg/m^2/day Days 1–14 q3w	PFS based on IRC, OS, and safety	Drug exposure, adverse events, ECHO/MUGA, and laboratory assessment	SCE; 991 randomized patients (495 to trastuzumab emtansine, 496 to lapatinib plus capecitabine). SCS: 978 treated patients (490 treated with trastuzumab emtansine)	Efficacy (including 1[st] interim OS analysis) and safety: 14 January 2012
Phase II Studies						
TDM4374g [a] (Phase II)	Study Design: A Phase II, single-agent, open-label study of trastuzumab emtansine Population: Patients with incurable, locally advanced, or metastatic HER2-positive breast cancer previously treated with an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine in the neoadjuvant, adjuvant, locally advanced, or metastatic setting and prior treatment with at least two lines of therapy for MBC	Single-agent: trastuzumab emtansine 3.6 mg/kg q3w until disease progression or unmanageable toxicity	ORR by IRF, safety	Drug exposure, adverse events, ECHO/MUGA, and laboratory assessment	SCE and SCS: 110 Treated patients	Efficacy (PFS, ORR, DOR, and TSP): Primary analysis: 17 September 2009, final analysis: 1 January 2010 Safety + OS: 26 April 2011

TDM4258g [a] (Phase II)	Study Design: A Phase II, single-agent, open-label study of trastuzumab emtansine Population: Patients with HER2-positive incurable, LABC or MBC; history of progression on HER2-directed therapy and at least one chemotherapy agent for MBC	Single-agent: trastuzumab emtansine 3.6 mg/kg q3w up to 1 year	ORR by IRF, safety	Drug exposure, adverse events, ECHO/MUGA, and laboratory assessment	SCE and SCS: 112 Treated patients	Efficacy: 25 January 2009 Safety: 25 June 2009
TDM4450g/ BO21976 [a] (Phase II)	Study Design:: A randomized, multicenter, Phase II study of the efficacy and safety of trastuzumab emtansine vs. trastuzumab (Herceptin®) and docetaxel (Taxotere®) Population: Patients withHER2-positive MBC who have not received prior chemotherapy for metastatic or locally advanced disease	Trastuzumab emtansine 3.6 mg/kg q3w until disease progression or unmanageable toxicity Or For Cycle 1: trastuzumab 8 mg/kg + docetaxel either 75 mg/m^2 or 100 mg/m^2 For subsequent cycles: trastuzumab 6 mg/kg on Day 1 q3w + docetaxel 75–100 mg/m^2	PFS based on investigator assess-ments and safety	Drug exposure, adverse events, ECHO/MUGA, and laboratory assessment	SCE: 137 randomized patients (67 to trastuzumab emtansine, 70 to trastuzumab + docetaxel) SCS: 135 treated patients (69 with trastuzumab emtansine, 66 with trastuzumab + docetaxel)	Efficacy (PFS, ORR, DOR, and time to symptom progression): 15 November 2010 Safety and OS: 31 August 2011
TDM4688g [a] (Phase II)	Study Design: A Phase II, open-label study to evaluate corrected QT interval effects of trastuzumab emtansine, and to evaluate the safety and tolerability of combined trastuzumab emtansine and pertuzumab in patients with early disease progression while receiving trastuzumab emtansine alone Population: HER2-positive, incurable LABC or MBC; history of progression on HER2-directed therapy and at least one chemotherapy agent for MBC	Trastuzumab emtansine 3.6 mg/kg q3w until disease progression	Duration of QTc interval	Cardiac safety data, drug exposure, adverse events, ECHO/MUGA, and laboratory assessment	SCS: 51 Treated patients	Safety; 30 May 2011
Phase I Study						
TDM3569g [a] (Phase I)	Study Design: A Phase I, open-label, dose-escalation study of the safety and PK of trastuzumab emtansine administered to patients with HER2-positive MBC who have previously received a trastuzumab-containing regimen Population: HER-positive MBC patients who previously received a trastuzumab-containing regimen	Single-agent: trastuzumab emtansine 3.6 mg/kg q3w until disease progression or unmanageable toxicity	Safety, PK, dose selection	Drug exposure, adverse events, and laboratory assessment	SCS: 15 Patients who received 3.6 mg/kg q3w dose	Safety: 24 August 2009
Extension Study						
TDM4529g/ BO25430	Study Design: Open-label extension study of trastuzumab emtansine. Patient population: Patients enrolled from parent Phase I and II studies included in pooled safety summary analyses	Same as that given in parent study, until disease progression or unmanageable toxicity	Safety	Drug exposure, ECHO/MUGA, and adverse events	SCS: 43 Treated patients	Safety: 17 January 2012

ECHO = echocardiogram; IRC = independent review committee, IRF = independent review facility; IV = intravenous; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; MUGA = multigated acquisition; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; q3w = every 3 weeks; SCE = summary of clinical efficacy SCS = summary of clinical safety, TSP = time to symptom progression.

2.4.2. Pharmacokinetics

Clinical pharmacological evaluations of trastuzumab emtansine are based on PK data obtained from 6 clinical studies.

Overview of Company-Sponsored Clinical Studies Providing Pharmacokinetic Data.

Study [a]	Study Title	Formulation (MFG Scale, DM1 Source [Manufacturer])	No. of Enrolled/PK-evaluable Patients	T-DM1 Doses and Regimens	Comments [b]
TDM3569g	A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of T-DM1 Administered Intravenously to Patients with HER2-Positive MBC Who Have Previously Received a Trastuzumab-Containing Regimen	Liquid (50 g EPPS [Immunogen])	q3w: n=24 qw: n=28 / q3w: n=15 (max) qw: n=16 (max)	q3w: 0.3, 0.6, 1.2, 2.4, 3.6, and 4.8 mg/kg qw: 1.2, 1.6, 2.0, 2.4, and 2.9 mg/kg	Intensive sampling in Cycle 1 and peak/trough PK sampling in subsequent cycles; NCA of PK data
TDM4258g	A Phase II, Single-Arm, Open-Label Study of T-DM1 Administered Intravenously to Patients with HER2-Positive MBC Who Have Progressed while Receiving HER2-Directed Therapy	Lyophilized (50 g EPPS/ 150 g EPPS [Lonza])	112 / 101 (Cycle 1) 69 (Cycle 4)	3.6 mg/kg q3w	Frequent [c] sampling in Cycles 1 and 4 for NCA of PK data; peak/trough PK sampling in subsequent cycles
TDM4374g	A Phase II, Single-Arm, Open-Label Study of T-DM1 Administered Intravenously to Patients with HER2-Positive Metastatic Breast Cancer Who Have Progressed While Receiving HER2-Directed Therapy	Lyophilized (150 g Sicor DM1 [Lonza])	110 / 105 (Cycle 1) 82 (Cycle 4)	3.6 mg/kg q3w	Frequent sampling in Cycles 1 and 4 for NCA of PK data; peak/trough PK sampling in subsequent cycles
TDM4688g	A Phase II, Open-Label Study to Evaluate Corrected QT Interval Effects of T-DM1 in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer and to Evaluate the Safety and Tolerability of Combined T-DM1 and Pertuzumab in Patients with Early Disease Progression While Receiving T-DM1 Alone	Lyophilized (1.5 kg Sicor DM1 [Lonza])	51 / 51 (Cycle 1) 47 (Cycle 3)	3.6 mg/kg q3w for up to 1 year [d]	Frequent sampling in Cycles 1 and 3 for NCA of PK data; QTc assessment pre– and post–T-DM1 dosing
TDM4450g/ BO21976	A Phase II, Randomized Study of T–DM1 vs. Trastuzumab and Docetaxel in Patients with HER2-Positive MBC Who Have Not Received Prior Therapy for MBC	Lyophilized (150 g Sicor DM1 [Lonza])	137 with 67 patients in T-DM1 arm / 62 (Cycle 1) 39 (Cycle 5) No PK in Control	3.6 mg/kg q3w	Frequent sampling in Cycles 1 and 5 for NCA of PK data; peak/trough PK sampling in every other cycles for T-DM1 arm patients
TDM4370g/ BO21977	A Phase III, Randomized Study of T–DM1 vs. Capecitabine and Lapatinib in Patients with HER2-Positive MBC and LABC Who Have Received Prior Trastuzumab-based Therapy	Lyophilized (1.5 kg Sicor DM1 [Lonza])	991 with 495 patients in T-DM1 arm / 292 (T-DM1 Cycle 1) 257 (T-DM1 Cycle 4) No PK in Control arm	3.6 mg/kg q3w	Frequent sampling in Cycles 1 and 4 for NCA of PK data; peak/trough PK sampling in cycle 2, 3 and every other cycles starting cycle 6 for PK patients in T-DM1 arm

ATA = anti-therapeutic antibody; EPPS = EagelPicher Pharmaceutical Services; HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; LABC= Locally advanced breast cancer; MFG = manufacturing; NCA = non-compartmental analysis; PK = pharmacokinetic; q3w = every 3 weeks; QTc = corrected QT; qw = every week.

Notes: In all studies, the analytes measured were trastuzumab emtansine, total trastuzumab, and DM1; the incidence of ATAs was also examined.

A population PK analysis was performed using trastuzumab emtansine PK data for all studies except Study TDM4688g.

[a] In the open-label extension study TDM4529g/BO25430, no PK assessment was done. PK assessment was done for these patients when they were enrolled into the parent studies TDM4258g and TDM4374g.

[b] ATA assessments were performed in all six studies.

[c] Frequent sampling denotes sufficient blood sampling to allow for characterization of the concentration—time curve; peak/trough (sparse) sampling does not allow for PK parameter estimation.

[d] The earliest a patient could begin treatment with trastuzumab emtansine in combination with pertuzumab was Cycle 4, Day 1, after all PK samples for single-agent trastuzumab emtansine had been obtained in Cycle 3. Pertuzumab dose: 840-mg loading dose, followed by 420 mg q3w for 1 year.

Absorption

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

The PK parameters of trastuzumab emtansine administered at 3.6 mg/kg q3w in each of these studies are summarized in the table below. Patients in TDM4370g/BO21977 who received 3.6 mg/kg of trastuzumab emtansine intravenously every 3 weeks had a mean maximum serum concentration (C_{max}) of trastuzumab emtansine of 83.4 (± 16.5) μg/mL. 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.

Mean clearance values ranged from 7 to 13 mL/day/kg, the volume of distribution was limited to the plasma volume, and terminal half-life was approximately 4 days.

PK Parameters of Trastuzumab Emtansine Conjugate Following 3.6 mg/kg Administered Intravenously to Patients on an Every-3-Week Regimen

			Mean (± SD)				
Study	Cycle [a]	No. of PK-evaluable Patients	C_{max} (µg/mL)	AUC (day • µg/mL)	$t_{1/2}$ (days)	V_{ss} (mL/kg)	CL (mL/day/kg)
TDM3569g	1	15	76.2 (±19.1)	300 (±65.8)	3.1 (±0.7)	58.4 (±12.4)	12.7 (±3.56)
TDM4258g	1	101	80.9 (±20.7)	457 (±129)	3.53 (±0.7)	28.4 (±12.9)	8.51 (±2.7)
TDM4258g	4	69	68.9 (±21.8)	461 (±136)	4.43 (±1.7)	45.2 (±43.0)	8.41 (±4.3)
TDM4374g	1	105	79.5 (±21.1)	486 (±141)	3.96 (±0.964)	31.2 (±10.9)	8.04 (±2.97)
TDM4374g	4	82	78.3 (±25.6)	456 (±162)	4.33 (±0.757)	39.3 (±32.8)	7.27 (±2.49)
TDM4688g	1	51	75.6 (±21.9)	431 (±126)	4.02 (±0.938)	41.2 (±24.5)	9.17 (±3.03)
TDM4688g	3	47	80.7 (±18.1)	475 (±150)	4.46 (±0.926)	43.6 (±40.7)	7.91 (±3.30)
TDM4450g/BO21976	1	62	84.2 (± 30.6)	495 (± 158)	3.49 (±0.743)	30.2 (±21.3)	8.23 (±3.95)
TDM4450g/BO21976	5	39	79.1 (± 23.7)	473 (± 141)	4.22 (±0.597)	33.6 (±12.4)	6.67 (±1.58)
TDM4370g/BO21977	1	292	83.4 (± 16.5)	489 (± 122)	3.68 (±0.886)	29.5 (±14.6)	7.81 (±2.18)
TDM4370g/BO21977	4	257	85.0 (± 33.4)	475 (± 127)	4.19 (±0.679)	33.3 (±11.4)	7.10 (±1.89)

AUC=area under the serum concentration–time curve from Time 0 extrapolated to infinity (AUC_{inf}) for Cycle 1 and area under the serum concentration–time curve from Time 0 to time of last measurable concentration (AUC_{last}) in that cycle for Cycle 3 or 4; CL=clearance; C_{max}=maximum observed concentration; $t_{1/2}$=terminal half-life; V_{ss}=volume of distribution at steady state.

[a] Results were from Cycle 1 after the first trastuzumab emtansine dose, Cycle 3 after the third trastuzumab emtansine dose at steady state, or Cycle 4 after the fourth trastuzumab emtansine dose at steady state.

The development of trastuzumab emtansine has been based solely on intravenous administration, therefore no BA studies were conducted and the bioavailability is expected to be 100%.

Distribution

The mean volume of distribution at steady-state (Vss) of trastuzumab emtansine observed across the six clinical studies in which the drug was administered at 3.6 mg/kg q3w, ranged from 28.4 mL/kg and 58.4 mL/kg after the first trastuzumab emtansine dose (Cycle 1) and from 33.3 mL/kg and 43.6 mL/kg at steady state (see table above).

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 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 (t1/2) 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 with the exception of body weight, 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.

Dose proportionality and time dependencies

One dose-escalating study was performed in T-DM1 (Study TDM3569g) where 6 doses q3w and 5 doses qw was assessed. Serum T-DM1 concentrations decreased, with a mean terminalphase half-life (t1/2) ranging from 1.3 to 4.1 days across the dose levels tested. No significant accumulation was observed with q3w dosing of T-DM1. Systemic exposure, as measured by Cmax and AUC, increased with increasing dose. Assessment of dose linearity was limited by the small number of patients evaluated, especially at doses below 2.4 mg/kg q3w. The volume of distribution at steady state (Vss) of T-DM1 approximated the physiologic serum volume, and did not appear to change considerably with dose. Study JO22591 was a dose escalating study that investigated the PK of 3 doses of T-DM1 (1.8, 2.4 and 3.6 mg/kg q3w). Results from JO22591 concluded that the pharmacokinetics of serum RO5304020 (T-DM1) and serum total trastuzumab was linear when the dose of RO5304020 (T-DM1) was in the range of 1.8 to 3.6 mg/kg.

PK-parameter values were obtained in cycle 1 and in cycle 3, 4 or 5, depending on study (TDM3569g; TDM4258g; TDM374g; TDM688g; TDM4450g; TDM4370g). For both total trastuzumab, conjugated T-DM1 and DM1, no relevant accumulation was observed. Also no change in T-DM1 PK parameters was observed from cycle 1 to subsequent cycles across studies.

In conclusion, 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.

Special populations

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.

No formal PK study has been conducted in patients with hepatic impairment.

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.

The pharmacokinetics of T-DM1 was best described in the population pharmacokinetics analysis by a two-compartment model with first-order elimination from the central compartment. The estimated clearance was 0.676 L/day, the central volume of distribution 3.127 L and elimination half-life 3.94 days. T-DM1 reached steady state concentrations within one treatment cycle. 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, with the exception of body weight, the magnitude of effect of these covariates was small and unlikely to have any clinically meaningful effect on trastuzumab emtansine exposure. In addition, exploratory analysis showed that the impact of renal function, race and age on the pharmacokinetics of total trastuzumab and DM1 was limited and was not clinically relevant.

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).

Pharmacokinetic interaction studies

No clinical interaction studies were performed. T-DM1 is expected to undergo catabolism by means of proteolysis in cellular lysosomes, with no significant involvement of CYP enzymes. As such, T-DM1 pharmacokinetics is unlikely to be affected by concomitant medications that are CYP inhibitors and inducers.

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. In-vitro studies showed that for concentrations up to 600 ng/ml DM1 did not induce or inhibit CYP metabolism.

DM1 is a P-gp substrate and not an inhibitor at 369 µg/ml and the highest Cmax measured in clinical studies was 59.7 ng/ml (see pharmacokinetics using biomaterials). . In human plasma, trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels.

A sensitivity analysis from the pivotal study TDM4370g/BO21977 showed that Cmax, AUC and clearance for T-DM1, total trastuzumab and DM1 were unaffected by concomitant medication with CYP3A inducers, CYP3 inhibitors, P-gp inhibitors and others (others = not CYP3A inhibitors, CYP3A inducers, or P-gp inhibitors). Also preliminary results from ongoing studies showed no

change in PK parameters for T-DM1, total trastuzumab, DM1, docetaxel, paclitaxel, and pertuzumab when co-administered.

Pharmacokinetics using human biomaterials

In vitro metabolism studies in human liver microsomes suggest that DM1, a catabolite of T-DM1, is metabolized mainly by CYP3A4 and, to a lesser extent, by CYP3A5. DM1 did not induce and/or inhibit CYP-mediated metabolism at concentrations up to 600 ng/mL. In addition, an in vitro metabolism experiment showed that DM1 is a substrate of P-gp and not an inhibitor of P-gp when tested at 0.5 µM (369 µg/mL). Currently available data show that clinical DM1 levels do not exceed 59.7 ng/mL.

Exposure relevant for safety evaluation

Exposure-safety evaluation was performed with the pooled patient population from 5 studies and for the pivotal study alone. In both groups evaluated, no associations of Grade 3 or 4 thrombocytopenia and hepatotoxicity adverse events and T-DM1 AUC and Cmax, total trastuzumab AUC, or DM1 Cmax were seen. Furthermore there were no associations of quartiles of T-DM1 AUC and Cmax, total Trastuzumab AUC and DM1 Cmax and values of ALT, AST, total bilirubin and platelet counts.

Immunogenicity

Of all patients treated with T-DM1, a total of 836 patients from six studies had at least one post-dose ATA timepoint evaluable for ATA response. Overall, confirmed positive ATA responses were detected in 44 of 836 (5.3%) patients across the six studies; 28 of these patients had negative baseline samples. Positive responses in all 44 patients were confirmed and characterized by competitive binding immunodepletion with T-DM1 and trastuzumab. The majority (37 of 44) of patients had a positive response immunodepleted by T-DM1 only. The positive response from one or more timepoints from 6 patients was immunodepletable by both T-DM1 and trastuzumab, and the response from 1 patient was immunodepleted by trastuzumab only.

The clinical significance of antibody development against T-DM1 is unknown; however, the impact of ATA response on pharmacokinetics was assessed. There was no obvious change in the pharmacokinetics of patients who tested ATA positive to T-DM1 when compared with data from patients who tested ATA negative.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies about the mechanism of action of T-DM1 were submitted (see Non-clinical pharmacodynamics).

Primary and Secondary pharmacology

QTc interval

A dedicated single arm QTc study (TDM4688g; N=51) was conducted in the target patient population, at the intended marketed dose regimen. The primary objective of Study TDM4688g, a multicenter, single-arm study in patients with HER2-positive locally advanced or metastatic breast cancer, was to evaluate the effect of T-DM1 on the duration of the QTc interval. QTc interval was measured as change from baseline to selected timepoints following T-DM1 administration, calculated using QTcF. Overall, no patients had a QTc interval > 480 ms and only 2 patients had changes from baseline QTc of more than 30 seconds (corrected with Bazetts formula). Mean baseline-adjusted average QTcF interval showed that the upper bound of the 90% two-sided CI did not exceed 10 ms, as recommended in the Guidance for industry: E14 Clinical evaluation on QT/QTc interval prolongation and proarrythmic potential for non-arrythmic drugs. The exploratory concentration-QTc analysis showed a trend between T-DM1, total trastuzumab and DM1 concentrations and QTc interval prolongation. However, at the observed concentration ranges of T-DM1, total trastuzumab and DM1, the upper bound of the 95% one-sided CI did not exceed 10 ms. In conclusion administration of T-DM1 was not shown to result in any significant QTc prolongation.

2.4.4. Discussion on clinical pharmacology

The PK of trastuzumab emtansine (T-DM1) was adequately investigated and sufficiently characterised. DM1 was detected in human plasma, as a result of cleavage from trastuzumab emtansine.

A Population PK analysis was performed, which identified several covariates with a significant effect on Poplation PK parameters. Yet, with the exception of body weight. the impact of these identified covariate on exposure was low. Body weight based dose of 3.6 mg/kg every 3 week withtout correction for other covariates is considered appropriate.

Elderly patients

A population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine. There are insufficient data to provide dosing recommendations in patients ≥ 75 years due to limited data in this subgroup, therefore no dose adjustment is proposed in the SmPC.

Renal impairment

The T-DM1 derived DM1 and metabolites MCC-DM1 and lys-MCC-DM1 has only been partially characterised in humans. However, the concentration of DM1 were always low, often lower than the LLOQ, which precluded a formal PK analysis. The impact of renal impairment on the PK of T-DM1 was investigated through a Population PK analysis. The results showed a lack of effect of renal impairment on the exposure to T-DM1, which is consistent with the protein moiety of drug being eliminated by ubiquitary proteolysis. The nonclinical data, a mass balance study in rats, and exploratory PK analyses in patients with and without renal impairment in Study TDM4688g

suggest that renal impairment has a minimal effect on the exposure to the DM1-containing catabolites, namely MCC-DM1 and Lys-MCC-DM1.

No adjustment to the starting dose is needed in patients with mild or moderate renal impairment (see section SmPC 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.

A dedicated study of the PK of trastuzumab emtansine and relevant catabolites in MBC patients with mild to moderate hepatic impairment is ongoing (see Risk-management plan).

Hepatic impairment

Liver function should be monitored prior to initiation of treatment and each dose (see SmPC section 4.4 and RMP). 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.

Interactions

The potential for interaction has been sufficiently investigated. In vitro metabolism studies in human liver microsomes suggest that DM1 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.

2.4.5. Conclusions on clinical pharmacology

The applicant will submit the results from a dedicated study of the PK of trastuzumab emtansine and relevant catabolites in MBC patients with mild to moderate hepatic impairment (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; see Risk-management plan).

2.1. Clinical efficacy

2.1.1. Dose response studies

Study tdm3569g was the basis for the recommended dose for the phase II studies. This was a Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of Trastuzumab-

MCC-DM1 (PRO132365) Administered Intravenously to Patients with HER2-Positive Metastatic Breast Cancer Who Have Previously Received a Trastuzumab-Containing Regimen. Approximately four centers in the United States were to participate in the study to enrol approximately 50-60 patients.

Cynomolgus monkeys were selected as the relevant species for toxicology studies designed to determine a Phase I starting dose as discussed in the non-clinical aspects. The highest non-severely toxic dose (HNSTD) in cynomolgus monkeys was 10 mg/kg for four injections every 3 weeks (equivalent to 120 mg/m2 when the dose was calculated using a body surface area conversion factor of 0.32 to convert cynomolgus monkey dose levels [mg/kg] to equivalent human dose levels [mg/kg]), which was below the no observable adverse effect level in that species and below one-tenth of the severely toxic dose in rats. The proposed starting dose in humans was 0.3 mg/kg body weight (equivalent to 10 mg/m2 body surface area).

Between 25 April 2006 and 20 May 2008, 54 patients were enrolled (26 and 28 patients in the q3w and qw cohorts, respectively) and 52 were treated.

The median treatment duration was 16.7 weeks in the q3w cohorts and 18.9 weeks in the qw cohorts. T-DM1 was generally well tolerated. No Grade > 1 nausea, vomiting, alopecia, neuropathy, or LVEF decline has been observed with the every-three-week schedule. No Grade > 1 LVEF decline has been observed with the weekly schedule.

Two patients at the 4.8 mg/kg dose level in the every-three-week cohorts had DLTs in the first cycle of treatment. Both were Grade 4 non serious thrombocytopenia. One patient at the 2.4 mg/kg dose level in the weekly cohorts had a DLT of Grade 2, nonserious thrombocytopenia that prevented re-treatment on Cycle 1, Day 8. Two patients at the 2.9 mg/kg dose level in the weekly cohorts had DLTs. One patient had Grade 3, non-serious thrombocytopenia that prevented re-treatment on Cycle 1 Day 8, and one patient had a laboratory abnormality Grade 3 elevated AST on Cycle 1, Day 2 that prompted the investigator to hold therapy on Cycle 1, Day 8. This patient was permitted to continue study treatment on Cycle 2 Day 1 per protocol and discontinued during Cycle 2 because of progressive disease. The MTDs for the every-three-week and weekly cohorts were 3.6 mg/kg and 2.4 mg/kg, respectively.

The most common adverse events in the weekly cohort were fatigue, nausea, diarrhea, and aspartate aminotransferase increased. The most common adverse events in the every-three-week cohort were thrombocytopenia, fatigue, and nausea. Thrombocytopenia was the most frequent adverse event in the every-three-week cohorts and a key DLT in both the every-three-week and weekly cohorts. Reversible elevations in hepatic transaminases were observed. Most of these elevations were mild to moderate in severity.

In the q3w cohorts, 5 of 24 treated patients had an objective partial response (ORR = 21%). Four responses occurred in the 3.6 mg/kg cohort, and one occurred in the 2.4 mg/kg cohort. Of the 15 patients that received the 3.6 mg/kg qw MTD, there were 9 patients with measurable disease of whom 4 achieved an objective partial response (ORR = 44 %). The median duration of response was 10.5 months (range, 1.7 + to 26.3 + months). Seven patients had stable disease longer than 6 months. The 6-month clinical benefit rate was 50%. Two patients have completed the study and transferred to the extension study TDM4259g.

In the qw cohorts, 13 of 28 treated patients had an objective partial response (ORR = 46%). Six responses occurred in 2.4 mg/kg cohort, two in the 2.0 mg/kg cohort, two in the 1.6 mg/kg cohort, and three in the 1.2 mg/kg cohort. Of the 16 patients that received the 2.4 mg/kg qw MTD, there were 15 patients with measurable disease of whom 6 achieved an objective partial response (ORR = 44%). The median duration of response was 18.6 months (range, 1.4 + −19.1 + months). Three patients had stable disease longer than 6 months; the 6-month clinical benefit rate was 57%. Six patients have completed the study and three were enrolled in the extension study TDM4259g.

The Phase II study, TDM4258g, showed similar tolerability at the 3.6 mg/kg every 3 weeks (q3w) dose level, with only a small percentage of patients (3 of 112 patients) requiring dose reduction. Thus, the T-DM1 dose of 3.6 mg/kg q3w was selected for testing in the phase III study TDM4370g/BO21977 based on the comparable efficacy and safety of the two regimens and convenience of a 3-week regimen for this patient population.

A formal dose-response analysis was not possible due to the limited number of patients in the dose escalating study. Results from the exposure-response analysis with patients from the pivotal study TDM4370g/BO21977 showed that for OR, PFS and OS, no association of T-DM1 AUC, T-DM1 Cmax, to total trastuzumab AUC and DM1 Cmax, when splitting the data in below and above median. Also the responder probability was not associated with of T-DM1 AUC, T-DM1 Cmax, to total trastuzumab AUC and DM1 Cmax. Similar results were seen in patients who were pretreated with HER2-directed therapies and in those not pretreated, suggesting that the response is independent of prior therapy.

2.1.2. Main studies

A Randomized, Multicenter, Phase III Open-Label Study Of The Efficacy And Safety Of Trastuzumab Emtansine (T-DM1) Vs. Capecitabine + Lapatinib In Patients With Her2-Positive Locally Advanced Or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy (TDM4370g/BO21977, EUDRACT No.: 2008-005 713-22; ClinicalTrials.gov Identifier: NCT00829166; "EMILIA")(Verma, Miles et al. 2012)

Methods

Study Participants

The participants selected for this trial are HER2+ (ICH and/or FISH centrally confirmed) unresectable LABC or MBC patients who had progressed after treatment, at the minimum, with trastuzumab and a taxane, both alone or in combination with other agents, in any breast cancer disease setting (i.e, adjuvant, unresectable, locally advanced or metastatic setting).

Progression must have occurred during or after the most recent treatment for locally advanced/metastatic breast cancer, or within 6 months after completing adjuvant therapy. Patients with both measurable and/or non-measurable disease were included.

Among the inclusion criteria patients were required to have:

- Cardiac ejection fraction > 50% by either ECOG or MUGA
- ECOG Performance Status 0-1

According to main exclusion criteria, patients with peripheral neuropathy grade > 3 per NCI CTCAE criteria v 3.0, CNS-only disease, with brain metastases untreated or requiring therapy to

control symptoms, history of congestive heart failure or serious cardiac arrhythmia requiring treatment were excluded.

Key Inclusion and Exclusion Criteria Across Studies

	TDM4370g/BO21977 (pivotal)	TDM4374g	TDM4258g	TDM4450g/BO21976
Age	≥ 18	≥ 18	≥ 18	≥ 18
HER2 Status	HER2-positive (3+ IHC or gene amplification by FISH) based on central testing	HER2-positive (3+ IHC or gene amplification by FISH) based on local testing	HER2-positive (3+ IHC or gene amplification by FISH) based on local testing	HER2-positive (based on IHC 3+ or gene amplification by FISH) based on local testing
Patient Population	Patients with HER2-positive unresectable LABC or MBC who progressed during or after their most recent treatment for MBC, or within 6 months of their most recent adjuvant treatment	Patients with HER2-positive unresectable LABC or MBC who have received at least 2 lines of HER2-directed therapy.	Patients with HER2-positive unresectable LABC or MBC who have progressed while receiving HER2-directed therapy	Patients with HER2-positive unresectable LABC and/or MBC who have not received prior chemotherapy for metastatic disease
Measurable disease by RECIST 1.0	Measurable and/or nonmeasurable disease	Measurable disease. Patients were to have at least one target lesion ≥ 2 cm on CT scan or ≥ 1 cm on a spiral CT scan	Measurable disease. Patients were to have at least one target lesion ≥ 2 cm on CT scan or ≥ 1 cm on a spiral CT scan	Measurable disease. Patients were to have at least one target lesion ≥ 2 cm on CT scan or ≥ 1 cm on a spiral CT scan
Cardiac Function	LVEF ≥ 50% at screening. Patients with symptomatic CHF requiring treatment, a history of CHF, serious cardiac arrhythmia requiring treatment, myocardial infarction or unstable angina within 6 months of randomization, current dyspnea at rest due to advanced malignancy or Grade ≥ 3 peripheral neuropathy were excluded.	LVEF ≥ 50% at screening. Patients with a history of significant cardiac disease, unstable angina, CHF, myocardial infarction, or ventricular arrhythmia requiring medication were excluded	LVEF ≥ 50% at screening. Patients with history of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment were excluded.	LVEF ≥ 50% at screening. Patients with history of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment were excluded.
Intolerance to trastuzumab	Patients with a history of intolerance to trastuzumab including Grade 3 or 4 IRR were excluded	Patients with a history of intolerance to trastuzumab including Grade 3 or 4 IRR were excluded	Patients with history of intolerance to trastuzumab including Grade ≥ 3 hypersensitivity reaction or Grade ≥ 1 IRR with the most recent trastuzumab infusion prior to study entry were excluded	Patients with a history of intolerance to trastuzumab including Grade 3–4 IRR or hypersensitivity to trastuzumab or murine proteins were excluded
Performance Status	ECOG PS of 0 or 1	ECOG PS of 0, 1, or 2	ECOG PS of 0, 1, or 2	ECOG PS of 0 or 1
Prior Anticancer Treatments	Prior treatment with a taxane and trastuzumab was required. Prior treatment with lapatinib or capecitabine was not	Prior treatment with an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine was	Prior treatment with at least one chemotherapy agent for MBC and with HER2-directed	Prior treatment with chemotherapy for MBC was not allowed (hormonal therapy was allowed).

	TDM4370g/BO21977 (pivotal)	TDM4374g	TDM4258g	TDM4450g/BO21976
Age	≥ 18	≥ 18	≥ 18	≥ 18
	allowed.	required. Prior treatment with at least two anti-HER2 agents in the MBC setting or unresectable LABC setting was required.	therapy in any setting was required.	

*, male patients were not excluded but all randomized patients were female.
IRR = infusion related reaction

Treatments

Control arm (lapatinib + capecitabine): Lapatinib 1250 mg/day orally with continuous daily dosing on a 3-week cycle + Capecitabine 1000 mg/m2 orally twice daily on Days 1−14 of a 3-week cycle

Tratuzumab emtansine arm: Trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of a 3-week cycle.

Study treatment was administered on a 3-week cycle and treatment continued until disease progression (PD) or unmanageable toxicity.

The initial dose of tratuzumab emtansine was to be administered over 90 minutes (± 10 minutes). Infusions could be be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs had to be be assessed pre-dose and post-dose. Following the initial dose, patients were to be observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine could be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion.

Objectives

The primary objectives for this study were as follows:

- To compare the efficacy of trastuzumab emtansine versus capecitabine plus lapatinib in patients with HER2-positive, unresectable, locally advanced breast cancer or MBC as measured by PFS on the basis of an independent review of tumor assessments;
- To compare the efficacy of trastuzumab emtansine 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 the safety of trastuzumab emtansine relative to the safety of capecitabine plus lapatinib.

Outcomes/endpoints

PFS and OS were co-primary efficacy endpoints for this study:

- PFS by IRC assessment, defined as the time from randomization to the first occurrence of progression, as determined by independent review of tumor assessments through use of modified RECIST {Therasse, 2000 #1593}(see Table below), or death from any cause;

- OS, defined as the time from randomization to death from any cause;

Secondary efficacy endpoints included:

- Objective tumor response (determined primarily by independent review of tumor assessments using modified RECIST); only patients with measurable disease at baseline were included in the analysis. Patients without a post-baseline tumor assessment were considered non-responders. Objective response rate (ORR) was defined as the proportion of patients with CR or PR.
- Time to treatment failure (TTF) was defined as time from randomization to discontinuation of treatment for any reason. In the lapatinib plus capecitabine arm, a patient was considered to have failed treatment only if both drugs were discontinued; the later of the two discontinuation dates was used as the treatment failure date if the two drugs were discontinued at different dates.
- Time to symptom progression (defined as the time from randomization to the first documentation of a $\geqslant$ 5-point decrease from baseline in the scoring of responses) was measured by patients' answers to questions in FACT-B TOI-PFB in the two treatment groups. The TOI-PFB is a subset of the FACT-B and includes the Physical, Functional and Breast subscales. Only patients with a baseline assessment and at least one follow-up assessment were included in this analysis. Analysis of time to symptom progression in the randomized population was based on female patients only. Data for patients who did not have an observed symptom progression at the time of data cutoff were censored at the last observed TOI-PFB assessment date. Patients without post-baseline TOI-PFB assessments were censored at the time of randomization plus 1 day.

Summary of main modification to RECIST

Measurability of Tumor Lesions at Screening	At screening, tumor lesions will be categorized as follows: On spiral CT, for images with lesions with a reconstruction interval of less than or equal to 5 mm, the minimum **measurable** lesion size will be 10 mm; if the reconstruction interval on spiral CT is greater than 5 mm, the minimum lesion size will be double the reconstruction interval. On conventional CT or MRI, for images with lesions with a reconstruction interval of less than or equal to 10 mm, the minimum measurable lesion size will be 20 mm; if the reconstruction interval on conventional CT or MRI is greater than 10 mm, the minimum lesion size will be double the reconstruction interval. **Nonmeasurable** lesions will include all other lesions, including small lesions and truly nonmeasurable lesions. Brain imaging acquired at screening or follow-up or an unscheduled timepoint will undergo radiology review. Brain lesions will be assessed as non-target lesions. Any brain lesions identified by the investigator sites will be taken into consideration by the oncologist in his/her assessment.
Clinical Examination / Chest X-Rays/ Ultrasound /Laparoscopy / Endoscopy	The radiologists will limit measurement of target lesions to CT and MRI scans, the best currently available and most reproducible methods.
Cytology and Histology	In the face of an enlarging effusion/ascites with no progressive non-target disease elsewhere, the radiologist will record tumor response for nontarget lesions as Unknown. New pleural effusion/ascites will be recorded as a new lesion but will not result in an overall response of PD for the timepoint. The oncologist will assign a response according to clinical data (e.g., cytological results).
Tumor Response Evaluation	Per protocol all subjects included in the study will be assessed, even if there are no measurable/target lesions as assessed by the radiologists.
	If a target lesion becomes less than 5 mm, but is still clearly present, a measurement of 5 mm will be assigned to the longest diameter and the SLD of target lesions will continue to be generated.
Overall Response	If Target Lesion Response is **CR**, but Non-Target Lesion Response is **Unknown** and there are no new lesions, the overall timepoint response will be **PR**. If Target Lesion Response is **PR**, but Non-Target Lesion Response is **Unknown** and there are no new lesions, the overall timepoint response will be **PR**. If Target Lesion Response is **SD**, but Non-Target Lesion Response is **Unknown** and there are no new lesions, the overall timepoint response will be **SD**.
	Overall response for **cases with no measurable / target** disease at screening as assessed by the

radiologists (non-measurable/non-target disease only) will be determined by the following criteria:

Non-Target Lesions	New Lesion(s)	Overall Response
CR	No	CR
Incomplete Response/ SD	No	SD
PD	Yes or No	PD
Any	Yes	PD

Overall response for **cases with no disease** at screening as assessed by the radiologists will be determined by the following criteria:

New Lesion(s) at Follow-	Overall Response
No	UNK
Yes	PD

PD will only be recorded based on unequivocal evidence of progressive disease.

Sample size

The sample size of the study was determined by the analysis of OS. To detect a HR of 0.8 in OS (a 25% improvement in median OS; i.e., from 17.2 months in the control arm to 21.5 months in the treatment arm), approximately 632 events were required to achieve 80% power at a two-sided 5% alpha level. A total of 980 patients were to be enrolled into the study over approximately 35 month. The primary analysis of PFS was to take place when approximately 508 IRC-assessed PFS events had occurred. This provides 90% power to detect an HR of 0.75 in PFS (a 33% improvement in median PFS; i.e., from 6.2 months in the control arm to 8.3 months in the treatment arm), with a two-sided alpha of 5%. The final analysis of PFS would not be conducted until the last patient was enrolled.

Randomisation

Upon verification of inclusion and exclusion criteria, eligible patients were randomized (1:1) to either trastuzumab emtansine or lapatinib + capecitabine using a hierarchical dynamic randomization procedure. The randomization scheme was designed to ensure approximately equal sample sizes for the treatment arms within each category of (in this order) 1) world region (United States, Western Europe, other), 2) number of prior chemotherapeutic regimens for locally advanced or metastatic disease (0−1 vs. >1), 3) visceral vs. non-visceral disease, and overall.

Blinding (masking)

The study was not blinded.

Statistical methods

To control for multiplicity due to having two primary endpoints, a fixed-sequence hypothesis testing procedure was implemented. The hypothesis test for PFS was conducted at a one-sided alpha of 2.5%. If the PFS was statistically different between the two arms, OS was to be tested at a one-sided alpha of 2.5%. If the primary endpoints of PFS (based upon independent review of tumor assessments) and OS were statistically significant, the secondary endpoints were to be tested in the following order: PFS (based upon investigator assessment), response rate (based upon independent review of tumor assessments), time to treatment failure, and time to symptom progression.

The two-sided log-rank test, stratified by world region (United States, Western Europe, Other), number of prior chemotherapeutic regimens for unresectable, locally advanced or metastatic

disease (0-1 vs. > 1), and visceral versus non-visceral disease was used as the primary analysis to compare PFS between the two treatment arms.

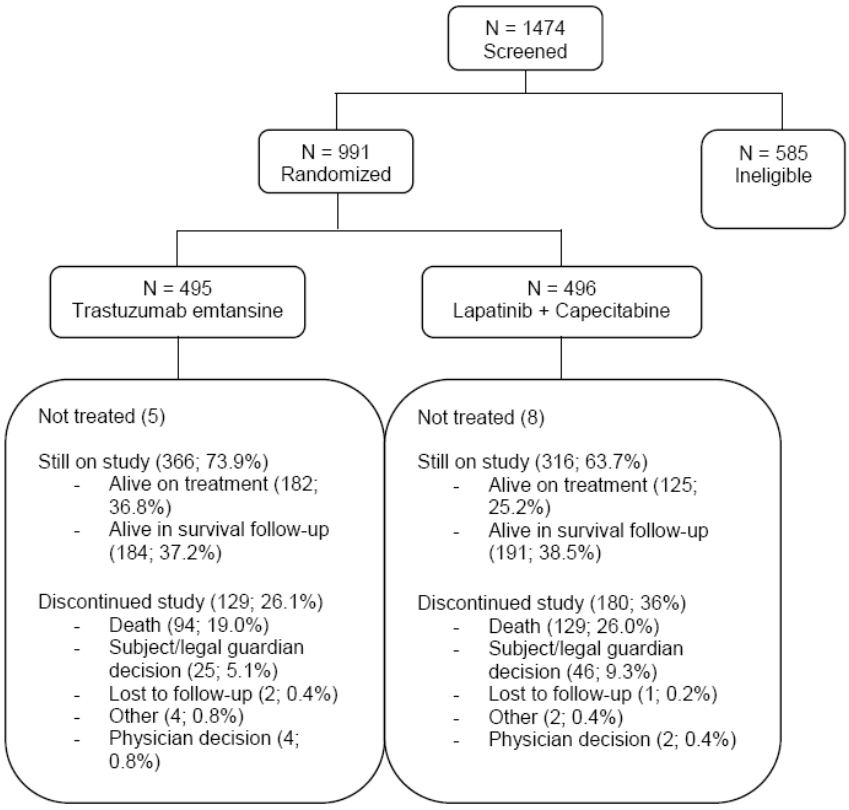
There was no interim analysis of PFS. An interim analysis of OS was planned to be conducted at the same time as the final analysis of PFS. At the interim analysis, OS would be tested at the significance level determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary, so that the overall two-sided Type I error rate would be maintained at the 5% level. The final analysis of OS was to be performed when 632 deaths have occurred.

In the original statistical analysis plan, no further interim analyses of OS were planned. However, in light of the large effect observed at the time of the primary PFS analysis, the applicant planned a second interim analysis for OS (when at least 50% of the target number of events had occurred). The cut-off date for this analysis was 31 July 2012. The 2nd OS interim analysis was added after observing a positive trend in OS improvement in the 1st interim analysis. The Lan-DeMets alpha spending function O'B-F boundary was used.

The analysis population to be used for the primary analysis of PFS was to be the randomized population, defined as all patients who were randomized into the study ≥ 3 months prior to the clinical data cutoff date for the final PFS analysis, regardless of whether they received any study treatment. All other efficacy endpoints were to be analyzed using the randomized population with two exceptions: 1) the analysis of objective response rate will only include patients in the randomized population who have measurable disease at baseline and 2) the analysis of duration of response will include only patients who were in the randomized population and who also achieved an objective response to study treatment. For all efficacy analyses, patients were to be counted towards the treatment group to which they were randomized.

Results

Participant flow



Recruitment

A total of 1474 patients were screened for the study, and 991 eligible patients were enrolled from 213 centers in 26 countries (Brazil, Canada, Bosnia and Herzegovina, France, Finland, Germany, Great Britain, Italy, Poland, Sweden, Bulgaria, Mexico, New Zealand, Slovenia, Republic of Korea, Republic of the Philippines, Russia, Singapore, Chinese Taipei, Chinese Hong Kong, Spain, Portugal, Denmark, Switzerland, India, United States). The first patient was randomized on 23 February 2009 and the last patient was randomized on 13 October 2011. The country with the highest enrollment was the US (270 patients). The other top recruiting countries were South Korea, Canada, France, United Kingdom, Brazil, and Italy; each country recruited more than 50 patients. Individual centers recruited between one and 33 patients but the majority of centers (155 of 213) recruited fewer than 5 patients.

Conduct of the study

The protocol was issued on 8 October 2008 and amended three times. The key changes to the protocol included specification of interim OS analysis; definition of PFS (include all deaths, beyond the initial limit of 30 days after the last dose of study treatment); OS specified as co-primary (instead of secondary) endpoint; sample size increased from 580 to 980 (powered for OS analysis).

Baseline data

Summary of demographic characteristics

Demographic and Baseline Characteristics
Randomized Subjects

	Lapatinib+Capecitabine (n=496)	Trastuzumab emtansine (n=495)
Age (yr)		
N	496	495
Mean (SD)	53.2 (10.8)	52.2 (11.0)
Median	53.0	53.0
Min Max	24.0 - 83.0	25.0 - 84.0
Sex		
N	496	495
Female	492 (99.2%)	494 (99.8%)
Male	4 (0.8%)	1 (0.2%)
ECOG Score		
N	488	493
0	312 (63.9%)	299 (60.6%)
1	176 (36.1%)	194 (39.4%)
Baseline LVEF by local assessment (%)		
N	472	489
Mean (SD)	62.1 (6.6)	62.4 (6.4)
Median	61.0	62.0
Min Max	50.0 - 88.0	50.0 - 87.0
Segmental wall abnormality at baseline by local assessment		
N	496	494
No	471 (95.0%)	477 (96.6%)
Yes	25 (5.0%)	17 (3.4%)
Baseline LVEF by cental assessment (%)		
N	370	377
Mean (SD)	61.2 (6.3)	61.6 (6.2)
Median	60.9	61.5
Min Max	41.0 - 82.0	31.3 - 81.0
Age (yr)		
N	496	495
Mean (SD)	53.2 (10.8)	52.2 (11.0)
Median	53.0	53.0
Min Max	24.0 - 83.0	25.0 - 84.0
Sex		
N	496	495
Female	492 (99.2%)	494 (99.8%)
Male	4 (0.8%)	1 (0.2%)
ECOG Score		
N	488	493
0	312 (63.9%)	299 (60.6%)
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Baseline LVEF by local assessment (%)		
N	472	489
Mean (SD)	62.1 (6.6)	62.4 (6.4)
Median	61.0	62.0
Min Max	50.0 - 88.0	50.0 - 87.0
Segmental wall abnormality at baseline by local assessment		
N	496	494
No	471 (95.0%)	477 (96.6%)
Yes	25 (5.0%)	17 (3.4%)
Baseline LVEF by cental assessment (%)		
N	370	377
Mean (SD)	61.2 (6.3)	61.6 (6.2)
Median	60.9	61.5
Min Max	41.0 - 82.0	31.3 - 81.0
Segmental wall abnormality at baseline by central assessment		
N	438	437
NE	45 (10.3%)	57 (13.0%)
No	381 (87.0%)	374 (85.6%)
Yes	12 (2.7%)	6 (1.4%)
Region		
N	496	495
United States	136 (27.4%)	134 (27.1%)
Western Europe	160 (32.3%)	157 (31.7%)
Asia	76 (15.3%)	82 (16.6%)
Other	124 (25.0%)	122 (24.6%)
Number of prior chemotherapy regimens for locally advanced or metastatic disease		
N	496	495
0-1	305 (61.5%)	304 (61.4%)
>1	191 (38.5%)	191 (38.6%)
Disease Involvement		
N	496	495
Visceral	335 (67.5%)	334 (67.5%)
Non-visceral	161 (32.5%)	161 (32.5%)
Baseline Height (cm)		
N	489	487
Mean (SD)	161.2 (7.3)	161.3 (7.4)
Median	161.0	162.0
Min Max	140.0 - 185.0	134.6 - 185.0
Baseline Weight (kg)		
N	487	495
Mean (SD)	70.9 (18.5)	69.3 (14.4)
Median	68.0	66.0
Min Max	37.2 - 221.0	43.0 - 133.0

Baseline Body Surface Area (m^2)		
N	487	487
Mean (SD)	1.8 (0.2)	1.8 (0.2)
Median	1.8	1.7
Min Max	1.3 - 3.1	1.4 - 2.5
Ethnicity		
N	496	495
Hispanic or Latino	57 (11.5%)	50 (10.1%)
Not Hispanic or Latino	390 (78.6%)	400 (80.8%)
Not Available	49 (9.9%)	45 (9.1%)
Race		
N	496	495
American Indian or Alaska Native	7 (1.4%)	6 (1.2%)
Asian	86 (17.3%)	94 (19.0%)
Black or African American	21 (4.2%)	29 (5.9%)
Native Hawaiian or Other Pacific Islander	3 (0.6%)	1 (0.2%)
White	374 (75.4%)	358 (72.3%)
Not Available	5 (1.0%)	7 (1.4%)
Measureable disease per investigator		
N	496	495
No	71 (14.3%)	64 (12.9%)
Yes	425 (85.7%)	431 (87.1%)
Measureable disease per IRC		
N	496	495
No	107 (21.6%)	98 (19.8%)
Yes	389 (78.4%)	397 (80.2%)
Number of metastatic sites per investigator		
N	496	495
1	134 (27.0%)	131 (26.5%)
2	160 (32.3%)	170 (34.3%)
3+	199 (40.1%)	194 (39.2%)
Missing	3 (0.6%)	(0.0%)
Number of metastatic sites per IRC		
N	496	495
1	151 (30.4%)	143 (28.9%)
2	156 (31.5%)	155 (31.3%)
3+	175 (35.3%)	189 (38.2%)
Missing	14 (2.8%)	8 (1.6%)

NE = Not Evaluable

Numbers analysed

Analysis Population	Lapatinib+Capecitabine	Trastuzumab emtansine
Randomized	496 (100.0%)	495 (100.0%)
Randomized at least 3 months prior to data cutoff date [1]	496 (100.0%)	495 (100.0%)
Randomized within 3 months of data cutoff date	(0.0%)	(0.0%)
Treated	488 (98.4%)	490 (99.0%)
Received at least one dose of study drug and randomized at least 3 months prior to data cutoff date [2]	488 (98.4%)	490 (99.0%)
Received at least one dose of study drug but randomized within 3 months of data cutoff date [3]	(0.0%)	(0.0%)

[1] This randomized patient set forms the basis for all except safety analyses
[2] This treated patient set forms the basis for all safety analyses
[3] Serious adverse events, deaths, and any other unexpected adverse events are listed for this patient set

Outcomes and estimation

Study TDM4370g /BO21977: Overview of Efficacy Results (ITT Population)

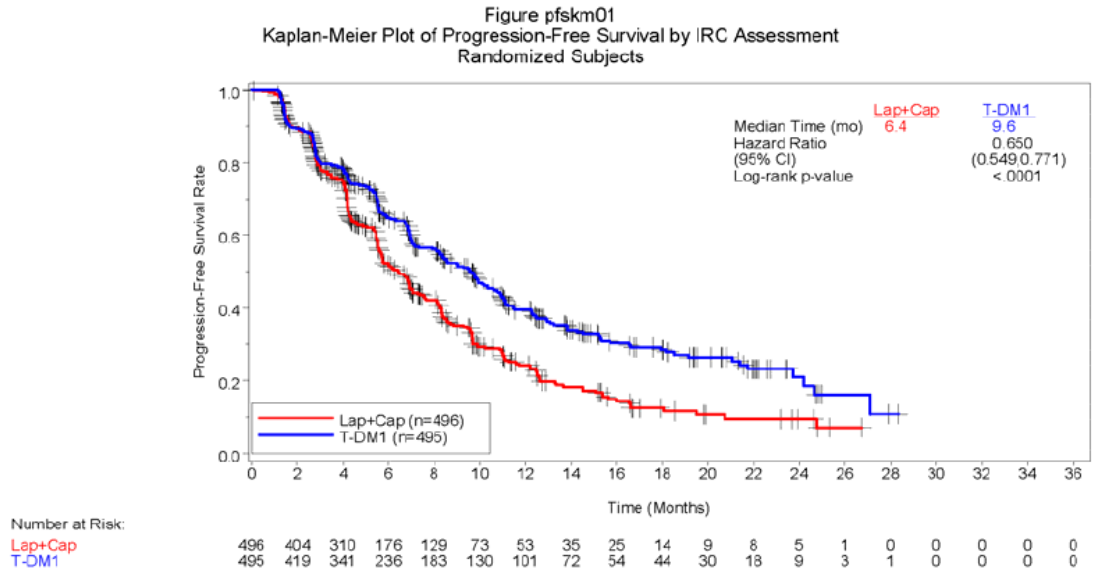
	Lapatinib + Capecitabine N = 496	**Trastuzumab Emtansine N = 495**
Primary Endpoints		
IRC-assessed PFS		
Number (%) of patients with event	304 (61.3%)	265 (53.5%)
Median duration of PFS (months)	6.4	9.6
Hazard Ratio (stratified[a])	0.650	
95% CI for Hazard Ratio	(0.594, 0.771)	
p-value (Log-Rank test, stratified[a])	<0.0001	
OS (2nd Interim Analysis)		
Number (%) of patients who died	182 (36.7%)	149 (30.1%)
Median duration of survival (months)	25.1	30.9
Hazard Ratio (stratified [a])	0.682	
95% CI for Hazard Ratio	(0.548, 0.849)	
p-value (Log-Rank test [a])	0.0006	
Key Secondary Endpoints		

	Lapatinib + Capecitabine N = 496	Trastuzumab Emtansine N = 495
Primary Endpoints		
Investigator-assessed PFS		
Number (%) of patients with event	335 (67.5%)	287 (58.0%)
Median duration of PFS (months)	5.8	9.4
HR [95% CI]; p-value (Log-Rank test [a])	0.658 [0.560, 0.774]; p < 0.0001	
ORR	**N=389**	**N=397**
Rate (%)	30.8%	43.6%
Diff, 95% CI; p-value (Mantel-Haenszel Chi-squared test [a])	12.7% [6.0%, 19.4%]; p = 0.0002	
Duration of Response *(N=responders)*	N=120	N=173
Median duration of response (months)	6.5	12.6
95% CI	5.45, 7.16	8.38, 20.76
Time to Treatment Failure		
Number (%) of patients with event	371 (74.8%)	313 (63.2%)
Median duration of PFS (months)	5.8	7.9
HR [95% CI]; p-value (Log-Rank test [a])	0.703 [0.602, 0.820]; p < 0.0001	
Time to Symptom Progression		
Number (%) of patients with event	257 (57.8%)	246 (54.7%)
Median time to event (months)	4.6	7.1
HR, [95% CI]; p-value (Log-Rank test [a])	0.796 [0.667, 0.951]; p = 0.0121	

NE = not estimable.

[a] 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.

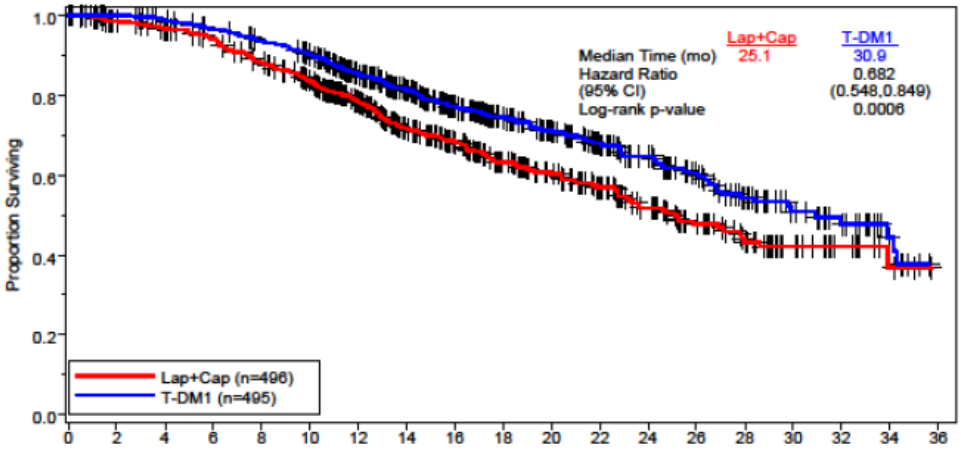
Study TDM4370g/BO21977: KM Plot of IRC-Assessed Progression-free Survival



T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine; IRC: independent review committee.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Study TDM4370g/BO21977: KM Plot of Overall Survival (2nd Interim Analysis)

Figure oskm01
Kaplan-Meier Plot of Overall Survival
Randomized Subjects



Number at Risk:

Lap+Cap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Source: Biostatistics(yongw) pgm(/onco/aherdm1/tdm4370g/unbl4370os/programs/g_km)
Database (CLOSED cutoff: 31JUL2012)

Kaplan Meier Plot of PFS by Investigator Assessment (ITT Population)

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Phase III Study: TDM4370g
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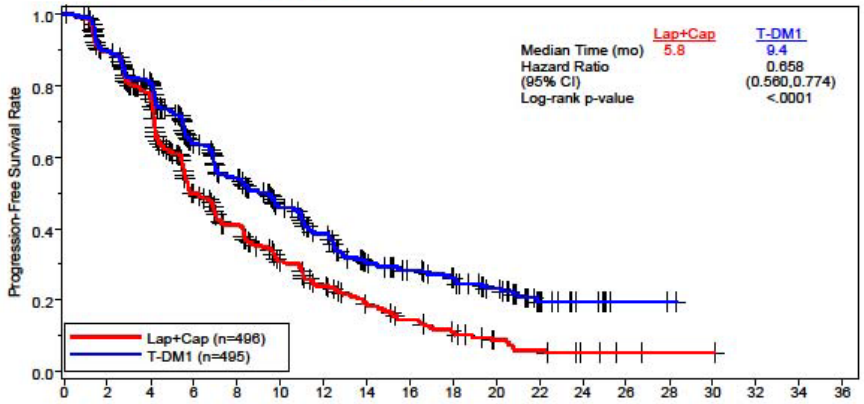
Figure pfsinvkm01
Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment
Randomized Subjects



Number at Risk:

Lap+Cap	496	414	336	182	140	88	63	43	32	21	12	8	4	2	1	1	0	0	0
T-DM1	495	429	366	248	195	142	107	72	58	46	32	15	7	2	1	0	0	0	0

T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

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Database (CLOSED)
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Objective Response Rate by IRC Assessment (ITT Population)

	Lap+Cap		T-DM1	
	n=389		n=397	
Complete Response (CR)	2	(0.5%)	4	(1.0%)
Partial Response (PR)	118	(30.3%)	169	(42.6%)
Stable Disease (NC)	187	(48.1%)	160	(40.3%)
Progressive Disease (PD)	64	(16.5%)	54	(13.6%)
CR+PR (95% CI)	30.8 % (26.3%, 35.7%)		43.6% (38.6%, 48.6%)	
Difference in CR+PR (95% CI)	12.7% (6.0%; 19.4%)			
P-value*	0.0002			

* Mantel-Haenszel chi-squared test 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

Time to treatment failure (ITT Population)

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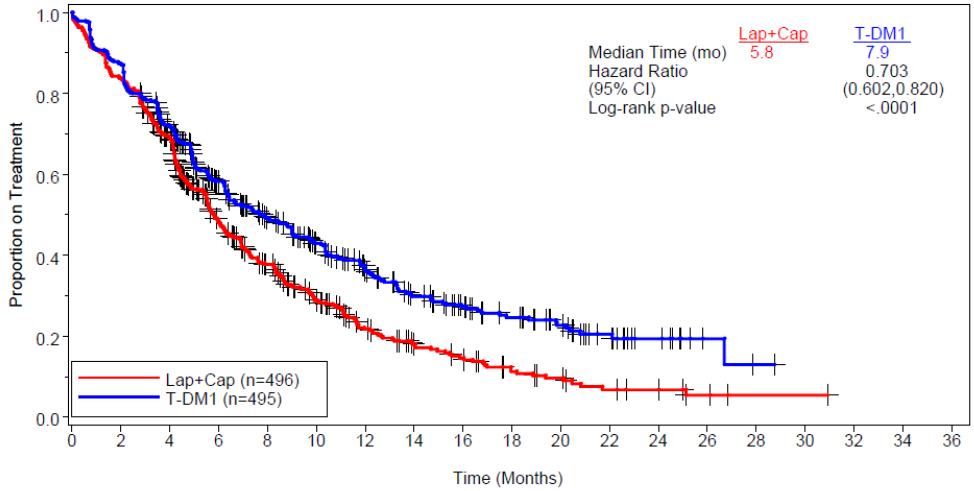
Phase III Study: TDM4370g
TRASTUZUMAB EMTANSINE

c_kmttf01. Kaplan-Meier Plot of Time to treatment Failure
Randomized Subjects



Number at Risk:

Lap+Cap	496	415	332	195	138	96	61	43	34	22	16	9	7	3	1	1	0	0	0
T-DM1	495	432	342	240	180	136	100	74	57	45	34	19	10	3	1	0	0	0	0

Data cut-off: 14Jan2012. T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on stratified Cox model; p-value is estimated based on stratified log-rank test. Strata are: world region, number of prior chemotherapeutic regimens for locally advanced or metastatic disease, and visceral vs. non-visceral disease.

TDM4370g/BO21977: Kaplan Meier Plot of Time to Symptom Progression

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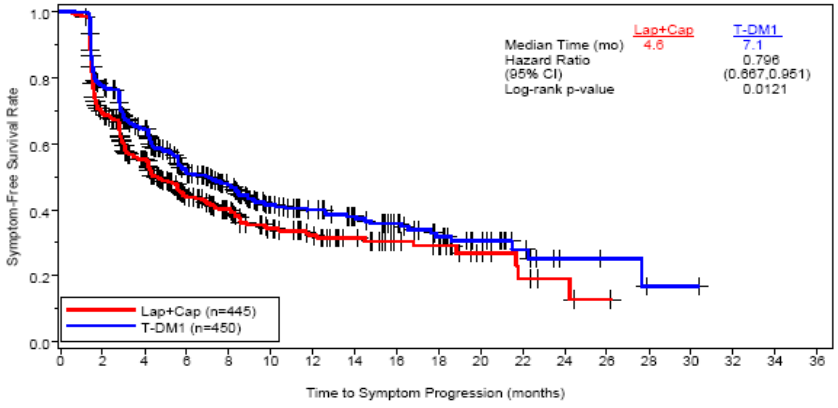
Phase III Study: TDM4370g
TRASTUZUMAB EMTANSINE

Figure ttspkm01
Kaplan-Meier Plot of Time to Symptom Progression
Randomized Female Patients with Baseline and at Least One Post-Baseline Valid Score



Number at Risk:

Lap+Cap	445	299	200	119	84	57	45	33	22	18	9	5	3	1	0	0	0	0
T-DM1	450	340	259	164	128	85	67	53	40	29	22	11	4	3	1	1	0	0

T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

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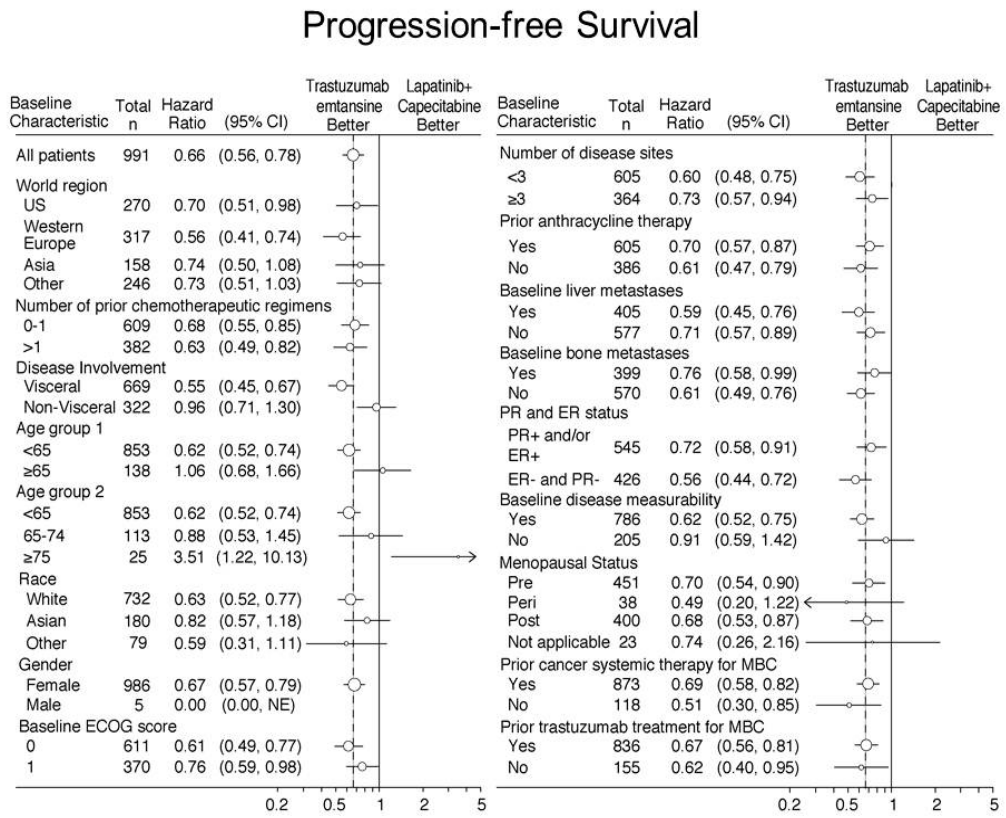
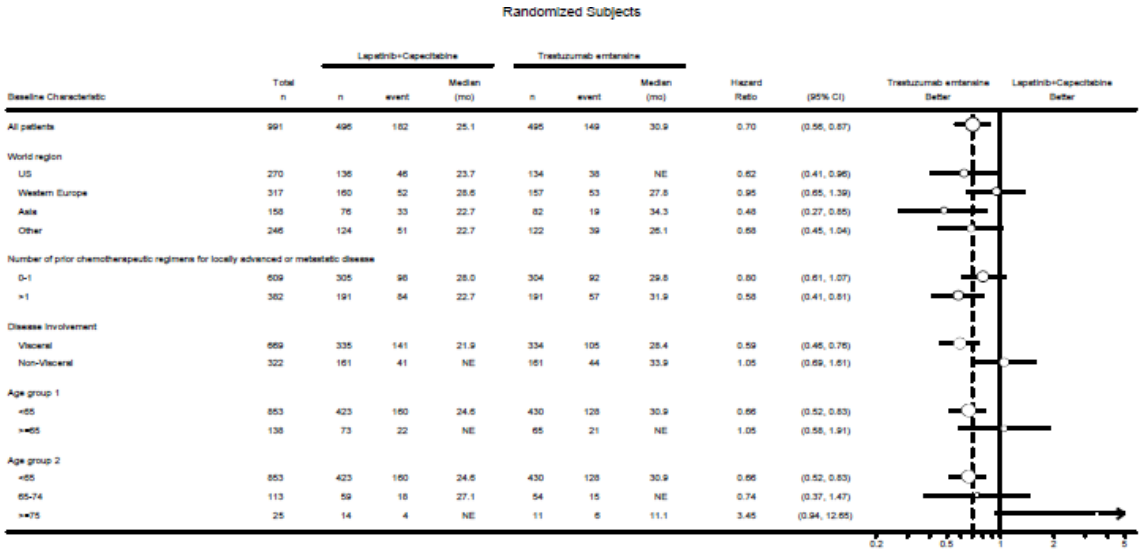
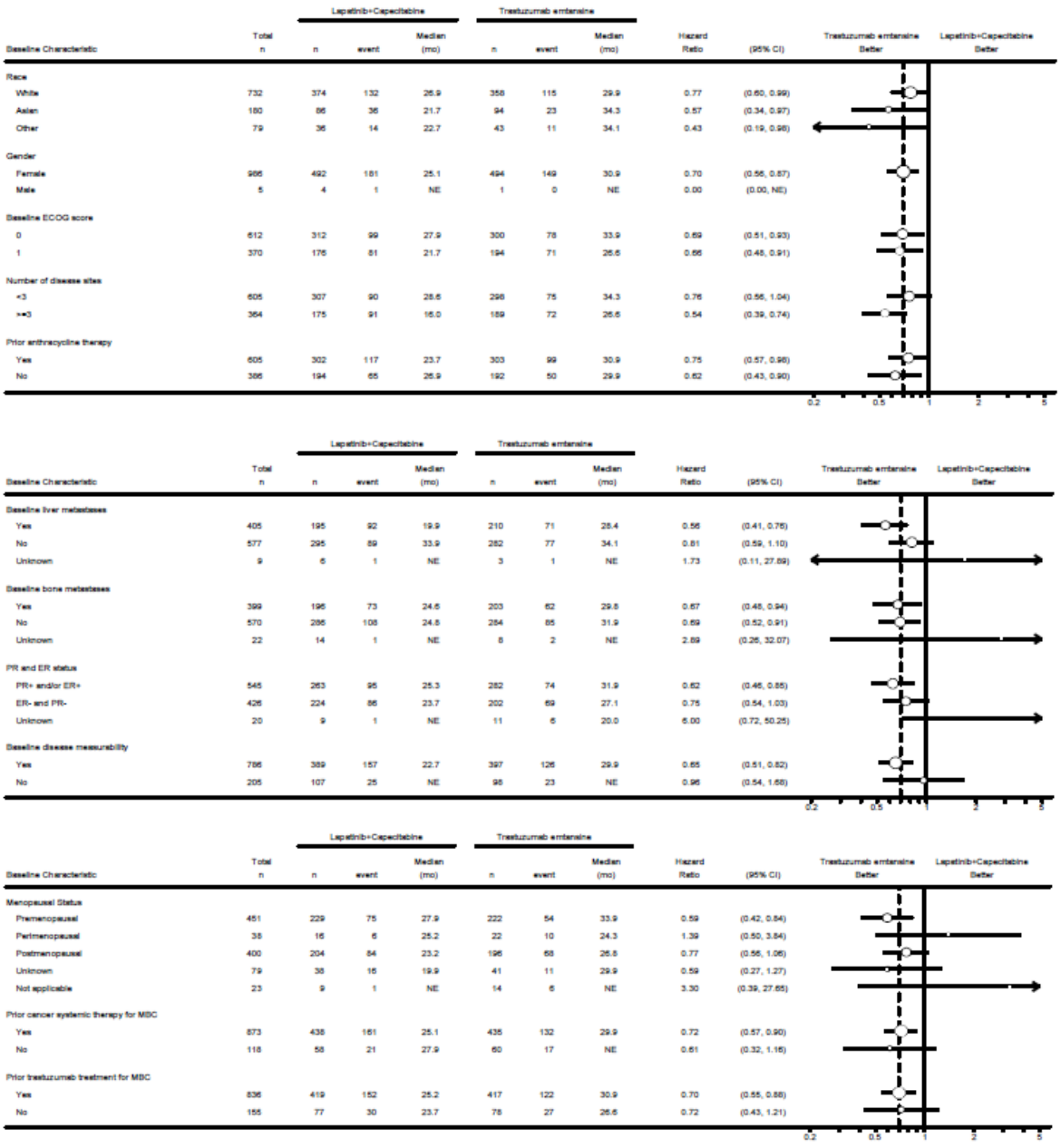
Ancillary analyses

TDM4370g/BO21977: Subgroup Analyses of Progression-Free Survival per IRC Assessment



TDM4370g/BO21977: Subgroup Analyses of Overall Survival by Baseline Risk Factors (2nd Interim Analysis)





NE = not estimable.
Median time to event variable was estimated from Kaplan-Meier curves. Hazard ratio relative to Lapatinib+Capecitabine group and 95% confidence interval (CI) for hazard ratio were estimated using Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The diameter of the circle is proportional to the square root of the total number of subjects.
The hazard ratios are from unstratified analysis. Baseline disease measurability and number of disease sites are based on IRC assessment.
Database (CLOSED cutoff: 31JUL2012)

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.

<u>No prior systemic anti-cancer therapy in the metastatic setting</u>

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.

Hormone receptor status

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.

Baseline disease measurability

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.

Elderly patients

In the subgroup of patients who were 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.

Non-visceral disease

There was a less impressive effect in patients with non-visceral disease, and a similar finding was seen for pertuzumab (data not shown). However, this was based solely on the study site classification at the time of randomization for which explicit guidance had not been provided (the applicant had expectations that sites/investigators had adequate knowledge of visceral and non-visceral disease definitions). The sites of disease involvement have been subsequently reviewed according to IRC data, and further PFS (based on IRC assessments, data cut-off 14 January 2012) and OS (data cut-off 31 July 2012) subgroup analyses have been conducted using baseline IRC tumor assessments and applying the following two definitions of visceral disease (a) vs. non-visceral disease (b):

Definition 1: a) Presence of disease in the lungs or liver (either target or non- target lesions) vs. b) absence of disease in both the lungs and liver

Definition 2: a) Presence of disease in the lungs or liver or ascites or pleural effusion (either target or non-target lesions) vs. b) absence of disease in all these 4 sites

When the IRC data are used and the revised classifications applied, a benefit of trastuzumab emtansine compared with lapatinib plus capecitabine was observed for patients with disease that did not involve visceral organs.

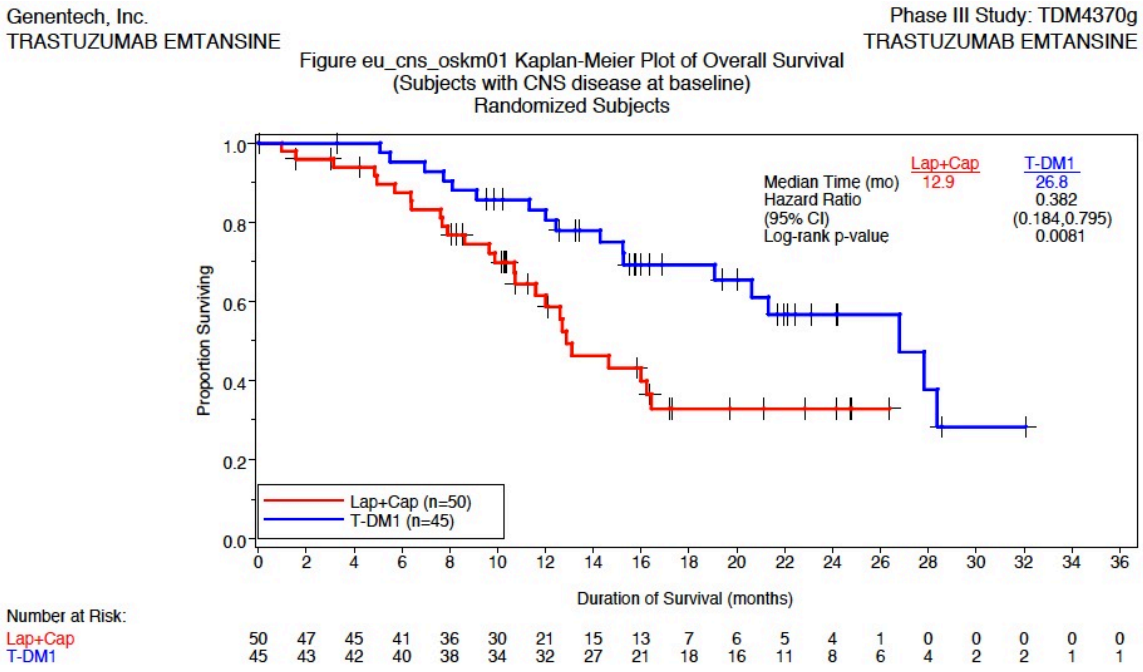
Additional analyses were performed to evaluate the safety of patients with non-visceral disease according to Definition 2b. The incidence of deaths, SAEs, Grade 3 or higher AEs and all AEs in

the trastuzumab emtansine arm were consistently lower than in the control arm, and there was no evidence of detriment associated with use of trastuzumab emtansine over lapatinib plus capecitabine.

Patients with Brain Metastases

Patients with treated brain metastases not requiring therapy to control symptoms were included and treated in the pivotal phase III trial. No difference was seen in PFS was observed but a clear benefit in favor of T-DM1 was seen with regard to OS.

Study TDM4370g/BO21977: OS in Patients with CNS Disease at Baseline



Data cut-off: 31Jul2012. T-DM1: trastuzumab emtansine; Lap: lapatinib; Cap: capecitabine.
Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Source: Biostatistics(junliu) pgm(/onco/aherdm1/tdm4370g/eu/programs/g_km_eu_b3)
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Immunogenicity (Anti-Therapeutic Antibodies, ATA)

In TDM4370g/BO21977 (EMILIA), positive ATA responses were detected in 20 of 460 ATA evaluable patients (4.3%) at one or more post-dosing time points. A lower median progression-free survival (PFS) was observed in the 20 ATA positive patients compared to the intent-to-treat (ITT) population (5.6 vs 9.6 months) while objective response rates were comparable.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial TDM4370g /BO21977

Title: **A Randomized, Multicenter, Phase III Open-Label Study Of The Efficacy And Safety Of Trastuzumab Emtansine (T-DM1) Vs. Capecitabine + Lapatinib In Patients With Her2-Positive Locally Advanced Or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy (Verma, Miles et al. 2012)**			
Study identifier	EUDRACT No.: 2008-005 713-22; ClinicalTrials.gov Identifier: NCT00829166; "EMILIA"		
Design	Randomized, open label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Trastuzumab Emtansine (T-DM1)		Tratuzumab emtansine arm: Trastuzumab emtansine 3.6 mg/kg intravenously (IV) on Day 1 of a 3-week cycle. Treatment continued until disease progression or unmanageable toxicity. No. randomized=495.
	Lapatinib + Capecitabine (Lap+Cap)		Lapatinib 1250 mg/day orally with continuous daily dosing on a 3-week cycle + Capecitabine 1000 mg/m2 orally twice daily on Days 1−14 of a 3-week cycle. Treatment continued until disease progression or unmanageable toxicity. No. randomized=496.
Endpoints and definitions	Co-primary: Progression-free survival	PFS	Time from randomization to the first occurrence of progression by IRC assessment according to modified RECIST (see text), or death from any cause
	Co-primary: Overall Survival	OS	Time from randomization to death from any cause
Database lock	PFS (14 January 2012); OS (31 July 2012)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Final analysis of PFS. Final analysis of OS.		
Descriptive statistics and estimate variability	Treatment group	T-DM1	Lap+Cap
	Number of subject	495	496
	PFS (HR) Logrank *P* Median (months)	0.650 <0.0001 9.6	n/a n/a 6.4
	95% CI of HR	(0.594, 0.771)	n/a

Title: **A Randomized, Multicenter, Phase III Open-Label Study Of The Efficacy And Safety Of Trastuzumab Emtansine (T-DM1) Vs. Capecitabine + Lapatinib In Patients With Her2-Positive Locally Advanced Or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy (Verma, Miles et al. 2012)**			
	OS (HR) Logrank *P* Median (months)	0.682 0.0006 30.9	n/a n/a 25.1
	95% CI of HR	(0.548, 0.849)	n/a
Notes	OS results are based on 2nd interim analysis (see text).		

Biomarker Analyses

The candidate biomarkers evaluated in Study TDM4370g/BO21977 were selected according to their function within the HER2 signaling pathway and/or impact on mode of action of trastuzumab emtansine (based upon existing nonclinical data and/or reports in the literature for HER2-targeted treatments, as well as the availability of appropriate assays). Markers included expression of HER-family receptors and ligands (EGFR, HER2, HER3 amphiregulin and betacellulin) and markers/components of the HER signal transduction or alternative signaling pathways (PTEN protein expression, mutational status of PIK3CA).

No biomarkers that clearly differentiated patient response could be identified from exploratory analyses of PFS, splitting patient subgroups by high (above median) and low (median and below) levels of mRNA expression for biomarkers analyzed, although slight differences were observed for HER3. Among all randomized patients, HER3 qRT-PCR data were available for 860 patients (424 patients in the trastuzumab emtansine arm and 436 patients in the lapatinib plus capecitabine arm). In patients whose tumors showed HER3 expression at or below the median (median = 0.438), the HR was 0.56 (95%CI = 0.45, 0.74). Median PFS was 5.7 months in the control arm and 9.3 months in the trastuzumab emtansine group. In patients whose tumors had HER3 expression above the median level, HR was 0.80 (95%CI = 0.62, 1.04). The median PFS was 6.9 months in the lapatinib plus capecitabine group and 9.8 months in the trastuzumab emtansine group.

Analysis performed across trials (pooled analyses and meta-analysis)

See supportive studies.

Clinical studies in special populations

No clinical studies in special populations have been submitted (see discussion on clinical efficacy and risk-management plan).

Number of Elderly Patients Participating in the Clinical Studies

Trials	Total Number of Subjects	N (%) Age 65–74	Age 75–84	Age 85+
Pharmacokinetics trial (TDM3569g) [a]	52	5 (9.62%)	1 (1.92%)	0
Pharmacodynamics trial (TDM4688g)	51	4 (7.84%)	3 (5.88%)	1 (1.96%)
Controlled trials (TDM4370g/BO21977, TDM4450g/BO21976)	1128	131 (11.6%)	31 (2.7%)	0
Non-controlled trials (TDM4258g,TDM4374g) [b]	222	21 (9.5%)	8 (3.6%)	0

[a] The figure for Study TDM3569g includes all patients treated with any dose of trastuzumab emtansine in qw and q3w regimens. Only patients treated with 3.6 mg q3w trastuzumab emtansine (15/52) were included in the efficacy and safety analysis in the MAA.
[b] No PK samples were obtained in the extension study, Study TDM4529g, and thus it is not included in this table. However, all patients in Study TDM4529g/BO25430 are included in their respective parent study (Studies TDM4258g, TDM4374g, TDM4688g, or TDM4450g/BO21976).

Supportive studies

See tables 1 and 2 for general information on study design for phase II studies 4374g, 4258g, and 4450g.

Summary of Key Supportive

Table 1. Studies with Single-agent Trastuzumab emtansine Contributing to Efficacy Evaluation

Protocol No.	Study Design	Population	Efficacy Parameters	Drug, Dose, Duration	No. of Patients
Phase II Studies – single arm (completed)					
TDM4374g	A Phase II single-arm, open-label study to evaluate efficacy and safety of trastuzumab emtansine.	Patients with HER2-positive incurable LABC or MBC with prior taxane, anthracycline, trastuzumab, lapatinib, and capecitabine treatment. Patients must have been treated with two or more regimens and have progressed on their most recent treatment.	Primary: IRC-assessed ORR Secondary: Investigator-assessed ORR, DOR, CBR, PFS and TSP based on FACT-B TOI-PFB. Data cut-off date for efficacy endpoints: 1 January 2010: PFS, ORR, DOR, and TSP 26 April 2011: efficacy and safety with longer follow-up	Trastuzumab emtansine: 3.6 mg/kg q3w Treatment until PD or unacceptable toxicity	110 Treated patients
TDM4258g	A Phase II single-arm, open-label study to evaluate efficacy and safety and tolerability of trastuzumab emtansine.	HER2-positive incurable LABC or MBC patients with a history of progression on HER2-directed therapy and at least one chemotherapy agent for MBC.	Primary: IRC-assessed ORR Secondary: investigator –assessed ORR, DOR, IRC- and investigator-assessed PFS. Data cut-off date for efficacy endpoints: 25 June 2009	Trastuzumab emtansine: 3.6 mg/kg q3w Treatment until PD or unacceptable toxicity for a maximum of 1 year	112 Treated patients
Phase II – randomized study (on-going for safety)					
TDM4450g/ BO21976	A Phase II, randomized, multicenter, open-label, two-arm study, to evaluate efficacy and safety of trastuzumab emtansine vs. trastuzumab + docetaxel.	Patients with HER2-positive unresectable LABC or MBC who have not received prior chemotherapy for metastatic disease.	Primary: Investigator –assessed PFS Secondary: OS, ORR, DOR, CBR and TSP based on FACT-B TOI-PFB Data cut-off date for efficacy endpoints: 15 November 2010: PFS, ORR, DOR and TSP 31 August 2011: OS	Arm A : Trastuzumab emtansine: 3.6 mg/kg q3w Arm B (control arm): Trastuzumab: 8 mg/kg loading dose; 6mg/kg q3w Docetaxel : 75 or 100 mg/m^2 q3w Treatment until PD or unacceptable toxicity and maximum treatment duration of 1 year	137 Randomized patients Arm A: N = 70 Arm B: N = 67

CBR = clinical benefit response, DOR = duration of response, FACT-B TOI-PFB = Functional Assessment of Cancer Therapy Breast-Trial Outcome Index as a measure of physical and functional well-being and breast cancer-specific symptoms, IRC = independent review committee, ORR = objective response rate, OS = overall survival, PFS = progression-free survival; q3w = every three weeks, PRO = patient-reported outcomes, TTF = time to treatment failure, TSP = time to symptom progression, MBC = metastatic breast cancer, PD = disease progression

Study TDM4374g

Study TDM4374g was a Phase II single-arm, open-label study to evaluate the efficacy and safety of trastuzumab emtansine in patients with HER2-positive MBC.

Trastuzumab emtansine was administered intravenously at a dose of 3.6 mg/kg every 3 weeks. Patients remained on study treatment until documented PD or unacceptable toxicity. At study closure, patients who continued to derive benefit from treatment with trastuzumab emtansine could enroll in an extension study, TDM4529g/BO25430 (An open-label, extension study of

trastuzumab emtansine in patients previously treated with trastuzumab emtansine in a Genentech-sponsored trastuzumab emtansine study). Tumor assessments were performed every 6 weeks. An IRC reviewed and assessed all patient scans and tumor response data.

Key inclusion criteria: Histologically documented MBC with measurable disease, HER2-positive documented as FISH positive or 3+ on IHC, with disease progression on the last regimen received; prior treatment with an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine in the neoadjuvant, adjuvant, locally advanced, or metastatic setting and prior treatment with at least two regimens of therapy (a regimen of therapy could have been a combination of two or more agents or a single agent) in the metastatic or locally advanced setting; prior treatment with at least two anti-HER2 agents in the metastatic setting or unresectable locally advanced setting. The HER2-targeted agents must have included trastuzumab and lapatinib, but in addition may also have included an investigational agent with HER2-inhibitory activity; a minimum of 6 weeks of trastuzumab for the treatment of metastatic or unresectable locally advanced disease; at least 14 days of exposure in the metastatic (or unresectable locally advanced) setting to lapatinib and capecitabine (given together or separately) unless patients were intolerant of lapatinib and/or capecitabine.

The study population was predominantly white (93/110 patients, 84.5%) with median age of 52.5 years (range: 34 – 77), and included two male patients (1.8%). As per protocol, most patients had an ECOG PS of 0 (49.1%) or 1 (48.2%); three patients (2.7%) had an ECOG PS of 2. All patients (except 1 patient) had HER2-positive disease by local laboratory assessment (3+ IHC and/or HER2 gene amplification determined on FISH): 23.6% of tumors were HER2 positive by both FISH and IHC, 45.5% by IHC alone, and 30.0% by FISH alone.

The majority of patients presented with infiltrating ductal carcinoma (81.7%); 8.3% with infiltrating lobular carcinoma and 17.4% with other histologies. At initial diagnosis, half of the patients' tumors were estrogen receptor and/or progesterone receptor positive.

At study entry, all patients had measurable disease (median sum of the longest dimension was 6.8 cm (range: 1.0 – 34.0) and had significant disease burden with 73.6% of them presenting with disease involvement in three or more sites. The most frequently involved sites with metastatic disease were lung (62.7%), bone (51.8%), and liver (44.5%). Nineteen patients (17.3%) had a history of CNS metastases; all but one of them had received whole-brain radiotherapy or localized therapy.

Patients had been heavily pretreated as demonstrated by the median number of prior anti-cancer agents in any setting, 8.5 (range: 5 -19), and in the metastatic setting, 7.0 (range: 3 – 17). All patients had received trastuzumab, lapatinib, capecitabine and an anthracycline prior to study entry and all but one had previously been treated with a taxane. About half of the patients (47.3%) had previously received hormone therapy. Patients had received a median of 2 prior trastuzumab-containing regimens (range: 1 - 8) for metastatic disease with a median duration of 19.7 months (range: 1.8 – 115.8). In addition, patients received a median of 1 lapatinib-containing regimen for MBC (range: 1 – 3) for a median duration of 6.8 months. The majority of patients (94%) had progressed on at least one HER2-based regimen in the metastatic setting and 66% had progressed on both a trastuzumab- and a lapatinib-containing combination regimen in the metastatic setting.

In this study, the median number of doses received was 7, and the median length of treatment duration was 19.3 weeks (ie, 4.4 months). Key efficacy results are summarized in Table 2.

Table 2. TDM4374g: Overview of Efficacy Results

	Trastuzumab Emtansine N= 110	
Primary Endpoint		
IRC-assessed ORR	**6 months follow-up[a]**	**9 months follow-up[b]**
Treated patients	110	110
Patients with objective response	36 (32.7%)	36 (32.7%)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	36 (32.7%)	36 (32.7%)
95% CI	(24.1%, 42.1%)	(24.1%, 42.1%)
Key Secondary Endpoints**		
Duration of Objective Response	**IRC assessment**	**Investigator assessment**
Patients with an objective response	36	36
Patients with an event*	15 (41.7%)	16 (44.4%)
Patients without an event*	21 (58.3%)	20 (55.6%)
Median duration of objective response (months)	NR	9.7
95% CI	(4.6, NR)	(6.6, NR)

*, An event was defined as disease progression or death from any cause on study, whichever occurred first.
**, Data is based on 9 months follow-up
[a], Data cut-off date of 17 September 2009; [b], Data cut-off date of 1 January 2010
CI = confidence interval, IRC = independent review committee, NR = not reached, ORR = objective response rate

Study TDM4258g

Study TDM4258g was a Phase II single-arm, open-label study of trastuzumab emtansine administered intravenously in patients with HER2-positive MBC who have progressed while receiving HER2-directed therapy.

In this study, trastuzumab emtansine was administered at a dose of 3.6 mg/kg by IV infusion every 3 weeks to patients with HER2-positive MBC. Patients could receive trastuzumab emtansine until documented PD or unacceptable toxicity for a maximum of 1 year (patients continuing to derive benefit from treatment could enroll in the extension study TDM4529g/BO25430).

Tumor response assessments were performed every 6 weeks (after two cycles of trastuzumab emtansine), between Days 15 and 21 of the relevant cycle. Study endpoints related to response were determined by an independent radiologic review of patient scans. A single radiologist reviewed all scans with no adjudication process.

Key inclusion criteria: Histologically documented, incurable, locally advanced or metastatic breast cancer with measurable disease, HER2-positive documented by local laboratory assessment as FISH-positive or 3 + by IHC; history of progression on HER2-directed therapy (or up to 60 days after receiving trastuzumab) for the treatment of HER2-positive breast cancer (minimum of 6 weeks exposure to HER2-directed therapy); for patients who had received HER2-directed therapy in the adjuvant setting only, there was the requirement for a radiographic documentation that disease progression did not occur prior to initiation of such therapy. At least one chemotherapy agent for MBC.

There were 111 women and one man who enrolled in this study (a total of 112 patients). Patients had a median age of 54.5 years and the majority of patients were white (90.2%). Most patients had ECOG PS of 0 (53.6%) or 1 (38.4%), and 1 patient had an ECOG PS of 3 (0.9%). All patients had HER2-positive disease by local assessment (3+ IHC and/or HER2 gene amplification by FISH): 26.8% of tumors were positive by both FISH and IHC, 33.0% by IHC alone, and 40.2% by FISH alone. The majority of patients (91.1%) initially presented with infiltrating ductal carcinoma and about half of the patients' tumors at initial diagnosis were ER and/or PR positive.

At study entry, all patients had measurable disease, as assessed by the investigator, with significant disease burden; 75% of patients had disease involvement in three or more distinct sites. The most frequently involved sites with metastatic disease were lung (56.3%), liver (56.3%), and bone (52.7%). Patients were heavily pre-treated with a median of eight anti-cancer agents received and most patients had received one or more chemotherapeutic agents used for the treatment of breast cancer: taxane (83.9%), anthracycline (70.5%), capecitabine (66.1%), and carboplatin (42.0%). Hormone therapy had previously been received by 41.1% of patients and, in accordance with the protocol, all patients had received HER2-directed therapy (trastuzumab and/or lapatinib) before entering the study. A total of 67 patients (59.8%) received both trastuzumab and lapatinib.

The median number of cycles received in this study was 7 and patients were on study treatment for a median duration of 18.1 weeks (ie, 4.2 months). Key efficacy results are summarized in the table below.

TDM4258g: Overview of Efficacy Results

	Trastuzumab Emtansine N= 112	
Primary Endpoint		
IRC-assessed ORR	**6 months follow-up**	**12 months follow-up**
Number of evaluable patients	109	108
Patients with objective response	28 (25.7%)	29 (26.9%)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	28 (25.7%)	29 (26.9%)
95% CI	(17.9%, 34.5%)	(19.2%, 35.8%)
Key Secondary Endpoints**		
Duration of Objective Response	**IRC assessment**	**Investigator assessment**
Efficacy evaluable patients	108	
Patients with an objective response	29	42
Patients with an event*	9 (31.0%)	18 (42.9%)
Patients without an event*	20 (69.0%)	24 (57.1%)

	Trastuzumab Emtansine N= 112	
Primary Endpoint		
Median duration of objective response (months) 95% CI	NR (6.2, NR)	9.4 (7.0, NR)
Analysis of ORR in patients previously treated with both trastuzumab and lapatinib**		
Efficacy evaluable patients previously treated with trastuzumab and lapatinib	66	
Objective response rate	16 (24.2%)	

*, An event was defined as disease progression or death from any cause on study, whichever occurred first.
**, Data is based on 12 months follow-up
CI = confidence interval, IRC = independent review committee, NR = not reached, ORR = objective response rate

Study TDM4450g/BO21976

Study TDM4450g/BO21976 is a Phase II, randomized, multicenter, international, two-arm, open-label clinical trial designed to explore the efficacy and safety of trastuzumab emtansine relative to the combination of trastuzumab and docetaxel in patients with HER2-positive, unresectable, LABC and/or MBC who have not received prior chemotherapy for metastatic disease.

Patients were randomized in a 1:1 ratio to one of the following treatment arms:

- Arm A: Trastuzumab emtansine 3.6 mg/kg intravenous (IV) on Day 1 of a 3-week cycle.
- Arm B: For Cycle 1, Day 1, trastuzumab 8 mg/kg IV + docetaxel either 75 mg/m^2 or 100 mg/m^2 IV. On Day 1 of all subsequent 3-week cycles, trastuzumab 6 mg/kg IV + docetaxel 75 – 100 mg/m^2 IV

Tumor assessments were conducted every 9 weeks from the start of treatment until documented PD or death on study.

In Treatment Arm A, patients who had not yet progressed but who had become intolerant to trastuzumab emtansine (i.e., experienced unacceptable toxicity requiring discontinuation from treatment with trastuzumab emtansine), and for whom single-agent trastuzumab was an option, were eligible to remain on the study and to receive trastuzumab administered according to prescribing guidelines in the metastatic setting until PD, clinical deterioration, and/or unacceptable toxicity for the duration of the trial. Trastuzumab emtansine treatment was to be permanently discontinued in these patients. At study close, patients from both treatment arms without PD could transfer to the extension study TDM4529g/BO25430.

In Treatment Arm B, patients who had not yet progressed but who had become intolerant to either docetaxel or trastuzumab (ie, experienced unacceptable toxicity that required discontinuation from docetaxel or trastuzumab) could remain in the study and receive single-agent trastuzumab or docetaxel, respectively, until PD, clinical deterioration, or intolerance. Patients in Treatment Arm B who discontinued study treatment because of PD were eligible to cross over to trastuzumab emtansine treatment, starting at 3.6 mg/kg, until a second PD event, clinical deterioration, and/or intolerance.

The primary endpoint was investigator-assessed PFS. Patients who were discontinued from study treatment for reasons other than PD were followed with tumor assessments every 9 weeks until PD. Subsequently, all patients are followed for survival and subsequent anti-cancer therapies

approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

This study enrolled 137 patients with 67 randomized to receive trastuzumab emtansine and 70 randomized to receive trastuzumab + docetaxel.

All patients were female, with a median age of approximately 54 years (range: 27 - 82). A higher percentage of patients in the trastuzumab emtansine arm were ≥65 years compared with the trastuzumab + docetaxel arm (22.4% vs. 12.9%).

The majority of patients were white (80.3%). As required by the protocol, all patients had ECOG PS of 0 (64.7%) or 1 (35.3%). Patients were confirmed to have HER2-positive disease (IHC3+ and/or FISH+) based on local laboratory assessment of tumor tissue specimens.

All patients in the trastuzumab emtansine arm and 69 patients (98.6%) in the trastuzumab + docetaxel arm had measurable disease at baseline, per investigator assessment, and the median sum of the longest tumor diameters per patient was similar in both treatment arms. There was a notable difference in the two arms in the number of sites of disease involvement; 40.3% and 20.3% of patients in the trastuzumab emtansine and trastuzumab + docetaxel treatment arms, respectively, had ≥ 4 sites of involvement.

Other breast cancer characteristics were comparable between the two treatment arms eg, ER and PR status and measurable disease at baseline. Disease-free interval was a stratification factor: 59.7% and 64.3% of patients in the trastuzumab emtansine and trastuzumab + docetaxel arms, respectively, had a disease-free interval ≤ 24 months, and the rest of the patients had a disease-free interval > 24 months.

The most common tumor histology at the time of diagnosis was infiltrating ductal carcinoma (85.1% vs. 89.9% for the trastuzumab emtansine arm and trastuzumab + docetaxel arm, respectively); 3.0% of patients in the trastuzumab emtansine arm and 8.7% of patients in the trastuzumab + docetaxel arm had infiltrating lobular carcinoma, and one patient (in the trastuzumab emtansine arm) had inflammatory breast carcinoma.

Overall, 22.6% of patients (17.9% in the trastuzumab emtansine arm and 27.1% in the control arm) had received prior (neo) adjuvant trastuzumab therapy. The most common prior therapies were anthracycline (46.7%) and taxane (36.5%), and were similar across treatment arms.

Hormone therapy had previously been received by 27.7% of patients in total; 30.0% in the trastuzumab + docetaxel arm and 25.4% in the trastuzumab emtansine arm.

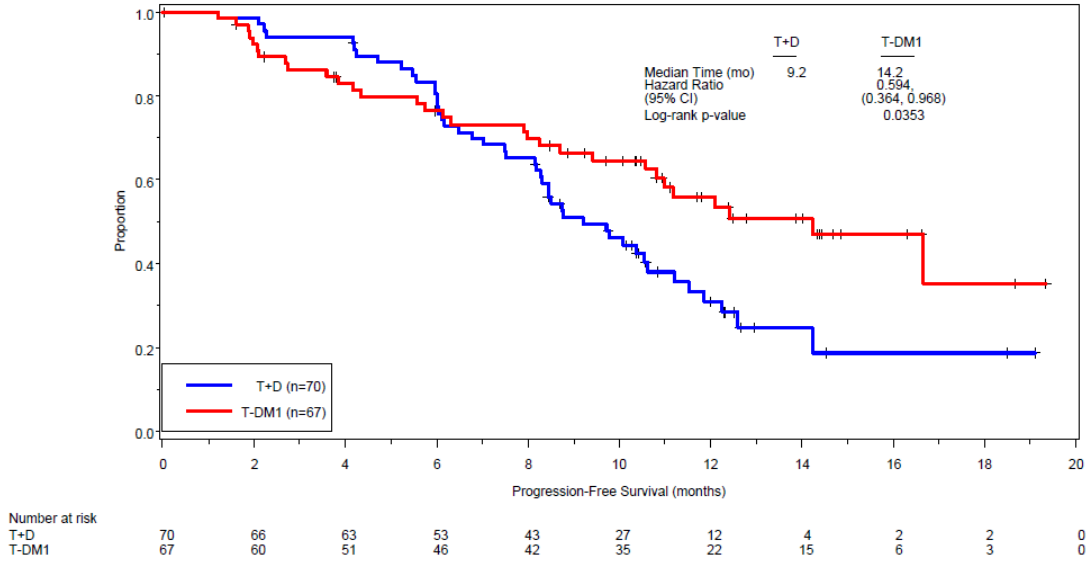
The median number of cycles of trastuzumab emtansine was 16.0 (range: 1 - 41) and the median duration of treatment was 10.4 months (range: 0 - 29). In the trastuzumab + docetaxel group, the median trastuzumab treatment duration was 8.1 months (range: 1 - 29) and the median docetaxel treatment duration was 5.5 months (range: 0 - 22). Key efficacy results are summarized in the below table.

TDM4450g/BO21976: Summary of Overall Efficacy Results (All Randomized Patients)

	Trastuzumab +Docteaxel (N = 70)	Trastuzumab Emtansine (N = 67)
Progression-free survival [a]		
Median (months)	9.2	14.2
Stratified analysis		
Hazard ratio [b]	NA	0.594
95% CI	NA	(0.364, 0.968)
p-value (log rank)	NA	0.0353
Objective Response Rate [c]		
Randomized patients with measurable disease at baseline	69	67
Patients with an objective response	40 (58.0%)	43 (64.2%)
95% CI	(45.5%, 69.2%)	(51.8%, 74.8%)
Number of patients with objective responses:		
Complete response	4 (5.8%)	7 (10.4%)
Partial response	36 (52.2%)	36 (53.7%)
Duration of Response		
Number of patients with an objective response	40	43
Median (months)	9.5	NR
95% CI	(6.6, 10.6)	(15.0, NR)
Overall Survival		
Stratified analysis		
Hazard ratio [b]	NA	1.059
95% CI	NA	(0.477, 2.352)
p-value (log rank)	NA	0.8885

NA = not applicable; NR = not reached.
[a], Event was defined as the earlier of disease progression prior to cross−over, or death on study from any cause as defined in the protocol.
[b], Relative to Trastuzumab+Docetaxel arm. Estimated by Cox regression stratified by world region (US vs. ex−US), prior adjuvant trastuzumab therapy (Yes vs. No), and disease−free interval (≤ 24 vs. >24 months) based on IVRS information.
[c], Defined as complete or partial response based on RECIST 1.0 determined on 2 consecutive tumor assessments at least 4 weeks apart.
[d], Defined as objective response any time during the study or maintained stable disease for at least 6 months from randomization.

TDM4450g/BO21976: Kaplan-Meier Estimates of PFS (all Randomized Patients)



T+D = trastuzumab + docetaxel; T-DM1 = trastuzumab emtansine

2.1.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study TDM4370g/BO21977 was a randomized, multicenter, international, two-arm, open-label trial designed to compare the safety and efficacy of trastuzumab emtansine with that of capecitabine plus lapatinib for patients with HER2-positive MBC or LABC who had previously received trastuzumab and a taxane. Results from the pivotal trial are supported by data from two single-arm Phase II studies in patients with HER-2 positive MBC, previously treated with HER2-directed therapies and chemotherapy (TDM4374g which enrolled heavily pre-treated patients in third or last line, and TDM4258g which enrolled patients for 2nd line treatment), and a two-arm randomized Phase II study in patients who have not received any systemic therapy in the MBC setting (TDM4450g/BO21976).

Potential bias in the adjudication of progression and response were minimized using an Independent Review Committee (IRC). However, the IRC charter for Study TDM4370g/BO21977 was not followed with respect to the blinding of treatment-specific toxicities which were required to be excluded by the charter. Information on toxicities were inadvertently included in the adverse event data provided to the independent central reader for review of the radiographic and clinical data by the oncology reviewer. Although this may have introduced bias in the adjudication of PFS, there was a high concordance rate (94%) between radiology (blind) and oncology (potentially unblinded) reviews and important bias could be ruled out.

A heterogeneous population has been enrolled in this study, ranging from heavily pretreated patients to those with early progression (within 6 months) after an adjuvant regimen, unresectable LABC, MBC. As per inclusion criteria, all patients were lapatinib naïve but should have already received trastuzumab and a taxane.

Lapatinib in combination with capecitabine is indicated for treatment of MBC following anthracycline, taxane and trastuzumab in a metastatic setting. Thus, the selected population included patients for whom lapatinib+capecitabine combination is currently not indicated (unresectable LABC or patients who progressed within 6 months of their most recent adjuvant treatment). This was based on the assumption that unresectable LABC, early progression, and MBC patient population are clinically similar.

The Applicant identified only 15 patients with LABC: 9 in the lapatinib + capecitabine arm and 6 in the T-DM1 arm. The numbers are very low and prohibit any reasonable analysis.

However, the chosen control of lapatinib+capecitabine was considered adequate to establish the efficacy of T-DM1 in this superiority design of study.

The dosing schedule of T-DM1, 3.6 mg/kg IV every 21 days, was chosen on the basis on the results of a phase 1 dose-escalation study. The recommended dose of trastuzumab emtansine is 3.6 mg/kg given as an IV infusion q3w until PD or unacceptable toxicity. The qw and q3w schedules of trastuzumab emtansine both showed activity in patients with previously treated HER2-positive MBC, with CBRs of 57% and 50%, respectively. Overall, the reason for choosing the q3w regimen was a more favorable safety and tolerability profile. The duration of response among patients with an objective partial response was longer in the q3w cohort (10.5 months) compared to the qw cohort (5.6 months), although the sample size was small. More patients in the qw group experienced at least one Grade > 3 adverse event compared to the q3w group. The median dose intensity was 99.7% in the q3w group and 82% in the qw group. Thus, the choice of the q3w regimen seems appropriate.

The choice of the 100 mg and the 160 mg presentations has been adequately justified to provide flexible combinations over the likely body weight range of patients while minimizing product waste.

During a GCP inspection, under-reporting of adverse events from one site was observed. The risk of a systemic under-reporting due to unclear guidelines for investigators was assessed. Based on reported inspection findings and procedures implemented, it was possible to conclude that systemic under-reporting of adverse events was unlikely.

Efficacy data and additional analyses

The demographic and baseline disease characteristics were well balanced in the two treatment arms and indicated a typical patient population as per protocol.

The pivotal study TDM4370g/BO21977 demonstrated a statistically significant improvement in IRC-assessed PFS in patients who received trastuzumab emtansine compared with patients who received lapatinib plus capecitabine. The robustness of the PFS finding was confirmed by all sensitivity analyses conducted (data not shown).

A statistically significant difference was also formally established for OS, objective response rate, time to treatment failure, and time to symptom progression. Concerning OS, statistical significance was based on an unplanned interim analysis, introduced in the statistical analysis plan after a favourable trend in OS had been observed. Data-driven interim analyses should generally be avoided as they can flaw the results of a clinical trial. However, in this case, the justification for conducting an additional OS analysis before the final analysis was provided on the basis of the public efficacy information and the wish to provide conclusive OS results as quickly as possible to allow one-way cross-over while meeting the objectives of the study. Concerning a possible inflation of the type-I error, this was not of major concern since the study the overall type I error of OS analyses was controlled by Lan-DeMets alpha spending function O'B-F boundary, and the p-value was well below the boundary for stopping for efficacy.

The differences in PFS and OS observed in a patient population previously treated with trastuzumab are considered clinically relevant. Given the poor survival prognosis of patients with HER2-positive MBC whose disease has progressed following trastuzumab-based therapy, the data suggest an important clinical benefit for this patient population.

As the OS analysis was based on an interim analysis, updated efficacy analyses of the TDM4370g trial will be provided (see Obligation to complete post-authorisation measures).

To date most studies in MBC have failed to demonstrate an appreciable difference in PRO between standard of care therapy and experimental agents. In contrast, treatment with trastuzumab emtansine appeared to confer a longer time to symptom progression (TSP), and hence a better quality of life, compared with lapatinib plus capecitabine. Based on the published data, a 5 points change in the score within these subscales of the FACT-B questionnaire appears as the minimal important difference for claiming the clinical relevance of the results. However, due to the open label character of the study, no firm conclusions can be drawn.

A consistent treatment benefit of trastuzumab emtansine was seen in the majority of pre-specified subgroups evaluated, supporting the robustness of the overall result. The Applicant presented additional analyses of PFS and OS for patients with non-visceral disease based on the baseline IRC tumor assessments and by applying different definitions of visceral disease. Based on these analyses, the effect in patients with non-visceral disease appeared consistent with the overall treatment effect.

As regards as a possibly reduced benefit in the older subgroup of patients, the interpretation is difficult due to the low number of patients. The results of the subgroup analysis by age are reflected in section 5.1 of the SmPC.

The initially proposed indication was changed to reflect important selection criteria in the pivotal trial:

"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 advanced disease or metastatic disease, or*
- *Developed disease recurrence during or within six months of completing adjuvant therapy."*

The results of the main study are supported by Study TDM4374g which included a heavily pre-treated patient population, with a high IRC-assessed ORR of 32.7% (95% CI: [24.1%, 42.1%]). Study TDM4258g was in a second line setting including previous HER2-directed therapy also observed a high IRC-assessed ORR of 26.9% (95% CI: [19.2%, 35.8%]). In study TDM4450g/BO21976 (MBC first line), treatment with trastuzumab emtansine was associated with a reduction in the risk of disease progression or death compared with trastuzumab + docetaxel treatment (stratified HR = 0.594; 95% CI [0.364, 0.968]; log-rank p-value = 0.0353). The median PFS was 14.2 months in the trastuzumab emtansine arm and 9.2 months in the trastuzumab + docetaxel arm.

Immunogenicity and its impact on efficacy

Immune responses against trastuzumab emtansine are expected to a certain extent, as for any biological medicine. The incidence was as expected for a humanized monoclonal antibody. Antibodies against trastuzumab emtansine may have an impact on efficacy as demonstrated by a lower median PFS although objective response rates were comparable. The clinical significance of anti-trastuzumab emtansine antibodies is not yet known (see SmPC section 4.8).

Assessment of paediatric data on clinical efficacy

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 in the indication of metastatic breast cancer (MBC).

2.1.4. Conclusions on the clinical efficacy

Trastuzumab emtansine demonstrated statistically significant and clinically relevant efficacy in the proposed indication (as amended):

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 advanced disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Submit the overall survival outcome data from the pivotal TDM4370g/BO21977/EMILIA study once available
- Submit the final study report from the MARIANNE study once available
- Submit the final study report from the TH3RESA study once available

2.2. Clinical safety

The clinical safety data supporting this Marketing Authorisation Application are derived

primarily from study TDM4370g/BO21977 (see Clinical efficacy; Main study). Additional supporting safety information is provided from five other studies; four Phase I and II single-arm studies of trastuzumab emtansine (TDM3569g, TDM4374g, TDM4258g, and TDM4688g), and one randomized Phase II study of trastuzumab emtansine versus trastuzumab plus docetaxel (TDM4450g/BO21976). In total, these studies provide safety data for 1,401 MBC patients (882 patients exposed to trastuzumab emtansine 3.6 mg/kg q3w and 519 patients exposed exclusively to the control treatments).

Patient exposure

In the pivotal study the median dose intensity (defined as total dose received divided by the expected total dose) was 99.9% for T-DM1 compared to 93.4% for lapatinib and slightly less (77.2%) for capecitabine. The median treatment duration was higher in the T-DM1 arm (5.7 months) compared to 4.9 months in the lapatinib arm and 4.8 months in the capecitabine arm.

In the supportive study TDM4450g/BO21976, the treatment duration was longer (median of 10.4 months in the T-DM1 arm and 8.1 months for trastuzumab/5.5 months for docetaxel) as these patients were all receiving 1st line therapy for MBC (less heavily pre-treated). The median dose intensity for T-DM1 was 99.3%. In comparison, the median dose intensity was 100% for trastuzumab and 95.3% for docetaxel.

Summary of Trastuzumab Emtansine Exposure (Treated Patients)

	TDM4370g/ BO21977 (T-DM1 arm) N = 490	**TDM4450g/ BO21976[c] (T-DM1 arm) N = 69**	**Pooled T-DM1[a] N = 288**	**Total T-DM1-exposed[b] N = 882**
Number of doses received				
n	490	69	288	882
Mean (SD)	11.7 (8.4)	17.4 (12.2)	12.1 (13.5)	12.2 (10.8)
Median	9.0	16.0	7.0	9.0
Range	1.0 – 41.0	1.0 – 41.0	1.0 – 69.0	1.0 – 69.0
Average dose received (mg/kg)				
n	490	69	287	881
Mean (SD)	3.49 (0.20)	3.5 (0.5)	3.51 (0.20)	3.50 (0.24)
Median	3.50	3.60	3.57	3.56
Range	2.70 – 4.00	3.00 – 6.00	2.50 – 4.19	2.50 – 6.00
Dose Intensity (%)[d]				
n	490	68	288	882
Mean (SD)	97.85 (10.92)	95.0 (11.9)	95.69 (8.38)	96.90 (10.58)
Median	99.92	99.30	99.49	99.70
Range	54.67 – 200.72	61 – 158	55.17 – 107.52	54.67 – 200.72
Treatment Duration (months)				
n	490	69	288	882
Mean (SD)	7.7 (6.1)	11.9 (8.8)	8.2 (10.1)	8.2 (7.9)
Median	5.7	10.4	4.2	5.6
Range	0.0 – 28.4	0 – 29	0.0 – 47.1	0.0 – 47.1
Duration on Treatment				
≤ 2 years	481 (98.2%)	65 (94.2%)	263 (91.3%)	843 (95.6%)
> 2 years	9 (1.8%)	4 (5.8%)	25 (8.7%)	39 (4.4%)
> 3 years	0.0%	0.0%	9 (3.1%)	9 (1.0%)
Infusion ever interrupted?				

	TDM4370g/ BO21977 (T-DM1 arm) N = 490	TDM4450g/ BO21976[c] (T-DM1 arm) N = 69	Pooled T-DM1[a] N = 288	Total T-DM1-exposed[b] N = 882
n No Yes	490 462 (94.3%) 28 (5.7%)	69 56 (81.2%) 13 (18.8%)	288 251 (87.2%) 37 (12.8%)	882 798 (90.5%) 84 (9.5%)
Infusion ever prematurely discontinued? n No Yes	 490 485 (99.0%) 5 (1.0%)[f]	 69 68 (98.6%) 1 (1.4%)[e]	 288 287 (99.7%) 1 (0.3%)[h]	 882 874 (99.1%) 8 (0.9%)[g]
Dose ever reduced? n No Yes T-DM1 Reduced to 3.0 mg/kg T-DM1 Reduced to 2.4 mg/kg	 490 410 (83.7%) 80 (16.3%) 58 (72.5%) 22 (27.5%)	 69 55 (79.7%) 14 (20.3%) 7 (10.1%) 7 (10.1%)	 181 154 (85.1%) 27 (14.9%) 18 (66.7%) 9 (33.3%)	 775 651 (84.0%) 124 (16.0%) 86 (69.4%) 38 (30.6%)

a Pooled trastuzumab emtansine includes patients from studies TDM4374g, TDM4258g, TDM3569g, and TDM4688g, with safety data also included for 43 patients who continued treatment in the extension study TDM4529g/BO25430, as follows:
-TDM3659g : 1 patient;
-TDM4258g: 19 patients;
-TDM4374g: 12 patients;
-TDM4688g: 7 patients;
-TDM4450g: 4 patients.

b Total trastuzumab emtansine-exposed includes patients from TDM4370g, TDM4450g, TDM4374g, TDM4258g, TDM3569g, TDM4529g and TDM4688g studies who have received at least one dose of trastuzumab emtansine. For Study TDM4450g/BO21976, patients in the "Total trastuzumab emtansine–exposed patients" group includes all patients from the trastuzumab emtansine arm and those patients in the control arm who crossed over to receive trastuzumab emtansine after progression. Safety data from 43 patients who continued treatment in the extension study TDM4529g/BO25430 are also included.

c The exposure for this column is based only on the time patients were in TDM4450g/BO21976. Data for the extension study for patients who rolled over into TDM4529g/BO25430 are not included.

d Dose intensity is defined as total dose received divided by the expected total dose.

e In Study TDM4450g/BO21976, the reason for premature discontinuation of trastuzumab emtansine infusion in this patient was a Grade 2 hypersensitivity AE on the first cycle of trastuzumab emtansine. This patient subsequently continued to receive trastuzumab emtansine without any further issues.

f In study TDM4370g/BO21977, the reason for premature discontinuation of trastuzumab emtansine infusion was AE for 3 out of the 5 patients.

g In study TDM4450g/BO21976, Patient no. 9526 (trastuzumab plus docetaxel arm) discontinued trastuzumab emtansine after crossing over to the trastuzumab emtansine arm. due to the reason “clinic was closing due to construciton and infusion started too late in the day”.

h In Study TDM4374g, Patient no. 4261 discontinued trastuzumab emtansine due to the reason “sponsor decision”.

Abbreviations: T-DM1=trastuzumab emtansine; SD=standard deviation
Sources:
Integrated analysis populations: t_dexp01 Study TDM4370g/BO21977: t_exp
Study TDM4450g/BO21976: t_exp ; t_tdmdur

Adverse events

The most common adverse drug reactions (ADRs) (≥25%) with trastuzumab emtansine were thrombocytopenia, fatigue, increased transaminases, nausea, headache, musculoskeletal pain and constipation. 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; version 3.0) Grade 3 or 4 ADRs (> 2%) were thrombocytopenia, fatigue, increased transaminases, anaemia, hypokalaemia, musculoskeletal pain and neutropenia. The most common serious ADRs were pyrexia, thrombocytopenia, vomiting, abdominal pain, nausea, constipation, diarrhoea, dyspnoea and pneumonitis (see Serious Adverse Events).

The table 3 presents an overview of the safety profile of T-DM1; Table 4 presents a summary of adverse events with difference in incidence rate ≥ 5%: between the trastuzumab emtansine arm and the lapatinib + capecitabine arms.

Table 5 presents frequency of adverse events by NCI CTCAE Grade, Adverse Drug Reaction (ADR) Preferred Term (PT). The ADR table in the SmPC is based on any AEs for which a causal relationship is at least a reasonable possibility without regards to incidence. The following methodology was used to select ADRs for inclusion into the SmPC ADR Table:

- The ADR evaluation was performed based on:
    - AE listing by SOC and MedDRA PT
    - Primarily data from the pivotal trial TDM4370g/BO21977
    - Data from Study TDM4450g/BO21976 (in which the majority of patients were trastuzumab naïve)
    - Data from the individual studies TDM4370g/BO21977, TDM4450g/BO21976, TDM4374g, TDM4258g, TDMTDM3569g, and TDM4688g, including data from 43 patients from these Phase I and II studies who enrolled in the extension study TDM4529g/BO25430.
- Clinical judgement of causality was applied for all AEs using the Bradford-Hill Paradigm (Bradford Hill, 1965):
- The reviewed PTs were grouped by diagnosis or clinical entity where appropriate (eg, a diagnosis vs. sign/symptom).
- The incidence for defined diagnosis/PT representing the clinical entity was calculated by summing the included PTs (example: thrombocytopenia + decreased platelet counts; anemia + decreased hemoglobin; neuropathy peripheral + peripheral sensory neuropathy + paraesthesia, etc.).

Table 3. Overview of Safety Profile (Safety Population)

	TDM4370g/BO21977		TDM4450g/BO21976		Pooled Trastuzumab Emtansine[1] N = 288	Total Trastuzumab Emtansine-exposed[2] N = 882
	Lapatinib + Capecitabine N = 488	Trastuzumab Emtansine N = 490	Trastuzumab + Docetaxel N = 66	Trastuzumab Emtansine N = 69		
Number (%) of Patients with:						
Any AE	477 (97.7)	470 (95.9)	66 (100.0)	66 (95.7)	288 (100.0)	857 (97.2)
AE NCI-CTC Grade ≥3	278 (57)	200 (40.8)	60 (90.9)	32 (46.4)	138 (47.9)	378 (42.9)
Death	128 (26.2)	94 (19.2)	12 (18.2)	14 (20.3)	7 (2.4)	119 (13.5)
Death due to PD	123 (25.2)	91 (18.6)	10 (15.2)	12 (17.4)	0	107 (12.1)
Death due to causes other than PD	5 (1.0)	3 (0.6)	1 (1.5)	2 (2.9)	7 (2.4)	12 (1.4)
SAE	88 (18)	76 (15.5)	17 (25.8)	14 (20.3)	73 (25.3)	164 (18.6)
AE leading to discontinuation	L: 37 (7.6) C: 46 (9.4)	29 (5.9)	23 (34.8)	5 (7.2)	21 (7.3)	55 (6.2)
AE leading to dose reduction	L: 92 (18.9) C:188 (38.5)	74 (15.1)	19 (28.8)	12 (17.4)	20 (6.9)	108 (12.2)
AE leading to dose delay of T-DM1	N/A	104 (21.2)	N/A	16 (23.2)	70 (24.3)	193 (21.9)

Table 4. Summary of Adverse Events with Difference in Incidence Rate ≥ 5%: Between the Trastuzumab Emtansine Arm and the Lapatinib+Capecitabine Arms: Pivotal Study TDM4370g/BO21977 (Safety Population)

	Lapatinib + Capecitabine (n = 488)	Trastuzumab Emtansine (n =490)
AEs occurring in at least 5% more patients in the trastuzumab emtansine arm		
Fatigue	136 (27.9%)	172 (35.1%)
Thrombocytopenia	12 (2.5%)	137 (28.0%)
Constipation	47 (9.6%)	124 (25.3%)
AST increased	46 (9.4%)	110 (22.4%)
ALT increased	43 (8.8%)	83 (16.9%)
Arthralgia	38 (7.8%)	85 (17.3%)
Pyrexia [a]	37 (7.6%)	85 (17.3%)
Dry mouth	24 (4.9%)	77 (15.7%)
Myalgia	18 (3.7%)	69 (14.1%)
Chills [a]	14 (2.9%)	39 (8.0%)
Headache	68 (13.9)	133 (27.1%)
Epistaxis	39 (8.0%)	99 (20.2%)
Urinary Tract Infection	17 (3.5%)	44 (9.0%)
AEs occurring in at least 5% more patients in the lapatinib plus capecitabine arm		
Diarrhea	389 (79.7%)	114 (23.3%)
Nausea	218 (44.7%)	192 (39.2%)
PPE syndrome	283 (58.0%)	6 (1.2%)
Vomiting	143 (29.3%)	93 (19.0%)
Rash	130 (26.6%)	52 (10.6%)
Mucosal inflammation	93 (19.1%)	33 (6.7%)
Stomatitis	61 (12.5%)	16 (3.3%)
Dry skin	49 (10.0%)	17 (3.5%)

	Lapatinib + Capecitabine (n = 488)	Trastuzumab Emtansine (n =490)
AEs occurring in at least 5% more patients in the trastuzumab emtansine arm		
Paronychia	52 (10.7%)	1 (0.2%)
Nail disorder	39 (8.0%)	11 (2.2%)
Hyperbilirubinemia	40 (8.2%)	6 (1.2%)
Skin fissures	27 (5.5%)	1 (0.2%)

Table 5. Adverse Events by NCI CTCAE Grade, Adverse Drug Reaction Category and Preferred Term (Total trastuzumab emtansine-exposed includes patients from TDM4370g, TDM4450g, TDM4374g, TDM4258g, TDM3569g, TDM4529g and TDM4688g studies who have received at least one dose of Trastuzumab Emtansine; N=882)

Adverse Drug Reaction Preferred Term	Grade 1-2 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)
Any adverse event	546 (62)	289 (33)	835 (95)
Abdominal pain upper	91 (10)	2 (0)	93 (11)
Abdominal pain	74 (8)	6 (1)	80 (9)
Alopecia	28 (3)	1 (0)	29 (3)
Anaemia	99 (11)	22 (2)	121 (14)
Haemoglobin decreased	16 (2)	3 (0)	19 (2)
Arthralgia	158 (18)	8 (1)	166 (19)
Asthenia	116 (13)	7 (1)	123 (14)
Blood alkaline phosphatase increased	49 (6)	3 (0)	52 (6)
Chills	97 (11)	0 (0)	97 (11)
Conjunctivitis	35 (4)	0 (0)	35 (4)
Constipation	220 (25)	5 (1)	225 (26)
Cough	171 (19)	1 (0)	172 (20)
Diarrhoea	171 (19)	8 (1)	179 (20)
Dizziness	81 (9)	2 (0)	83 (9)
Hypersensitivity	19 (2)	0 (0)	19 (2)
Bronchospasm	4 (0)	0 (0)	4 (0)
Dry eye	48 (5)	0 (0)	48 (5)
Dry mouth	158 (18)	0 (0)	158 (18)
Dysgeusia	65 (7)	0 (0)	65 (7)
Dyspepsia	78 (9)	1 (0)	79 (9)
Dyspnoea	115 (13)	12 (1)	127 (14)
Epistaxis	201 (23)	4 (0)	205 (23)
Fatigue	372 (42)	28 (3)	400 (45)
Gingival bleeding	28 (3)	0 (0)	28 (3)
Headache	248 (28)	5 (1)	253 (29)
Hepatic failure	0 (0)	1 (0)	1 (0)
Hepatotoxicity	0 (0)	3 (0)	3 (0)
Hypertension	46 (5)	8 (1)	54 (6)
Hypokalaemia	101 (11)	26 (3)	127 (14)
Blood potassium decreased	8 (1)	3 (0)	11 (1)
Infusion related reaction	39 (4)	1 (0)	40 (5)
Insomnia	94 (11)	2 (0)	96 (11)
Lacrimation increased	42 (5)	0 (0)	42 (5)
Ejection fraction decreased	10 (1)	2 (0)	12 (1)

Adverse Drug Reaction Preferred Term	Grade 1-2 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)
Left ventricular dysfunction	5 (1)	1 (0)	6 (1)
Leukopenia	34 (4)	4 (0)	38 (4)
White blood cell count decreased	11 (1)	0 (0)	11 (1)
Memory impairment	11 (1)	1 (0)	12 (1)
Back pain	124 (14)	11 (1)	135 (15)
Pain in extremity	108 (12)	4 (0)	112 (13)
Musculoskeletal pain	79 (9)	3 (0)	82 (9)
Muscle spasms	68 (8)	0 (0)	68 (8)
Bone pain	51 (6)	7 (1)	58 (7)
Musculoskeletal chest pain	39 (4)	4 (0)	43 (5)
Musculoskeletal discomfort	2 (0)	0 (0)	2 (0)
Myalgia	107 (12)	3 (0)	110 (12)
Nail disorder	22 (2)	0 (0)	22 (2)
Nausea	364 (41)	9 (1)	373 (42)
Neuropathy peripheral	99 (11)	11 (1)	110 (12)
Peripheral sensory neuropathy	46 (5)	5 (1)	51 (6)
Paraesthesia	47 (5)	0 (0)	47 (5)
Neutropenia	40 (5)	17 (2)	57 (6)
Neutrophil count decreased	6 (1)	1 (0)	7 (1)
Nodular regenerative hyperplasia	1 (0)	0 (0)	1 (0)
Oedema peripheral	73 (8)	1 (0)	74 (8)
Palmar-plantar erythrodysaesthesia syndrome	10 (1)	0 (0)	10 (1)
Pneumonitis	7 (1)	1 (0)	8 (1)
Portal hypertension	1 (0)	0 (0)	1 (0)
Pruritus	46 (5)	1 (0)	47 (5)
Pyrexia	200 (23)	2 (0)	202 (23)
Rash	106 (12)	0 (0)	106 (12)
Oropharyngeal pain	47 (5)	0 (0)	47 (5)
Mucosal inflammation	49 (6)	1 (0)	50 (6)
Stomatitis	40 (5)	0 (0)	40 (5)
Thrombocytopenia	163 (18)	90 (10)	253 (29)
Platelet count decreased	23 (3)	10 (1)	33 (4)
Aspartate aminotransferase increased	167 (19)	36 (4)	203 (23)
Alanine aminotransferase increased	109 (12)	25 (3)	134 (15)
Transaminases increased	15 (2)	4 (0)	19 (2)
Liver function test abnormal	8 (1)	3 (0)	11 (1)
Gamma-glutamyltransferase increased	7 (1)	6 (1)	13 (1)
Hepatic enzyme increased	2 (0)	2 (0)	4 (0)
Hepatic function abnormal	1 (0)	2 (0)	3 (0)
Urinary tract infection	95 (11)	3 (0)	98 (11)
Cystitis	20 (2)	0 (0)	20 (2)
Urticaria	9 (1)	0 (0)	9 (1)
Vision blurred	42 (5)	0 (0)	42 (5)
Vomiting	176 (20)	7 (1)	183 (21)

Events of special interest

Identified and potential risks of treatment with trastuzumab emtansine (and the corresponding tests, monitoring and precautions that have been put in place in clinical trials) were based on all available nonclinical and clinical data relating to trastuzumab emtansine, as well as on the clinical toxicities associated with trastuzumab and the parent molecule of DM1, maytansine.

Transaminases increased (AST/ALT)

Increase in serum transaminases (Grade 1-4) has been observed during treatment with trastuzumab emtansine in clinical studies. 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 28% of patients in clinical studies. Grade 3 or 4 increased AST and ALT were reported in 4.1% and 2.8% of patients respectively and usually occurred in the early treatment cycles (1-6). 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.

A multivariate analysis of patients receiving trastuzumab emtansine in Study TDM4370g/BO21977, using the clinical cut−off date of 31 July 2012, was conducted to determine whether there are potential risk factors for developing a hepatotoxicity event. A multivariate logistic model was fit using the following independent variables at baseline: AST, ALT, and TBL values, presence of liver metastases, hepatotoxic drug use, world region, prior chemotherapy regimen in locally advanced/metastatic setting, presence of visceral disease, age, race, number of disease sites, prior anthracycline therapy, Eastern Cooperative Oncology Group (ECOG) performance status, progesterone receptor (PR) and estrogen receptor (ER) status, presence of measurable disease, menopausal status, prior anticancer therapy, prior trastuzumab therapy, and HER2 status by FISH and IHC results. The dependent variable used in the model was post-baseline development of a severe hepatic event, defined as a Grade 3-5 adverse event (AE) from among the preferred terms in the pre-defined selected AE basket of hepatotoxicity or a Grade 3-5 event of AST, ALT or TBL increase. Results from this analysis showed baseline ALT (actual value in U/L) to be a potential risk factor for developing a severe hepatic event (odds ratio=1.02; 95% CI: 1.00, 1.03). The value of the odds ratio suggests that for every increase of one unit in the baseline ALT value there is an approximately 2% increase in the odds of experiencing a severe hepatic event.

Left ventricular dysfunction

Left ventricular dysfunction was reported in 2.0% of patients in 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 0.3% of patients. These uncommon Grade 3 or 4 events usually occurred in the early treatment cycles (1-2). Additional LVEF monitoring is recommended for patients with LVEF ≤ 45% (See Table 5 in section 4.2 for specific dose modifications).

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 4.5% of patients in clinical studies with trastuzumab emtansine, with one Grade 3 and no Grade 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 section 4.2 and 4.4.

Hypersensitivity reactions

Hypersensitivity was reported in 2.6% of patients in clinical studies with trastuzumab emtansine, with no Grade 3 or 4 events reported. 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 section 4.2 and 4.4.

Thrombocytopenia

Thrombocytopenia or decreased platelet counts were reported in 31.4% of patients in clinical studies with trastuzumab emtansine and was the most common adverse reaction leading to treatment discontinuation (1.4%). The majority of the patients had Grade 1 or 2 events ($\geq$ 50,000/mm^3), with the nadir occurring by day 8 and generally improving to Grade 0 or 1 ($\geq$ 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 11.3% in patients treated with trastuzumab emtansine. The incidence of severe haemorrhagic events (Grade $\geq$3) occurred in 1.7% of the overall trastuzumab emtansine treated patients and 1% of Asian trastuzumab emtansine treated patients. In some of the observed cases the patients were also receiving anti-coagulation therapy. Cases of bleeding events with a fatal outcome have been observed. For dose modifications for thrombocytopenia, see section 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 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to trastuzumab emtansine. Following dosing, 5.3% (44/836) of patients tested positive for anti-trastuzumab emtansine antibodies at one or more post-dose time points. The clinical significance of anti-trastuzumab emtansine antibodies is not yet known.

Extravasation

Reactions secondary to extravasation have been observed in clinical studies with trastuzumab emtansine. These reactions were usually mild 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. Specific treatment for trastuzumab emtansine extravasation is unknown at this time.

Serious adverse event / deaths / other significant events

The most common serious ADRs were pyrexia, thrombocytopenia, vomiting, abdominal pain, nausea, constipation, diarrhoea, dyspnoea and pneumonitis.

Summary of Serious Adverse Events by System Organ Class Occurring in ≥ 1% of Patients in Either Treatment Arm: Pivotal Study TDM4370g/BO21977 (Safety Population)

	TDM4370g/BO21977		TDM4450g/BO21976		Pooled Trastuzumab Emtansine[2]	Total Trastuzumab Emtansine-exposed[3]
	Lapatinib + Capecitabine N = 488	Trastuzumab Emtansine N = 490	Trastuzumab + Docetaxel N = 66	Trastuzumab Emtansine N = 69	N = 288	N = 882
Patients with AEs by NCI-CTCAE Grade, n (%)						
1	43 (8.8%)	52 (10.6%)	0.00%	7 (10.1%)	34 (11.8%)	96 (10.9%)
2	57 (11.7%)	57 (11.6%)	0.00%	14 (20.3%)	30 (10.4%)	107 (12.1%)
3	23 (4.7%)	41 (8.4%)	1 (1.5%)	11 (15.9%)	17 (5. %)	70 (7.9%)
4	0.00%	2 (0.4%)	0.00%	0.00%	3 (1.0%)	5 (0.6%)
5	0.00%	0.00%	0.00%	0.00%	2 (0.7%)	2 (0.2%)
Total	123 (25.2%)	152 (31.0%)	1 (1.5%)	32 (46.4%)	86 (29.9%)	280 (31.7%)
Patients with AEs NCI-CTCAE Grade≥3, n (%)						
AST Increased	4 (0.8%)	21 (4.3%)	0.00%	6 (8.7%)	9 (3.1%)	36 (4.1%)
ALT Increased	7 (1.4%)	14 (2.9%)	0.00%	7 (10.1%)	4 (1.4%)	25 (2.8%)
ALP Increased	2 (0.4%)	1 (0.2%)	0.00%	2 (2.9%)	0.00%	3 (0.3%)
Bilirubin Increased	4 (0.8%)	2 (0.4%)	0.00%	0.00%	1 (0.3%)	3 (0.3%)
Hypoalbuminemia	1 (0.2%)	0.00%	1 (1.5%)	1 (1.4%)	1 (0.3%)	2 (0.2%)
Transaminases Increased	1 (0.2%)	4 (0.8%)	0.00%	0.00%	0.00%	4 (0.5%)
Hyperbilirubinemia	4 (0.8%)	1 (0.2%)	0.00%	0.00%	1 (0.3%)	2 (0.2%)
LFT Abnormal	0.00%	1 (0.2%)	0.00%	0.00%	2 (0.7%)	3 (0.3%)
G-GT Increased	0.00%	4 (0.8%)	0.00%	2 (2.9%)	0.00%	6 (0.7%)
Ascites	0.00%	0.00%	0.00%	0.00%	2 (0.7%)	2 (0.2%)
Hepatic Enzyme Increased	0.00%	1 (0.2%)	0.00%	0.00%	1 (0.3%)	2 (0.2%)
Hepatic function abnormal	1 (0.2%)	0.00%	0.00%	0.00%	2 (0.7%)	2 (0.2%)
Hepatotoxicity	0.00%	1 (0.2%)	0.00%	0.00%	2 (0.7%)	3 (0.3%)
Hepatic failure	0.00%	0.00%	0.00%	0.00%	1 (0.3%)	1 (0.1%)
AST Abnormal	0.00%	1 (0.2%)	0.00%	0.00%	0.00%	1 (0.1%)
Hepatitis toxic	0.00%	1 (0.2%)	0.00%	0.00%	0.00%	1 (0.1%)
Cholestatic jaundice	1 (0.2%)	0.00%	0.00%	0.00%	0.00%	1 (0.1%)
Cytolytic hepatitis	1 (0.2%)	0.00%	0.00%	0.00%	0.00%	0.00%

Source: t_ae10, , Table 50 from TDM4370g/BO21977 CSR; Table 30 from study TDM4450g/BO21976 CSR.

1. Selected AEs were analyzed using Standardized MedDRA Queries (SMQs), where available, as these are a consistent set of AE grouped terms globally recognized by regulatory authorities. If no SMQs were available, baskets of MedDRA Adverse Event Grouped Terms (AEGTs) were used. Details are provided in Section 1.1.7.3.2 and Appendix 3.

2. Pooled trastuzumab emtansine includes patients from TDM4374g, TDM4258g, TDM3569g, TDM4529g and TDM4688g studies.

3. Total trastuzumab emtansine-exposed includes patients from TDM4370g, TDM4450g, TDM4374g, TDM4258g, TDM3569g, TDM4529g and TDM4688g studies who have received at least one dose of trastuzumab emtansine.

In the pivotal study TDM4370g/BO21977, deaths due to causes other than PD were low: 3 patients (0.6%) in the trastuzumab emtansine arm and 5 patients (1.0%) in the lapatinib plus capecitabine arm.

Deaths and Cause of Death: Pivotal Study TDM4370g/BO21977 (Safety Population)

Genentech, Inc.
TRASTUZUMAB EMTANSINE

Phase III Study: TDM4370g
TRASTUZUMAB EMTANSINE

Table death01
Deaths and Cause of Death
Safety Evaluable Subjects

	Lapatinib+Capecitabine (n=488)	Trastuzumab emtansine (n=490)
All deaths	128 (26.2%)	94 (19.2%)
<= 30 days from last study drug administration	17 (3.5%)	4(0.8%)
> 30 days from last study drug administration	111 (22.7%)	90 (18.4%)
Cause of death		
Progressive Disease	123 (25.2%)	91 (18.6%)
Adverse Event*	5 (1.0%)	3 (0.6%)

*Include all deaths due to reasons other than progressive disease.

Source: Biostatistics(junliu) pgm(/onco/aherdm1/tdm4370g/final/programs/t_death)
Database (CLOSED) Datasets (pat)
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Adverse Events Leading to Death on Study Treatment: Pivotal Study TDM4370g/BO21977 (Safety Evaluable Patients)

Genentech, Inc.
TDM4370g
TRASTUZUMAB EMTANSINE
EMTANSINE

Phase III Study:
TRASTUZUMAB

Table ae12
Adverse Events Leading to Death by System Organ Class and Preferred Term
Safety Evaluable Subjects

MedDRA System Organ Class Preferred Term	Lapatinib+Capecitabine (n=488)	Trastuzumab emtansine* (n=490)
-Any Adverse Events-	5 (1.0%)	1 (0.2%)
CARDIAC DISORDERS		
- Overall -	1 (0.2%)	(0.0%)
CORONARY ARTERY DISEASE	1 (0.2%)	(0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
- Overall -	1 (0.2%)	(0.0%)
MULTI-ORGAN FAILURE	1 (0.2%)	(0.0%)
NERVOUS SYSTEM DISORDERS		
- Overall -	2 (0.4%)	1 (0.2%)
COMA	1 (0.2%)	(0.0%)
HYDROCEPHALUS	1 (0.2%)	(0.0%)
METABOLIC ENCEPHALOPATHY	(0.0%)	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
- Overall -	1 (0.2%)	(0.0%)
ACUTE RESPIRATORY DISTRESS SYNDROME	1 (0.2%)"	(0.0%)

treatment-emergent adverse events are adverse events with an onset date on or after the first day of treatment with study medication.
on study treatment period is fom date of first dose of study treatment to 30 days after last dose.
two additional deaths due to reasons other than progressive disease on the trastuzumab emtansine arm occurred after the study treatment period.

source: Biostatistics(tonyti) pgm(/onco/aherdm1/tdm4370g/final/programs/t_ae)
Database (CLOSED) Datasets (pat,ae)
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Laboratory findings

Pivotal Study TDM4370g/BO21977

More patients in the trastuzumab emtansine arm had decreased hemoglobin level (7 of 352 patients [2.0%] shifted from Grade 0 to Grade ≥ 3) compared with the lapatinib plus capecitabine arm (2 of 360 patients [0.6%] shifted from Grade 0 to Grade ≥ 3); fewer patients in patients in the trastuzumab emtansine arm had decreased neutrophil counts (15 of 450 patients [3.3%] shifted from Grade 0 to Grade ≥ 3) compared with the lapatinib plus capecitabine arm (33 of 473 patients [7.0%] shifted from Grade 0 to Grade ≥ 3). There was no shift in lymphocytes count in either of the treatment arms.

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

Parameter	Trastuzumab emtansine		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hepatic			
Increased bilirubin	20	< 1	0
Increased AST	98	7	< 1
Increased ALT	82	5	< 1
Haematologic			
Decreased platelets	84	14	3
Decreased haemoglobin	62	4	1
Decreased neutrophils	39	4	< 1
Potassium			
Decreased potassium	34	3	<1

Safety in special populations

An overview of AEs by subgroup revealed that Asians had more severe events than other races, primarily due to a higher risk of thrombocytopenia as previously described. When focusing on AEs by age categories in the T-DM1 arm, the large majority of patients in the pivotal trial included patients < 65 years of age (426 patients). Only 64 patients were ≥ 65 years of age. When comparing these subgroups, slightly more Grade≥ 3 events were observed in patients ≥ 65 years of age (46.9%) compared with patients < 65 years of age (39.9%). A similar pattern was observed for SAEs (≥ 65: 21.9%, < 65: 14.6%) and for discontinuations due to AEs (≥ 65 : 12.5%, < 65: 4.9%). Overall the observed frequencies of severe events, SAEs and discontinuations due to AEs were consistently higher in the lapatinib+capecitabine arm compared to the T-DM1 arm in patients ≥ 65 years of age. There was no higher risk of developing cardiotoxicity, hemorrhage or hepatotoxicity in patients ≥ 65 years of age when treated with T-DM1. The subgroup of patients ≥ 75 years of age only included 11 patients.

Summary of Adverse events by age and treatment group.

	Lapatinib + Capecitabine			Trastuzumab emtansine		
Age Group	n	Grade 3-5	Overall	n	Grade 3-5	Overall
<65 years	415	239 (57.6%)	406 (97.8%)	426	186 (43.7%)	412 (96.7%)
≥65 years	73	52 (71.2%)	72 (98.6%)	64	32 (50.0%)	62 (96.9%)
≥64 - <74 years	59	42 (71.2%)	58 (98.3%)	53	29 (54.7%)	51 (96.2%)
≥75 years	14	10 (71.4%)	14 (100%)	11	3 (27.3%)	11 (100%)

Use in Pregnancy and Lactation

No reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. Post-marketing case reports of trastuzumab indicate that use during pregnancy increases the risk of oligohydramnios during the second and third trimester. To date, no pregnancies have been reported in patients treated with trastuzumab emtansine, and no studies of trastuzumab emtansine have been conducted in pregnant women.

Women of childbearing potential should use effective contraception while receiving trastuzumab emtansine and for 6 months following the last dose of trastuzumab emtansine. Male patients or their female partners should also use effective contraception.

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.

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 6 months after concluding treatment.

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 (see SmPC section 4.9).

Safety related to drug-drug interactions and other interactions

No additional information is currently available.

Discontinuation due to adverse events

In pivotal study TDM4370g/BO21977, 29 patients (5.9%) discontinued trastuzumab emtansine due to an AE, compared with 37 patients (7.6%) discontinuing lapatinib, and 46

patients (9.4%) who discontinued capecitabine due to AEs. In the lapatinib plus capecitabine arm, 6 patients (1.2%) discontinued only lapatinib, 15 patients (3.1%) discontinued only capecitabine, and 31 patients (6.4%) discontinued both study drugs (Study TDM4370g/BO21977 CSR). The most common AEs leading to trastuzumab emtansine withdrawal were in the SOC of blood and lymphatic system disorders (primarily thrombocytopenia) and investigations (liver enzyme increases). For both capecitabine and lapatinib, discontinuations were most commonly due to gastrointestinal disorders (diarrhea and vomiting) or skin and subcutaneous tissue disorders (principally PPE syndrome).

In pivotal study TDM4370g/BO21977, fewer patients in the trastuzumab emtansine arm had AEs that led to dose reductions compared with the patients in lapatinib plus capecitabine arm

Summary of Adverse Events Leading to Dose Reduction in ≥ 1% of Patients: Pivotal Study TDM4370g/BO21977 (Safety Population)

MedDRA Preferred Term	Lapatinib (n=488)	Capecitabine (n=488)	Trastuzumab emtansine (n=490)
Any Adverse Events	92 (18.9%)	188 (38.5%)	74 (15.1%)
Thrombocytopenia	0%	0%	24 (4.9%)
Neutropenia	0%	6 (1.2%)	3 (0.6%)
Diarrhea	42 (8.6%)	70 (14.3%)	1 (0.2%)
Nausea	5 (1.0%)	16 (3.3%)	0%
Vomiting	7 (1.4%)	12 (2.5%)	0%
Mucosal inflammation	2 (0.4%)	9 (1.8%)	1 (0.2%)
Fatigue	3 (0.6%)	6 (1.2%)	1 (0.2%)
Paronychia	9 (1.8%)	5 (1.0%)	0%
AST increased	0%	0%	19 (3.9%)
ALT increased	0%	0%	13 (2.7%)
Neuropathy peripheral	0%	0%	5 (1.0%)
PPE syndrome	18 (3.7%)	98 (20.1%)	0%

Post marketing experience

As trastuzumab has not been granted an approval in any territory there is no information available.

2.2.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The size of the safety database and the exposure are considered adequate to allow assessment and characterization of the safety profile of T-DM1. Standard methods have been used for the detection and reporting of adverse events. Dose modification guides are adequately described in the SmPC (see section 4.2).

Common adverse event

Common AEs known to be associated with trastuzumab are infusion-reactions, flu-like symtoms, haematological toxicities and cardiotoxicity. Maytansine is a cytotoxic agent that

inhibits the assembly of microtubules. Its clinical use has so far been limited due to its lack of tumour specificity and unacceptable adverse effects (severe nausea and vomiting as well as neurotoxicity). As expected based on the well-characterised toxicities associated with the respective components of these regimens, the most common AEs (>20%) reported in the *T-DM1* arm were nausea (39.2%), fatigue (35.1%), thrombocytopenia (28.0%), headache (27.1%), diarrhea (23.3%), AST increased (22.4%), decreased appetite (20.6%) and epistaxis (20.2%). In comparison, the most common AEs in the lapatinib+capecitabine arm were diarrhea (79.7%), Palmar-Plantar Erythrodyseastesia (PPE) syndrome (58.0%), nausea (44.7%), vomiting (29.3%), rash (26.6%) and decreased appetite (23.2%).

Severe, life-threatening adverse events, and serious adverse events

In the pivotal study 40.8% of patients in the T-DM1 arm reported Grade ≥ 3 AEs (most commonly thrombocytopenia and ASAT increased in 12.9% and 4.3% of patients, respectively). In comparison, 57.0% of patients in the lapatinib+capecitabine arm reported Grade ≥ 3 AEs events (most commonly diarrhoea and PPE syndrome in 20.7% and 16.4% of patients, respectively). Grade 5 events were rare (5 events in the lapatinib+capecitabine arm vs. 3 events in the T-DM1 arm). A similar pattern was observed in the supportive studies. A slightly lower frequency of SAEs was observed in the T-DM1 arm (15.5%) compared to the lapatinib+capecitabine arm (18.0%) in the pivotal trial. In general, the reported SAEs were represented by many different events with no particular or unexpected accumulation. The most common (>1%) SAEs by System Organ Class (SOC) in the T-DM1 arm were Infections and infestations (4.1%, no predominant preferred terms were observed). Of note, sepsis and bacteriemia only represented 0.4% and 0.2% of these events, respectively. In the lapatinib+capecitabine arm the most common SAEs by SOC were Gastrointestinal disorders (5.9%, mainly diarrhea). In the total T-DM1-exposed safety population 18.6% of patients had reported SAEs which is in line with the frequency observed in the pivotal trial.

Hepatotoxicity

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. 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. 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.

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. Dose reductions or discontinuation for increased serum transaminases and total bilirubin are specified in section 4.2 of the SmPC.

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.

A hepatic impairment study (BO25499) will prospectively evaluate the safety and tolerability of trastuzumab emtansine in patients with mild or moderate hepatic impairment compared with patients with normal hepatic function (see RMP). Dose modifications in the event of increased transaminases, are reflected in the SmPC section 4.2 and 4.4.

Thrombocytopenia

In the pivotal study the frequency of thrombocytopenia was 30.4% in the T-DM1 arm and only 2.9% in the lapatinib+capecitabine arm. Grade ≥3 events represented 13.9% of events in the T-DM1 arm. In general, platelet counts recovered before the next scheduled dose. Thrombocytopenia was the most common adverse reaction leading to treatment discontinuation (see section 4.8).

Asian patients more commonly experienced thrombocytopenia (51.1%), these patients also had a higher risk of developing Grade 3-4 thrombocytopenia (41.3%). No association between exposure and the risk of developing thrombocytopenia could be demonstrated. A similar pattern was observed in the total T-DM1-exposed safety population.

Cases of bleeding events with a fatal outcome have been observed. Severe cases of haemorrhagic events, including central nervous system haemorrhage, have been reported in clinical studies; these events were independent of ethnicity. In some of the observed cases the patients were also receiving anti-coagulation therapy.

It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Patients with thrombocytopenia (≤ 100,000/mm3) 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/mm3 prior to initiation of treatment. In the event of

decreased platelet count to Grade 3 or greater (< 50,000/mm3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥ 75,000/mm3) (see section SmPC 4.2).

Infusion and hypersensitivity reactions

All patients in the pivotal study had previously received treatment and tolerated trastuzumab and a low rate of infusion- and hypersensitivity reactions was expected in the T-DM1 arm (3.9%). All events were of mild or modest severity (Grade 1 or 2). In the total T-DM1 exposed safety population infusion reactions and hypersensitivity reactions were noted in 6.7% of patients.

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 SmPC section 4.2).

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 (see SmPC section 4.3).

Pneumonitis

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. Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. Six cases of pneumonitis were reported in the T-DM1 arm of the pivotal study (1.2% of patients). All events were of Grade 2 severity. In the total T-DM1-exposed safety population 9 patients (1.0%) developed pneumonitis. One case was fatal. The SmPC contains relevant warnings (see section 4.3). It is recommended that treatment with trastuzumab emtansine be permanently discontinued in patients who are diagnosed with ILD or pneumonitis. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events.

Cardiotoxicity

Cardiotoxicity (mainly decreased EF) is a common AE associated with the use of trastuzumab. Although most events are manageable, cardiac failure can be observed in 2% of patients (see SmPC of trastuzumab). Decreased left ventricular ejection fraction is also commonly observed in patients treated with lapatinib (see SmPC of lapatinib).

With T-DM1 the risk of cardiotoxicity seems overall to be low and most events were of mild/modest severity. It should be noted that that all patients enrolled in the pivotal study had a LVEF value ≥ 50% at baseline and that patients with symptomatic CHF requiring treatment, a history of CHF, serious cardiac arrhythmia requiring treatment, myocardial infarction or unstable angina within 6 months of randomization, current dyspnea at rest due to advanced malignancy or Grade ≥ 3 peripheral neuropathy were excluded from the study.

Cardiac dysfunction is an identified risk and relevant warnings and recommended dose modifications in case of Left Ventricular Dysfunction have been included in the SmPC (see section 4.2 and 4.3). 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 SmPC 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 medications, previous therapy with an anthracycline and high BMI (> 25 kg/m2).

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

Hypokalaemia

Hypokalemia was reported in 9.2% of patients in both the TDM-1 and lapatinib+ capecitabine arms, respectively. Hypokalemia was reported in 15.4% of patients in the total TDM-1-exposed safety population. Most of these events were of Grade 1 or 2. The mechanism by which the T-DM1 causes hypokalemia is unknown but appeared to be unrelated to renal dysfunction.

Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, was reported by 23.3% of patients in the T-DM1 arm and by 18.2% of patients in the lapatinib+capecitabine arm in the pivotal study. Patients with Grade ≥ 3 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 (see SmPC section 4.3).

Special populations

When focusing on AEs by age categories in the T-DM1 arm, the large majority of patients in the pivotal trial included patients < 65 years of age (426 patients). Overall the observed frequencies of severe events, SAEs and discontinuations due to AEs were consistently higher in the lapatinib+capecitabine arm compared to the T-DM1 arm in patients ≥ 65 years of age. However, only 64 patients were ≥ 65 years of age and as such the safety population is considered too small especially with regard to assessment of cardiotoxicity. The Applicant will provide a separate analysis of the safety in patients ≥ 65 years from the ongoing studies (see Pharmacovigilance development plan, and RMP).

Prior treatment with pertuzumab

The Applicant has conducted an analysis of the safety data for patients who have received prior treatment with pertuzumab (data not shown). The analysis did not show any concerning safety signals, and the safety profile was consistent with the safety profile of the total patient population in the T-DM1 arm. However, a higher incidence of infusion/hypersensitivity events has been reported (9.8% vs 3.9% overall). This information has been included in Section 4.4 of the SmPC. The Applicant will report back at regular intervals (e.g. together with the PSURs) on the safety of T-DM1 following previous exposure with trastuzumab and pertuzumab.

Medication error

In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not trastuzumab (see section 4.2 of the SmPC).

Six cases of medication error occurred in the clinical trials. Of these 4 were due to a confusion between trastuzumab emtansine and trastuzumab. The medication errors occurred with a product labeled for clinical trials, which had no tradename or specific distinguishing features to differentiate the two products. By making a distinct difference of vials and packages between Kadcyla and Herceptin, the risk of medication error is minimized. Furthermore, Kadcyla and Herceptin will only be prescribed by a physician and administered under the supervision of a healthcare professional who is experienced in the treatment of cancer patients which will further reduce the risk of medication error. Finally, the applicant shall ensure that in parallel to the launch of Kadcyla, all health care professionals who may prescribe, dispense or administer Kadcyla and/or Herceptin are provided with a health care professional (HCP) educational pack. This HCP educational pack shall consist of the Kadcyla SmPC and health care professional information regarding correct administration of Kadcyla and differentiation from Herceptin in order to prevent medication errors (see RMP and additional risk minimisation measures in Annex II of the Product Information as well as in the condition to the Marketing Authorisation in the Recommendations section below).

Non-validated HER2 testing

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) 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 (see SmPC section 4.2).

There is a risk for false-positive HER2 scores using non-validated tests before initiating trastuzumab emtansine treatment, and with this a potential lack of benefit due to the absence or insufficient expression of the target. Additionally, a false-negative HER2 score will take away the opportunity for treatment with trastuzumab emtansine. However, it is difficult to quantify these risks, either in terms of the number of patients being tested with non-validated tests or the accuracy of these tests. Use of a non-validated HER2 test has been included as a safety concern as missing information. Data from the ongoing MO28231 study will be used to quantify use of validated tests as additional pharmacovigilance measure (see RMP).

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects on the ability to drive and to use machines have been performed. 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 should be advised not to drive and use machines until symptoms abate (see SmPC section 4.7).

Assessment of paediatric data on clinical safety

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 in the indication of metastatic breast cancer.

2.2.2. Conclusions on the clinical safety

The safety profile of T-DM1 is considered acceptable in the proposed indication and compared favourably to the lapatinib+capecitabine regimen in the main clinical study.

The CHMP considers the following measures necessary to address issues related to safety:

- Submission of analysed data from the safety database for all cases in which patients have had previous exposure to trastuzumab and/or pertuzumab, is requested as part of the PSUR/PBRER at 6-monthly intervals for the first four years following marketing approval in the EU.

2.3. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.4. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.1, the PRAC considers by consensus that the risk management system for Trastuzumab emtansine (Kadcyla) in the treatment of metastatic breast cancer is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

  The applicant identified the following safety concerns in the RMP:

  Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	ILD/ARDS Hepatic Toxicity Nodular regenerative hyperplasia Infusion-related reaction Hypersensitivity Left ventricular dysfunction Thrombocytopenia Peripheral neuropathy Neutropenia Anaemia
Important potential risks	Fetal harm Decreased fertility Medication error
Missing information	Use in patients with hepatic impairment Use in patients with severe renal impairment Use in patients with LVEF <50% Use in elderly patients (≥ 75 years) Use in pregnant women Use in lactating women Use in male patients Clinical impact of anti-therapeutic antibodies Use of non-validated HER2 tests Confirmation of incidence of left ventricular dysfunction in patients with prior exposure to trastuzumab or pertuzumab.

- **Pharmacovigilance plans**

Ongoing and planned studies in the PhV 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
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	Primary • 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 Secondary • To evaluate the safety and feasibility of trastuzumab emtansine when given with concurrent radiotherapy • To evaluate the	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)
	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 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			

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)
	For patients receiving neoadjuvant treatment: (optional) • Correlation of trastuzumab emtansine efficacy (as measured by pathological response) with biomarkers in tumor tissue			

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)
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 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	Safety in Elderly Patients	Ongoing	• Study end May 2014 • Clinical study report November 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)
	(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			
TDM4788g/BO22589 (MARIANNE)	Primary Objectives: • Progression Free Survival (PFS): 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 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.	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Started	• Primary Analysis Q3 2014 • Primary Clinical Study Report (CSR) Q1 2015 • Study end April 2016 • Final report April 2017
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	Left Ventricular Dysfunction Safety in Elderly	Started	• Primary Analysis June 2013 • Primary CSR July 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)
	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.	Patients		• Final Analysis August 2015 • Final CSR August 2016
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
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	Started	• Study start April 2013 • Primary Analysis Q3 2018 • Primary CSR Q4 2018 • Final Analysis Q2 2023 • Final CSR Q3 2023
BO28407 (KAITLIN; planned)	EBC - Adjuvant	Left Ventricular	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)
	TBD	Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies		
BO28408 (KRISTINE; planned)	EBC – Neoadjuvant TBD	Left Ventricular Dysfunction Safety in Elderly Patients Anti-therapeutic antbodies	Planned	• TBD
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	PhV	any signal or changes in incidence /severity of AEs	Ongoing	• February 2014 and monthly updates

- **Risk minimisation measures**

  Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
ILD/ARDS	*Routine Labeling* SmPC Section 4.4, Special warnings and precautions for use; Pulmonary Toxicity An overview is provided of observed cases of interstitial lung disease, including pneumonitis, some leading to acute respiratory distress syndrome, among patients treated with trastuzumab emtansine, as well as a recommendation that treatment with trastuzumab emtansine should be discontinued in patients diagnosed with ILD or pneumonitis. It is noted that patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. SmPC Section 4.8, Undesirable effects A statement is provided that dyspnea and pneumonitis were among the most common serious ADRs.	None proposed
Hepatic toxicity	This risk is sufficiently described in labeling documents. *Routine Labeling* SmPC 4.2 Posology and method of administration; Posology; Dose modifications Recommendations are provided for temporary interruption, dose reduction, or treatment discontinuation for elevated AST/ALT or hyperbilirubinemia, of different degrees of intensity (Grade 2 – Grade 4). SmPC Section 4.4 Special warnings and precautions for use; Hepatotoxicity An overview of hepatotoxicity events observed in the clinical trial population is provided. Healthcare providers are advised that a patient's liver function should be monitored prior to initiation of treatment and prior to each dose of trastuzumab emtansine. They are advised that 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. A cross-reference is provided to Section 4.2. of the SmPC. SmPC Section 4.8 Undesirable effects A summary is provided of events of hepatotoxicity in	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	clinical trials.	
Nodular regenerative hyperplasia	This risk is sufficiently described in labeling documents. *Routine Labeling* <u>SmPC Section 4.4 Special warnings and precautions for use; Hepatotoxicity</u> An overview of NRH events is provided. Healthcare providers are advised that NRH should be considered in all patients with clinical symptoms of portal hypertension but with normal transaminase levels and no manifestations of cirrhosis; and that trastuzumab emtansine treatment must be discontinued upon diagnosis of NRH. <u>SmPC Section 4.8 Undesirable effects</u> A brief summary is provided of events of NRH and portal hypertension in clinical trials. Hepatotoxicity, Hepatic failure, Nodular regenerative hyperplasia, and Portal hypertension are labeled as uncommon adverse reactions.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Left ventricular dysfunction	This risk is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.2, Posology and method of administration; Posology; Dose modifications Recommendations are provided for temporary interruption or treatment discontinuation for different degrees of reduction of LVEF. SmPC Section 4.4, Special warnings and precautions for use; Left Ventricular Dysfunction An overview is provided of events of left ventricular dysfunction observed in clinical trials of trastuzumab emtansine, as well as of general risk factors for a cardiac event.. Healthcare providers are advised that standard cardiac function testing should be performed prior to initiation of treatment and at regular interval during treatment with trastuzumab emtansine. It is noted that all patients enrolled in the pivotal study for trastuzumab emtansine had LVEF ≥50% at baseline, and that 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. A cross-reference is provided to Section 4.2. SmPC Section 4.8, Undesirable effects A summary is provided of events of left ventricular dysfunction in clinical trials of trastuzumab emtansine.	None proposed
Infusion-related reaction	This risk is sufficiently described in labeling documents. *Routine Labeling* SmPC Section 4.2 Posology and method of administration; Posology Healthcare providers are advised to administer the initial dose as a 90 minute infusion. Guidelines are also provided for observation periods during and after infusions. Healthcare providers are advised to slow or interrupt the rate of trastuzumab emtansine infusion if the patient develops infusion related symptoms, and to discontinue trastuzumab emtansine for life-threatening infusion reactions. SmPC Section 4.4 Special warnings and precautions for use; Infusion-Related Reactions, Hypersensitivity	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Reactions An overview is provided of infusion related reactions that were observed in clinical trials of trastuzumab emtansine. Healthcare providers are advised that treatment may be required to be interrupted or discontinued in the event of a severe or life-threatening infusion related reaction. A cross-reference is provided to Section 4.2. Additionally, healthcare providers are advised that patients should be observed for hypersensitivity reactions, especially during the first infusion, and that medications and equipment to treat such reactions should be available for immediate use. SmPC Section 4.8 Undesirable effects A summary is provided of events of infusion related reactions in clinical trials, and guidelines are reported for interruption of treatment.	
Hypersensitivity	This risk is sufficiently described in labeling documents. *Routine Labeling* SmPC Section 4.2 Posology and method of administration; Posology Healthcare providers are advised to administer the initial dose as a 90 minute infusion. Guidelines are also provided for observation periods during and after infusions. Healthcare providers are advised to slow or interrupt the rate of trastuzumab emtansine infusion if the patient develops infusion related symptoms, and to discontinue trastuzumab emtansine for life-threatening infusion reactions. SmPC Section 4.3 Contraindications Hypersensitivity to the active substance and to its excipients is listed as a contraindication to treatment with trastuzumab emtansine. SmPC Section 4.4 Special warnings and precautions for use; Infusion-Related Reactions, Hypersensitivity Reactions Healthcare providers are advised that serious, allergic/anaphylactoid-like infusion reactions have been observed in clinical studies. It is noted that patients should be observed for hypersensitivity reactions, especially during the first infusion, and that medications and equipment to treat such reactions should be available for immediate use. SmPC Section 4.8 Undesirable effects A summary is provided of events of drug hypersensitivity in clinical trials. Drug hypersensivity is labeled as a common adverse drug reaction.	None proposed
Thrombocytopenia	This risk is sufficiently described in labeling documents.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Routine Labeling SmPC Section 4.2, Posology and method of administration; Dose modification. Recommendations are provided for temporary interruption, dose reduction, or treatment discontinuation for different degrees of intensity of thrombocytopenia (Grade 3 – Grade 4). SmPC Section 4.4, Special warnings and precautions for use; Thrombocytopenia Healthcare providers are advised that thrombocytopenia was commonly reported in clinical studies and that it was the most common adverse reaction leading to treatment discontinued. An overview is provided of bleeding events in clinical studies, including events with fatal outcome. Healthcare providers are advised that patients with thrombocytopenia or who are on anti-coagulant treatment should be monitored closely while on treatment with trastuzumab emtansine. It is noted also that trastuzumab emtansine has not been studied in patients with platelet counts that were $\leq 100{,}000/mm^3$ prior to treatment. It is recommended that platelet counts should be monitored prior to each dose of trastuzumab emtansine, and that in the event of decreased platelet count to Grade 3 or greater, trastuzumab emtansine should not be administered until platelet counts recover to Grade 1. A cross-reference is provided to Section 4.2. SmPC Section 4.8, Undesirable effects A summary is provided of events of thrombocytopenia in clinical trials. Haemorrhage and Thrombocytopenia are labeled as very common adverse reactions.	
Peripheral neuropathy	This risk is sufficiently described in labeling documents. *Routine Labeling* SPC Section 4.2, Posology and method of administration; Dose modification. Recommendations are provided for temporary interruption and dose reduction at retreatment for Grade 3 or Grade 4 peripheral neuropathy until improvement to Grade 2 or milder. SmPC Section 4.4, Special warnings and precautions for use, Neurotoxicity An overview is provided of events of neurotoxicity in clinical trials. Healthcare providers are advised that	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	trastuzumab emtansine should be temporarily discontinued in patients who experienced Grade 3 or Grade 4 peripheral neuropathy and until it improves to Grade 2 or resolves. It is noted that patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity. SPC Section 4.8, Undesirable effects A summary is provided of events of neurotoxicity in clinical trials. Peripheral neuropathy is labeled as a very common adverse reactions.	
Neutropenia	*Routine Labeling* SPC Section 4.8, Undesirable effects. Neutropenia is labeled as a common adverse reaction	None proposed.
Anaemia	SPC Section 4.8, Undesirable effects. Anaemia is labeled as a very common adverse reaction	None proposed.
Important potential risks		
Fetal harm	This risk is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.6, Fertility, pregnancy and lactation An overview is provided of fetal harm caused by trastuzumab in the post-marketing setting. It is noted that the DM1 component of trastuzumab emtansine is expected to be teratogenic and possibly embryotoxic. Healthcare professionals are advised that administration of trastuzumab emtansine to pregnant women is not recommended; that women who become pregnant must contact their physician, and that pregnant women should be advised of the possibility of harm to the fetus. It is additionally recommended that if a pregnant woman is treated with trastuzumab emtansine, close monitoring of the pregnancy should be performed by a multidisciplinary team. It is also recommended that female patients of childbearing potential be advised to use effective contraception during treatment with trastuzumab emtansine and for 6 months after treatment has concluded, and that male patients or their female partners should also use effective contraception. SmPC Section 5.3, Preclinical safety data; Impairment of fertility and teratogenicity Labeling states that dedicated fertility studies have not been conducted with trastuzumab emtansine, and that although developmental toxicity of trastuzumab was not predicted in the non-clinical program, it has been identified in the clinical setting. It is also noted that developmental toxicity of maytansine has been identified in non-clinical studies, suggesting that DM1 may be similarly teratogenic and potentially	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	embryotoxic.	
Decreased fertility	This risk is sufficiently described in labeling documents. *Routine Labeling* SmPC Section 4.6, Fertility, pregnancy and lactation. The SmPC states that no reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine SPC Section 5.3, Preclinical safety data; Impairment of fertility and teratogenicity Labeling states that dedicated fertility studies have not been conducted with trastuzumab emtansine, and that although developmental toxicity of trastuzumab was not predicted in the non-clinical program, it has been identified in the clinical setting. It is also noted that developmental toxicity of maytansine has been identified in non-clinical studies, suggesting that DM1 may be similarly teratogenic and potentially embryotoxic.	None proposed.
Medication error	This risk is sufficiently described in labeling documents and is addressed in routine packaging. *Routine Labeling* SPC Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use; and Section 6.6, Special precautions for disposal and other handling. These sections advise healthcare professionals to check vial labels to ensure that the correct medication is being administered in order to prevent medication errors.	Educational materials regarding medication errors: • Explanatory brochure Kadcyla SmPC
Missing information		
Use in patients with hepatic impairment	The status of present knowledge of safety in patients with hepatic impairment is sufficiently described in labeling documents. *Routine Labeling* SmPC 4.2 Posology and method of administration, Posology; Patients with hepatic impairment Labeling states that the safety and efficacy of trastuzumab emtansine have not been studied in patients with hepatic impairment. SmPC Section 5.2, Pharmacokinetic properties; Posology; Hepatic impairment Labeling states that no formal pharmacokinetic study has been conducted in patients with hepatic impairment.	None proposed
Use in patients with severe renal	The safety of patients with severe renal impairment is currently unknown. The status of present knowledge of	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
impairment	safety in patients with mild to moderate renal impairment is sufficiently described in labeling documents. *Routine Labeling* SmPC 4.2 Posology and method of administration, Patients with renal impairment Labeling states that no adjustment to the starting dose of trastuzumab emtansine is necessary in patients with mild to moderate renal impairment but that the potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data. Physicians are advised that patients with severe renal impairment should be monitored carefully. SmPC Section 5.2, Pharmacokinetic properties; Renal impairment Labeling states that creatinine clearance does not affect the pharmacokinetics of trastuzumab emtansine in patients with mild or moderate renal impairment, and that the pharmacokinetic data in patients with severe renal impairment are limited, and that therefore no dosage recommendations can be made.	
Use in patients with LVEF <50%	The status of present knowledge of safety in patients with LVEF under 50% is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.4, Special warnings and precautions for use Labeling states that treatment with trastuzumab emtansine has not been initiated in patients with LVEF <50% at baseline.	None proposed
Safety in elderly patients (≥ 75 years)	The status of present knowledge of safety in elderly patients is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.2, Posology and method of administration, Posology, Elderly patients Healthcare providers are advised that no dose adjustment is required in patients 65 years of age or older, and that there are insufficient data to establish the safety and efficacy in patients ≥ 75 years due to the limited data in this subgroup, and that age did not affect the PK of trastuzumab emtansine. SPC Section 5.1. Clinical efficacy. Labeling states that in patients ⩾ 65 years old the hazard ratios for progression-free survival and Overall Survival	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. SmPC Section 5.2, Pharmacokinetic properties, Elderly patients Labeling states that age did not affect the PK of trastuzumab emtansine.	
Use in pregnant women	The status of present knowledge of safety in pregnant women is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.6, Fertility, pregnancy and lactation An overview is provided of fetal harm caused by trastuzumab in the post-marketing setting. It is noted that the DM1 component of trastuzumab emtansine is expected to be teratogenic and possibly embryotoxic. Healthcare professionals are advised that administration of trastuzumab emtansine to pregnant women is not recommended; that women should be advised of the possibility of harm to the fetus before they become pregnant, and that women who become pregnant must contact their physician It is additionally recommended that if a pregnant woman is treated with trastuzumab emtansine, close monitoring of the pregnancy should be performed by a multidisciplinary team. It is also recommended that female patients of childbearing potential be advised to use effective contraception during treatment with trastuzumab emtansine and for 6 months after treatment has concluded, and that male patients or their female partners should also use effective contraception. SmPC Section 5.3, Preclinical safety data, Impairment of fertility and teratogenicity Labeling states that dedicated fertility studies have not been conducted with trastuzumab emtansine, and that although developmental toxicity of trastuzumab was not predicted in the non-clinical program, it has been identified in the clinical setting. It is also noted that developmental toxicity of maytansine has been identified in non-clinical studies, suggesting that DM1 may be similarly teratogenic and potentially embryotoxic.	None proposed
Use in lactating women	The status of present knowledge of safety in lactating women is sufficiently described in labeling documents *Routine Labeling* SmPC Section 4.6, Fertility, pregnancy and lactation	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Labeling states that it is not known whether trastuzumab emtansine is excreted in human milk; that women should discontinue nursing prior to initiating treatment with trastuzumab emtansine since many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from trastuzumab emtansine; and that women may begin nursing 6 months after concluding treatment.	
Use in male patients	The status of present knowledge of safety in male patients is sufficiently described in labeling documents *Routine Labeling* SmPC Section 5.2, Pharmacokinetic properties, Other special populations It is noted that most patients in clinical studies were females and that as a result the effect of gender on the pharmacokinetics of trastuzumab emtansine was not formally evaluated.	None proposed
Clinical impact of anti-therapeutic antibodies	The incidence of anti-therapeutic antibodies -positivity is relatively low, making it difficult to reach a firm conclusion about its impact. *Routine Labeling* SmPC Section 4.8 Undesirable effects Physicians are advised of the potential for an immune response to trastuzumab emtansine, and an overview is provided of anti-therapeutic antibody responses to trastuzumab emtansine in the clinical studies. It is stated that the presence of ATAs did not appear to have an impact on the PK, safety profile and treatment effectiveness of trastuzumab emtansine.	None proposed
Use of a non-validated HER2 test	SPC Section 4.2 Posology and method of administration Physicians are advised that patients treated with Kadcyla 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) 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.	None proposed
Confirmation of incidence of left ventricular dysfunction in patients with prior exposure to trastuzumab or pertuzumab	Inclusion in 6-monthly PBRER/PSURs of analysis of safety data from cases of patients who had previous exposure to trastuzumab and/or pertuzumab, for first four years following marketing approval in the EU.	None proposed

The CHMP endorsed this advice without changes.

2.5. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pivotal Phase III trial (TDM4370g/BO21977, EMILIA) of trastuzumab emtansine in metastatic breast cancer patients previously treated with a taxane and trastuzumab, and several supportive studies, showed that trastuzumab emtansine is associated with a statistically and clinically significant improvement in progression-free survival and overall survival compared to lapatinib plus capecitabine. There was a 35% reduction in the risk of PD or death (HR = 0.650, 95% CI: 0.549, 0.771, p<0.0001) and increased median PFS of 9.6 months vs. 6.4 months. The robustness of the PFS finding was confirmed by sensitivity analyses. For OS, the HR was 0.682 (95% CI: 0.548, 0.849, p=0.0006). The estimated median duration of survival was 25.1 months in patients treated with lapatinib plus capecitabine and 30.9 months in patients treated with trastuzumab emtansine.

There was a consistent improvement in secondary efficacy endpoints, including IRC-assessed ORR (43.3% vs. 30.8%, difference 12.7% [6.0%, 19.4%]; p = 0.0002), DOR (median 12.6 as compared to 6.5 months), and time to treatment failure (TTF; the time from randomization to discontinuation of treatment for any reason; median 7.9 months as compared to 5.8 months).

Response rates were also more durable (the DOR in the trastuzumab emtansine arm was almost double that in the lapatinib and capecitabine arm).

To date most studies in MBC have failed to demonstrate an appreciable difference in PRO between standard of care therapy and experimental agents. In contrast, treatment with trastuzumab emtansine appeared to confer a longer time to symptom progression (TSP), and hence a better quality of life, compared with lapatinib plus capecitabine. However, due to the open label character of the study, no conclusions can be drawn.

Uncertainty in the knowledge about the beneficial effects

Even though the clinical relevance of the pivotal OS results recently published is acknowledged, the results are based on an interim analysis that had a limited number of events and duration of follow-up. To ensure that early events have not biased the estimation, the applicant will submit an updated analysis (see Obligation to complete post-authorisation measures).

A consistent treatment benefit of trastuzumab emtansine was seen in the majority of pre-specified subgroups evaluated, supporting the robustness of the overall result. As regards as a possibly reduced benefit in the older subgroup of patients, the interpretation is difficult due to the low number of patients. The results of the subgroup analysis by age are reflected in section 5.1 of the SmPC.

Risks

Unfavourable effects

The size of the safety database and the exposure are considered adequate to allow assessment and characterization of the safety profile of T-DM1. Standard methods have been used for the detection and reporting of adverse events. As expected based on the well-characterised toxicities associated with the respective components of these regimens, the most common AEs (>20%) reported in the *T-DM1* group of the pivotal study were nausea (39.2%), fatigue (35.1%), thrombocytopenia (28.0%), headache (27.1%), diarrhea (23.3%), AST increased (22.4%), decreased appetite (20.6%) and epistaxis (20.2%). In comparison, the most common AEs in the *lapatinib+capecitabine* arm were diarrhea (79.7%), Palmar-Plantar Erythrodyseastesia (PPE) syndrome (58.0%), nausea (44.7%), vomiting (29.3%), rash (26.6%) and decreased appetite (23.2%).

The overall safety profile of T-DM1 is considered sufficiently characterised. No specific safety concerns are evident in older patients (≥65 years) treated with T-DM1, although the number of patients older than 75 years is very limited.

Uncertainty in the knowledge about the unfavourable effects

Hepatotoxicity, thrombocytopenia, and neuropathy are the most important recorded AEs, and those that more frequently led to T-DM1 dose reduction in the pivotal trial. Further investigation on T-DM1 induced hepatic toxicity and neuropathy is needed in order to envisage appropriate and effective risk minimisation procedures (see RMP). In addition, a number of AEs known to be associated with trastuzumab use, infusion-related (IRR) and hypersensitivity reactions, severe pulmonary events and cardiac dysfunction, are assumed to occur also with T-DM1 and need to be continuously monitored (see RMP).

A priority review of missing cases of suspected adverse drug reactions is ongoing in the context of the assessment of deficiencies in the applicant's safety reporting system. In light of the significant clinical benefit of Kadcyla it is considered acceptable to receive the data post-authorisation (see RMP).

Benefit-risk balance

Importance of favourable and unfavourable effects

Trastuzumab emtansine demonstrated statistically significant and clinically relevant efficacy both against lapatinib plus capecitabine in several MBC subpopulations in pre-treated patients (including heavily pre-treated patients with few alternatives). The gain in PFS and in OS over standard therapy is considered clinically relevant. On the basis of the magnitude of the benefit in PFS and OS, the favourable effects of T-DM1 in the treatment of MBC are considered

important. The evidence of efficacy is sufficiently robust. The safety profile of T-DM1 appears overall manageable.

Benefit-risk balance

The benefit-risk balance of trastuzumab emtansine is positive.

Discussion on the benefit-risk balance

Trastuzumab emtansine confers relevant clinical efficacy together with an acceptable and manageable toxicity across a range of clinical scenarios as regards previous line of treatment. The safety profile of T-DM1 compares favourably to that of available alternatives (lapatinib in combination with capecitabine) and appears sufficiently manageable, although some AEs need further clarifications and investigations and additional safety information in patients with prior exposure to trastuzumab and/or pertuzumab will be provided on an ongoing basis (see RMP). The beneficial effects are considered to outweigh the risks associated with T-DM1 therapy.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kadcyla in the following indication “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.” is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the content and format of the Kadcyla educational material and a communication plan with the National Competent Authority in the Member State before Kadcyla is launched in each Member State.

The MAH shall ensure that in parallel to the launch of Kadcyla, all health care professionals who may prescribe, dispense or administer Kadcyla and/or Herceptin are provided with a health care professional (HCP) educational pack. This HCP educational pack shall consist of the following:

- Kadcyla SPC
- Health care professional information

The HCP information shall contain the following key messages:

1. Kadcyla and Herceptin are two very different products with different active substances never to be used interchangeably. Kadcyla is NOT a generic version of Herceptin and has different properties, indications and dose.

2. Kadcyla is an antibody-drug conjugate containing humanized anti-HER2 IgG1 antibody trastuzumab and DM1, a microtubule-inhibitory maytansinoid.

3. Do not substitute or combine Kadcyla with or for Herceptin

4. Do not administer Kadcyla in combination with chemotherapy

5. Do not administer Kadcyla at doses greater than 3.6 mg/kg once every 3 weeks

6. If a prescription for Kadcyla is written electronically, it is important to ensure that the medication prescribed is trastuzumab emtansine and not trastuzumab.

7. Both the invented name Kadcyla and its full non-proprietary name (trastuzumab emtansine) should be used and confirmed when prescribing, preparing the infusion solution and administering Kadcyla to patients. It must be verified that the non-proprietary name is trastuzumab emtansine.

8. In order to prevent medication errors it is important to review the Summary of Product Characteristics and to check the outer carton and vial labels to ensure that the medicinal product being prepared and administered is Kadcyla and not Herceptin.

9. Description of the key differences between Kadcyla and Herceptin in relation to indication, dose, administration and packaging differences.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Submit the overall survival outcome data from the pivotal study (TDM4370g/BO21977/EMILIA) once available	30/11/2014
Submit the final study report from the MARIANNE study once available	30/04/2017
Submit the final study report from the TH3RESA study once available	31/08/2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that trastuzumab emtansine is qualified as a new active substance.

REFERENCES:

Cameron, D., M. Casey, et al. (2008). "A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses." Breast Cancer Res Treat 112(3): 533-543.

Ferlay, J., H. R. Shin, et al. (2010). "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008." Int J Cancer 127(12): 2893-2917.

Guarneri, V. and P. Conte (2009). "Metastatic breast cancer: therapeutic options according to molecular subtypes and prior adjuvant therapy." Oncologist 14(7): 645-656.

Howlader, N., A. Noone, et al. (2011). "SEER Cancer Statistics Review 1975-2008, National Cancer Institute, Bethesta, MD." SEER data submission, posted to the SEER web site.

Jemal, A., F. Bray, et al. (2011). "Global cancer statistics." CA Cancer J Clin 61(2): 69-90.

Marty, M., F. Cognetti, et al. (2005). "Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group." J Clin Oncol 23(19): 4265-4274.

Parkin, D. M., F. Bray, et al. (2001). "Estimating the world cancer burden: Globocan 2000." Int J Cancer 94(2): 153-156.

Sant, M., C. Allemani, et al. (2003). "Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe." Int J Cancer 106(3): 416-422.

Slamon, D. J., G. M. Clark, et al. (1987). "Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene." Science 235(4785): 177-182.

Slamon, D. J., B. Leyland-Jones, et al. (2001). "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2." N Engl J Med 344(11): 783-792.

Verma, S., D. Miles, et al. (2012). "Trastuzumab emtansine for HER2-positive advanced breast cancer." N Engl J Med 367(19): 1783-1791.