



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for trastuzumab emtansine

Proprietary Product Name: Kadcyla

Sponsor: Roche Products Pty Ltd

March 2014

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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Contents

List of abbreviations	4
I. Introduction to product submission	6
Submission details	6
Product background	6
Regulatory status	7
Product information	8
II. Quality findings	8
Drug substance (active ingredient)	8
Drug product	9
Biopharmaceutics	10
Quality summary and conclusions	10
III. Nonclinical findings	10
Introduction	10
Pharmacology	12
Pharmacokinetics	14
Toxicology	16
Nonclinical summary and conclusions	23
IV. Clinical findings	26
Introduction	26
Pharmacokinetics/pharmacodynamics	26
Efficacy	27
Safety	27
List of questions	27
Clinical summary and conclusions	27
V. Pharmacovigilance findings	28
Risk management plan	28
VI. Overall conclusion and risk/benefit assessment	37
Quality	37
Nonclinical	37
Clinical	37
Risk management plan	47
Risk-benefit analysis	48
Outcome	53
Attachment 1. Product Information	53

Attachment 2. Extract from the Clinical Evaluation Report _____ 54**List of abbreviations**

Abbreviation	Meaning
ADCC	antibody dependent cell mediated cytotoxicity
AE	adverse event
ALT	alanine transaminase
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity
C _{max}	peak plasma drug concentration
CHF	congestive heart failure
CMI	Consumer Medicine Information
EC ₅₀	half maximal effective concentration
ECD	extracellular domain
EMA	European Medicines Agency
FcγRIa	Fc gamma receptor Ia
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
HR	hazard ratio
IC ₅₀	half maximal inhibitory concentration
GLP	Good Laboratory Practice
KD	equilibrium binding constant
LABC	locally advanced breast cancer
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
NCE	normochromatic erythrocytes

Abbreviation	Meaning
NOAEL	No Observed Adverse Effect Level
NSCLC	non small cell lung cancer
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PCE	polychromatic erythrocytes
PFS	progression free survival
PI	Product Information
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	serious adverse event
SSP	strong stability preserving
$t_{1/2}$	elimination half life
T-DM1	trastuzumab emtansine
ULN	Upper Limit of Normal
V_d	apparent volume of distribution
V_{ss}	apparent volume of distribution at steady state
WFI	Water for Injection

I. Introduction to product submission

Submission details

<i>Type of submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 August 2013
<i>Active ingredient:</i>	Trastuzumab emtansine
<i>Product name:</i>	Kadcyla
<i>Sponsor's name and address:</i>	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2099
<i>Dose form:</i>	Powder for injection
<i>Strengths:</i>	100 mg and 160 mg
<i>Container:</i>	Vials
<i>Pack size:</i>	Single vial
<i>Approved therapeutic use:</i>	Kadcyla, as a single agent, is indicated for the treatment of patients with HER2 positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease or, • Developed disease recurrence during or within six months of completing adjuvant therapy.
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	3.6 mg trastuzumab emtansine/kg body weight administered as an intravenous infusion every 3 weeks
<i>ARTG numbers:</i>	201621 and 201622

Product background

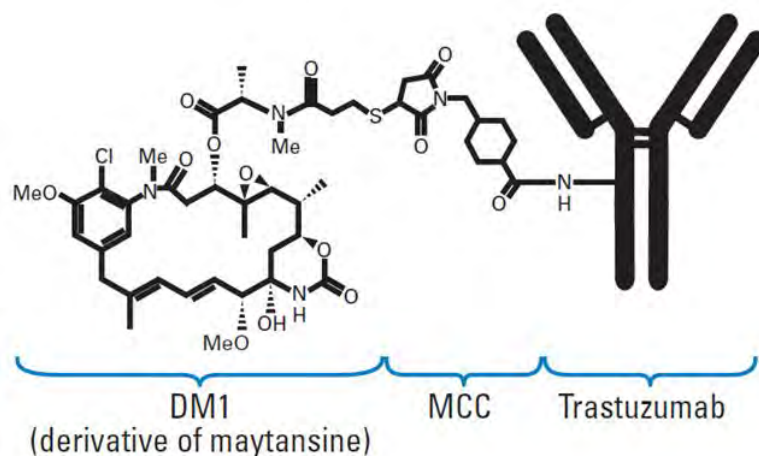
This AusPAR describes a submission by the sponsor, Roche Products Pty Ltd, to register a new chemical entity, trastuzumab emtansine (Kadcyla), for the following indication:

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

Trastuzumab emtansine (T-DM1) (Figure 1) is a novel antibody/drug conjugate containing trastuzumab (humanised anti HER2 IgG1) that is covalently linked via a

thioether linker (SMCC, designated MCC after conjugation)¹ to DM1, a microtubule polymerisation inhibitor. DM1 is a microtubule inhibitory maytansinoid.

Figure 1: Schematic of trastuzumab-DM1 (T-DM1), including the [N-maleimidomethyl]cyclohexane-1-carboxylate (MCC) linker.



Trastuzumab emtansine binds to HER2 and triggers the same anti tumour activity as trastuzumab including suppression of HER2 signalling pathways, HER2 extracellular domain (ECD) shedding, and mediation of antibody dependent cell mediated cytotoxicity. Trastuzumab emtansine is then internalised and degraded to DM1 containing cytotoxic components which cause inhibition of cell division and cell growth and eventually cell death.

No antibody/drug conjugates are registered in Australia. Trastuzumab emtansine was designated as an orphan drug in Australia on 2 May 2012. Trastuzumab (Herceptin) was registered in 2000 and currently has indications in localised breast cancer, locally advanced breast cancer/metastatic breast cancer (LABC/MBC), and advanced gastric cancer.

Regulatory status

Kadcyla has been approved for use in the US (by the US Food and Drug Administration [FDA]), Switzerland, Georgia and Kuwait (Table 1). In the European Union, Kadcyla was submitted for assessment to the European Medicines Agency (EMA) on 31 August 2011; the product was not approved as of 1 July 2013. At the time of this Australian assessment, submission to Canada and New Zealand was pending.

¹ The MCC linker is described as not biologically active.

Table 1: International regulatory approval status for Kadcyla (trastuzumab emtansine) at the time of submission.

Country	Approval Date	Approved Indication
US	22 February 2013	KADCYLA, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: - Received prior therapy for metastatic disease, or - Developed disease recurrence during or within six months of completing adjuvant therapy.
Switzerland	3 May 2013	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.
Georgia	21 June 2013	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.
Kuwait	22 May 2013	Indicated in the single-drug therapy of patients with HER-2 positive, inoperable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings**Drug substance (active ingredient)**

The structure of the drug substance is shown in Figure 1.

Trastuzumab, the active agent in Herceptin, is used as a raw material for the modification reaction and was not evaluated in this application. DM1 and SMCC raw materials are synthesised prior to antibody covalent linking. The manufacture of DM1 and SMCC was evaluated in conjunction with drug substance manufacture.

The antibody/drug conjugate constitutes the Drug Substance bulk, which contains 20 mg/mL trastuzumab emtansine in sodium succinate, sucrose, and polysorbate 20. Trastuzumab emtansine Drug Substance bulk is stored at a temperature of -15°C to -25°C or colder until shipment.

All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the modification and conjugation reactions.

Biological and immunochemical properties

Trastuzumab emtansine exhibits potent *in vitro* activity against a number of cultured cell lines that over express p185HER2. 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 different from that of unconjugated trastuzumab, the two molecules are similar with respect to a number of biological activities:

- Trastuzumab emtansine and unconjugated trastuzumab showed similar binding to recombinant HER2 extracellular domain, Fc gamma receptor (FcγR) Ia (FcγRIa), C1q binding, neonatal Fc receptor (FcRn) and comparable FcγRIII binding.
- Trastuzumab emtansine showed moderately increased (2 to 3 fold) binding to FcγRIIa, IIb, compared to unconjugated trastuzumab.
- Trastuzumab emtansine showed similar antibody dependent cell mediated cytotoxicity (ADCC) activity compared to unconjugated trastuzumab using a natural killer cell line.

Impurities

Product variants, process related impurities and potential impurities, such as conjugated DM1 impurities, free maytansinoids, high molecular weight species, organic volatiles/trace metals and those potentially derived from SMCC and DM1, were identified and quantitated.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance. The company has proposed a shelf life of 36 months at -20°C.

The evaluator recommends a shelf life of 24 months at -20°C for trastuzumab emtansine drug substance based on real time storage of commercial batches.

Drug product

Formulation

Trastuzumab emtansine is provided as a lyophilised powder, which after reconstitution with sterile Water for Injection (WFI) yields a solution containing 20 mg/mL trastuzumab emtansine, sodium succinate, sucrose, and polysorbate 20. The two configurations are dose proportional and differ only in the fill volumes.

Trastuzumab emtansine is supplied in a single use, 15 mL or 20 mL vial, sealed with a fluoro resin coated grey butyl rubber stopper. The rubber stopper is sealed with an aluminium seal and plastic flip off cap neither of which contact the Drug Product.

The drug product is reconstituted with 8.0 mL (160 mg/vial) or 5.0 mL (100 mg/vial) sterile WFI, the reconstituted trastuzumab emtansine drug product is then diluted into an intravenous bag for intravenous infusion. The trastuzumab emtansine Drug Product is compatible with polyvinyl chloride or polyolefin intravenous bags and intravenous infusion sets. Intravenous bags containing 0.45% saline may be used without an in line filter. When intravenous bags containing 0.9% saline are used, the use of 0.2 µm pore size rating in line filters is required.

Manufacture

The product is manufactured by thawing the drug substance and filling into either 15 mL or 20 mL vials. Filled vials are then lyophilised, sealed then packaged. The thawed drug substance is sterilised by sterile filtration prior to filling and lyophilisation.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is photostable.

The company has proposed a shelf life of 3 years when stored at 2-8°C based on real time storage of a single Phase III batch and stressed storage.

The evaluator recommends a shelf life of 24 months at 2-8°C be applied equally to the 100 mg and 160 mg Drug Product presentations based on real time storage of commercial batches.

In use stability data was also submitted. The proposed shelf life and storage conditions for the reconstituted/diluted product are 24 h/days when stored at 2-8°C.

Biopharmaceutics

This product is an IV monoclonal antibody and Biopharmaceutic data are not required.

Quality summary and conclusions

Summary

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The issue of free maytasinoid levels during storage was raised by the Pharmaceutical Subcommittee (PSC) who supported the recommendation of the reduced shelf life for both the drug substance and drug product. The recommendations for the reduced shelf life storage were based upon the initial stability data submitted for evaluation. However, the company submitted further stability data outside the strong stability preserving (SSP) requirements. If registered, it is recommended that the company submit a Category 3 to extend the shelf life.

Free maytansinoid levels are controlled through release and shelf life specifications and the company complied with requests to tighten both the drug product and drug substance specifications during the evaluation process. In this evaluation, free maytansinoids levels are approached from a manufacturing aspect and do not consider their toxicological aspects. The level of the toxicity of the free maytansinoids in the drug product is best assessed in the clinical studies.

Conclusion

The evaluator recommends Kadcyła 100 mg powder for injection vial and Kadcyła 160 mg powder for injection vial should be approved.

III. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, trastuzumab emtansine (Kadcyla), as a single agent, for the treatment of patients with HER2 positive, unresectable locally advanced or metastatic (Stage IV) breast cancer who have received prior treatment

with trastuzumab and a taxane. The proposed treatment regimen is 3.6 mg/kg, administered as an intravenous infusion every 3 weeks.

Trastuzumab (Herceptin) alone is currently approved for the treatment of HER2 overexpressing breast cancer and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Initial recommended loading doses range from 4-8 mg/kg as an intravenous infusion, with subsequent 3 weekly intravenous infusions of 2-6 mg/kg.

Trastuzumab emtansine is a HER2 targeted monoclonal antibody/drug conjugate containing the humanised anti HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor, DM1 (a maytansinoid). The trastuzumab component of trastuzumab emtansine is a humanised monoclonal antibody (IgG1 isotype) directed against the ECD of HER2. The DM1 component of trastuzumab emtansine is an inhibitor of tubulin polymerisation which binds to the beta subunit of tubulin at the same binding site as the vinca alkaloids. This new antibody/drug conjugate is intended to combine the targeted therapy actions of trastuzumab with the cytotoxic action of DM1 to HER2 positive breast cancer cells.

Overall quality of the nonclinical dossier

The submitted nonclinical data were in general accordance with International Conference on Harmonisation (ICH) guidelines on the nonclinical evaluation of biotechnology products² and anticancer drugs.³ The nonclinical testing strategy examined primary and safety pharmacology (limited to cardiovascular and blood systems) *in vitro* and *in vivo*, acute and repeat dose toxicity, genotoxicity and tissue cross reactivity of trastuzumab emtansine and/or DM1. Bridging toxicology studies were also performed with a related test material. Standard carcinogenicity studies were not performed and this is acceptable for a therapeutic product intended to treat patients with advanced cancer.⁴ Reproductive toxicology studies were also not performed for trastuzumab emtansine, which is acceptable taking into account the indication and intended population,⁵ known reproductive hazards of DM1 and prior reproductive toxicity assessment of trastuzumab. No dedicated local tolerance studies were performed but intravenous infusion sites were examined histologically in pivotal acute and repeat dose toxicity studies for local reactions. Antibody responses were also determined in some pivotal acute and repeat dose toxicity studies to assess potential immunogenicity. Overall, the nonclinical submission is considered sufficient to characterise the pharmacological and toxicological profile of trastuzumab emtansine.

² European Medicines Agency, "Committee for medicinal products for human use (CHMP): ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals, Step 5 (EMA/CHMP/ICH/731268/1998)", June 2011, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002828.pdf>.

³ European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

⁴ European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

⁵ European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

Pharmacology

Primary pharmacology

The primary pharmacologic target for trastuzumab emtansine (trastuzumab-(S)MCC-DM1) is the HER2 receptor (for trastuzumab) and microtubules (for DM1).

In vitro binding studies with trastuzumab emtansine demonstrated that trastuzumab emtansine binds to the ECD of HER2 (HER2-ECD), to both high and low affinity Fcγ receptors, and to complement C1q. Trastuzumab emtansine and trastuzumab were shown to bind to HER2-ECD with similar affinity (EC₅₀ values of 170 pM and 155 pM, respectively). The average equilibrium binding constant (KD) for the binding of trastuzumab emtansine and trastuzumab to HER2 was also comparable (1.08 and 1.01 nM, respectively). The KD and EC₅₀ were well below the plasma concentration of trastuzumab emtansine (~85 µg/mL or ~537 nM) in patients at the proposed clinical dose regimen. Binding of trastuzumab emtansine to the high affinity Fcγ cell surface receptor RIa (EC₅₀ = 5.8 ng/mL; 0.039 nM) was also comparable with that observed for trastuzumab (EC₅₀ = 5.6 ng/mL; 0.038 nM). Binding of trastuzumab emtansine to low affinity Fcγ RII and RIII receptors was in the µg/mL range and around 3 fold greater than that of trastuzumab (RIIa 5.4 cf 19.2 nM; RIIIa 2.0 cf 8.2 nM). Binding to the complement component C1q was also similar for both trastuzumab emtansine and trastuzumab, and of relatively low affinity (EC₅₀ = 1.4 µg/mL and 1.2 µg/mL, respectively).

Anti proliferative and anti tumour effects of trastuzumab emtansine were demonstrated in cancer cell lines *in vitro*. Trastuzumab emtansine caused cytotoxicity, decreased cellular proliferation, and activation of caspase 3 and 7 (demonstrating induction of apoptosis) in human tumour cell lines of breast cancer, ovarian, gastric or non small cell lung cancer [NSCLC] expressing varying amounts of HER2 *in vitro*. These changes were not observed with trastuzumab, which inhibits cellular proliferation, but is not directly cytotoxic. Cytotoxicity of trastuzumab emtansine increased with dose in cells expressing high levels of HER2. Trastuzumab emtansine was cytotoxic in both trastuzumab sensitive and resistant cell lines. The half maximal inhibitory concentration (IC₅₀) against cell proliferation of breast cancer cell lines expressing HER2 were in the range of 5-150 ng/mL. The antiproliferative activity of trastuzumab emtansine was considerably greater than that of unconjugated DM1 (IC₅₀ against BT-474 cells, a HER2 positive breast cancer cell line: 1.6 nM DM1 in trastuzumab emtansine compared to 33.5 nM unconjugated DM1). The addition of the MCC linker to DM1 decreased the cytotoxicity of DM1 (IC₅₀ 114 nM for MCC-DM1 compared to 32 nM DM1 against the BT-474 cell line; ~50 nM for MCC-DM1 compared to ~5 for DM1 against the SK-BR3 cells).

In flow cytometry experiments with HER2 positive breast cancer cells, trastuzumab or low dose trastuzumab emtansine showed little effects on cell division, while cell cycle arrest with DM1 or high dose trastuzumab emtansine was predominantly at the G2/M phase. Similar cell cycle arrests were observed with 20 nM DM1 or 300 ng/mL (7.7 nM DM1 equivalent) trastuzumab emtansine. These findings demonstrated the mechanisms of action of the cytotoxic component, DM1 and increased cytotoxicity of the trastuzumab DM1 conjugate in HER2+ cancer cells.

Binding of both trastuzumab emtansine and trastuzumab to HER2 positive breast cancer BT-474-M1 cell line was also shown to cause a rapid dose dependent but incomplete decrease in phosphorylation of AKT. The response of other cellular biomarkers (XIAP, pH3, and PARP) suggested that both DM1 and trastuzumab emtansine induced apoptosis.

Binding of trastuzumab or trastuzumab emtansine was also shown to diminish the extent of shedding of the extracellular domain of HER2 from the cell surface *in vitro*. Maximal inhibition of HER2-ECD shedding was 42% with trastuzumab exposure and 43% with trastuzumab emtansine exposure. The IC₅₀ values for the antibodies were 0.30 µg/mL (~2

nM) and 0.18 µg/mL (~1.2 nM), respectively. The relevance of this inhibition to the mechanism of action of trastuzumab emtansine is unclear.

Anti tumour activity of trastuzumab emtansine was also demonstrated in mouse models (BT-474 EEI, MMTV-HER2 F05, MCF7-neo/HER2 and KPL-4) of HER2 positive breast cancers *in vivo*. Trastuzumab emtansine inhibited tumour growth in all of these models following an intravenous bolus dose in the range of 10 to 30 mg/kg when administered once every 3 weeks for a total of three doses (similar to the proposed clinical treatment regimen). In the BT-474 EI breast cancer model, significant inhibition of tumour growth was seen at 10 mg/kg, with 10% and 60% of the animals showing complete responses at 10 and 15 mg/kg, respectively. Trastuzumab alone showed minimal or no tumour growth inhibition at 15 mg/kg. Similar tumour growth inhibition was demonstrated with 9 doses at 10 mg/kg weekly or 5 doses at 9 or 18 mg/kg every 2 weeks.

In the MMTV-HER2 F05 model (resistant to trastuzumab), significant tumour growth inhibition was observed at trastuzumab emtansine doses of 10-30 mg/kg every 3 weeks. Similar or greater anti tumour effects were observed with 9 weekly doses at 5 or 10 mg/kg. No anti tumour activity was observed in studies with trastuzumab emtansine against a HER2 negative tumour (MMTV WNT cell line) or a control antibody drug conjugate against F05 tumours.

In other HER2 expressing breast cancer models, trastuzumab emtansine suppressed growth of KPL-4 and MCF7-neo/HER2 by a single intravenous injection of 3-15 mg/kg. The time to tumour doubling of KPL-4 implants was significantly prolonged (75.4 days at 3 mg/kg compared to 10.4 days in the vehicle treated control group) in one study. In another study with KPL-4, complete regression was observed for the study period of 126 days after a single dose of 15 mg/kg trastuzumab emtansine. In the MCF7-neo/HER2 tumour model, trastuzumab emtansine at 3 or 10 mg/kg prolonged tumour doubling time to 20.8 and 37.6 days, respectively, compared to the vehicle control of 8.1 days, but the single dose treatment resulted in no complete tumour regression.

The dose regimen of 10 mg/kg every 3 weeks in the animal models of human breast cancer resulted in trastuzumab emtansine peak plasma drug concentration (C_{max}) of ~170 µg/mL and an area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of 500 µg.day/mL, linearly extrapolated from the pharmacokinetic study in athymic mice at 3 and 15 mg/kg (Study 05-0278-1459). The C_{max} in mice at the effective dose of 10 mg/kg was higher than the clinical value (85 µg/mL) at the recommended clinical dose of 3.6 mg/kg, but the AUC was similar to the clinical AUC (475 µg.day/mL).

Overall, these studies demonstrated anti proliferative and anti tumour activities of trastuzumab emtansine *in vitro* and *in vivo*, mediated by trastuzumab's action at the HER2 positive cancer cell site and accompanied release of cytotoxic DM1.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacology studies were performed. In a published study cited by the sponsor,⁶ cell proliferation of normal human mammary epithelial cells and normal human epidermal keratinocytes was decreased only at high concentrations of trastuzumab emtansine (2-10 µg/mL). Based on the mechanism of action, DM1 is expected to target all rapidly dividing cells. Limited Good Laboratory Practice (GLP) compliant safety pharmacology studies assessed potential cardiovascular effects of DM1 *in vitro* and trastuzumab emtansine *in vivo* and potential blood effects of trastuzumab emtansine and DM1 *in vitro*.

⁶ Lewis Phillips GD, et al. (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res.* 68: 9280-9290.

DM1 inhibited hERG channel current by only 2.5% at the highest concentration tested (29.5 μ M). Thus, based on an IC_{50} of >29.5 μ M, average plasma DM1 concentrations detected in trastuzumab emtansine treated patients (6 ng/mL), and 93% plasma protein binding (Study 05-1047-1459), a large safety margin is anticipated for DM1 effects on the hERG channel current. Single intravenous doses of up to 30 mg/kg trastuzumab emtansine to female monkeys caused slight increases in blood pressure (systolic, diastolic, mean arterial and pulse pressure; peak increase of 16-28%) from Days 1-5 onwards. While these effects persisted throughout the study, the effects were generally mild and not observed at a lower dose (10 mg/kg), which was associated with plasma values (trastuzumab emtansine C_{max} ~260 μ g/mL and DM1 C_{max} ~20 ng/mL, based on single dose pharmacokinetic studies) 3-4 times those anticipated clinically (trastuzumab emtansine C_{max} = 85 μ g/mL, DM1 C_{max} 5.1 ng/mL).

Trastuzumab emtansine did not display any haemolytic activity in monkey or human whole blood and was compatible with monkey or human serum or plasma *in vitro* at concentrations (1.25-5 mg/mL) well above those anticipated clinically. While no direct effects of trastuzumab emtansine or DM1 on platelet function were observed, impaired megakaryocyte and platelet production were seen at clinically relevant trastuzumab emtansine concentrations (25 μ g/mL). These results suggest that potentially observed thrombocytopenia effects in toxicity studies may be a consequence of impaired platelet production from megakaryocytes in the bone marrow.

No dedicated safety pharmacology studies were performed examining potential CNS, renal or gastrointestinal effects of trastuzumab emtansine or DM1. However, potential toxicity in these organs, were assessed, to some degree, in the acute and repeat dose toxicity studies. There was no remarkable evidence of CNS or gastrointestinal toxicity, however there was evidence of minor renal effects at potential therapeutic doses in rats and axonal degeneration of peripheral nerve and spinal cord in monkeys (refer to 'Toxicity' section).

Pharmacokinetics

Pharmacokinetic studies with trastuzumab emtansine were performed in mice, rats, and cynomolgus monkeys. Studies conducted in non tumour bearing mice and rats aimed to assess the HER2 independent pharmacokinetics of trastuzumab emtansine. In contrast, the cynomolgus monkey was deemed the most appropriate species for assessing HER2 dependent pharmacokinetics in single and repeat dose studies. Toxicokinetic parameters of trastuzumab emtansine, total trastuzumab (conjugated and unconjugated trastuzumab) and DM1 were evaluated in pivotal rats and monkey toxicity studies. However, results for trastuzumab emtansine and DM1 are the primary focus of this evaluation.

The pharmacokinetics of trastuzumab emtansine across all three nonclinical species were broadly consistent with those in humans at the proposed dose regimen (3.6 mg/kg intravenous every 3 weeks) and other monoclonal antibodies, as characterised by a relatively long terminal half life (3 to 7 days; 4 days in humans), a slow clearance (10-20 mL/day/kg; 7-13 mL/day/kg in humans), and volume of distribution approximating the plasma volume (initial apparent volume of distribution [V_d] around 30-70 mL/kg and apparent volume of distribution at steady state [V_{ss}] 50-150 mL/kg for all species). Exposure increased with dose, no gender differences were apparent in any species, and evidence of only slight accumulation with repeated dosing was observed in monkeys at high doses and humans at the proposed treatment regimen. Antibody responses to trastuzumab emtansine in some monkeys repeatedly dosed had no remarkable effect on trastuzumab emtansine pharmacokinetics.

Pharmacokinetic assessment of DM1 demonstrated maximum plasma DM1 levels immediately following dosing, which gradually decreased over time. DM1 levels were consistently low across studies in all species, including humans. Maximum observed DM1

concentrations at the maximally tolerated single intravenous trastuzumab emtansine dose of 20 mg/kg in rats and 30 mg/kg in monkeys approximated 40-70 ng/mL. Repeated intravenous doses (every 3 weeks) of up to 10 mg/kg in monkeys (8 cycles) and 3.6 mg/kg in humans (4 cycles) resulted in C_{max} values averaging 12 and 5 ng/mL, respectively.

The degradation pathways of trastuzumab emtansine are primarily non specific (that is, lysosomal degradation/proteolytic cleavage)⁷ and are not expected to differ between nonclinical species and humans in the linear pharmacokinetic range. Thus, the sponsor considered the rat an appropriate species to characterise the distribution and elimination of trastuzumab emtansine. Tissue distribution studies in rats demonstrated that conjugation of trastuzumab does not alter its distribution, while conjugation of DM1 limited its distribution to highly perfused organs, similar to that of other monoclonal antibodies. In contrast, free DM1 was rapidly and extensively distributed to many tissues.

DM1 was shown to be highly bound to rat (97.1%), monkey (91.5%), and human plasma proteins (92.5%), with a similar amount of free (7.5-8.5%) DM1 observed in the pivotal nonclinical species used for toxicity testing (monkeys) and humans.

Following administration of [3H]-trastuzumab emtansine to rats, the main circulating plasma analyte was, as expected, trastuzumab emtansine, with the majority of DM1 (>95%) conjugated to trastuzumab and a small fraction present as low molecular weight DM1 containing catabolites. DM1 containing catabolic products identified in plasma, urine, and bile following trastuzumab emtansine administration to rats were Lys-MCC-DM1, MCC-DM1, and low molecular mass DM1 adducts. The molar concentrations of these catabolites in plasma were <10% of trastuzumab emtansine at all sampling times. These catabolites were also reported in patient plasma following trastuzumab emtansine administration. The primary route of elimination of these DM1 related catabolites was bile/faeces, with ~80% of dosed radioactivity eliminated over 14 days. Urinary excretion was minor (<5% of dosed radioactivity).

Following administration of [3H]-DM1 to rats, radioactivity was rapidly cleared from blood and quickly distributed to various highly perfused tissues without accumulation. DM1 was extensively metabolised with unchanged DM1 constituting less than 2% of the total radioactivity in bile; however, no single metabolite made up more than 10% of the excreted radioactivity. The metabolism of DM1 was not studied in humans *in vivo*. *In vitro* assays in human liver microsomes showed DM1 is mainly metabolised by CYP450 3A4 and, to a lesser extent 3A5. Three metabolites that were found in rats were monitored and detected in the *in vitro* assays with human microsomes and in rat microsomes, and they were M2 (sulfonation metabolite), M3 (sulfonation metabolite) and M7 (hydrolytic metabolite). Additional metabolites were also formed in rats. Approximately 100% of the administered radioactivity was eliminated in faeces over 5 days, primarily by biliary excretion. There were no data on the metabolism of DM1 in monkeys, which is the species used in the repeat dose toxicity studies.

MCC-DM1 and Lys-MCC-DM1 were also rapidly cleared in rats, with a large volume of distribution, approximating total body water. The elimination half life ($t_{1/2}$) was < 10 min for both molecules. The conversion from MCC-DM1 or Lys-MCC-DM1 to DM1 or from Lys-MCC-DM1 to MCC-DM1 was low (2%), suggesting that most MCC-DM1 or Lys-MCC-DM1 is either eliminated as an intact molecule or converted into a metabolite other than DM1.

Overall, these studies suggest that conjugation of trastuzumab does not markedly alter its pharmacokinetic profile and that the pivotal monkey species chosen for toxicity testing is an appropriate nonclinical model for humans in terms of the trastuzumab component. The lack of metabolism studies on DM1 in monkeys and humans is a deficiency of the data

⁷ Erickson HK, et al. (2006) Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. *Cancer Res.* 66: 4426-4433.

package. However, similar toxicity findings in rats, monkeys and in clinical trials suggest that the rats and monkeys are appropriate animal models for DM1.

Pharmacokinetic drug interactions

DM1 was shown to be a substrate of P-glycoprotein (P-gp), but did not inhibit P-gp activity at concentrations (0.5 μ M or 369 ng/mL) well above those anticipated clinically (5.1 ng/mL). Potential drug interactions via other transporters (for example, BCRP and MRP2, which are biliary transporters in addition to P-gp) were not studied. Since DM1 and metabolites are excreted mainly in the bile, P-gp inhibitors may decrease the elimination and excretion of DM1 and its metabolites. In addition, drug resistance may develop as a result of increased P-gp expression in cancer cells, which have been observed for other anti-tubulin drugs, such as taxanes, after repeated administration.

DM1 was metabolised by CYP450 enzymes CYP3A4 and to a lesser extent, CYP3A5, *in vitro*. However, DM1 does not induce or inhibit cytochrome P450 mediated metabolism at the highest concentration tested (600 ng/mL) *in vitro*. Plasma DM1 concentrations may be affected by CYP3A4/5 inhibitors or inducers.

Toxicology

The toxicology program for trastuzumab emtansine and/or free DM1 (its cytotoxic component) examined acute toxicity in rats and monkeys, repeat dose toxicity in monkeys (up to 5 months or 8 cycles; a 2 week study was performed in rats), genotoxicity *in vitro* and/or *in vivo* and tissue cross reactivity. Bridging acute toxicology studies were also performed with a related test material in rats and monkeys.

Pivotal studies complied with GLP, with trastuzumab emtansine or DM1 administered once in acute studies or once every 3 weeks by intravenous infusion in repeat dose studies (monkeys), consistent with the proposed clinical route of administration and dosing regimen. Treatment free periods were included in the pivotal studies to assess the reversibility of any toxicity findings. Monkeys were considered an appropriate species for evaluating both antigen dependent and independent toxicity of trastuzumab emtansine since trastuzumab binds the human and cynomolgus monkey HER2 and erbB2, respectively, with similar affinity but does not cross react with the corresponding rodent receptor neu.⁸ In contrast, the rat was utilised as a second species for assessment of antigen independent toxicity related to non specific (endocytotic) uptake of the antibody drug conjugate or exposure of organ systems to degradation products (including DM1). Both species also demonstrated qualitatively similar pharmacokinetic and disposition profiles of trastuzumab emtansine, although the metabolism of DM1 in monkeys has not been studied. Group sizes in pivotal studies were adequate. Dose levels employed were adequate to identify target organs of toxicity and were limited by dose limiting toxicity and/or maximum feasible dose limitations. Exposures (C_{max} and/or AUC) achieved in the toxicity studies exceeded the expected clinical exposure (see Table 2).

The overall quality and design of studies was adequate to assess the toxicological profile of trastuzumab emtansine and consistent with requirements for a therapeutic product intended to treat patients with advanced cancer.⁹

⁸ Fendly BM, et al. (1990) Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. *Cancer Res.* 50: 1550-1558.

⁹ European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

Relative exposure

Exposure ratios were calculated for trastuzumab emtansine based on animal:human plasma $AUC_{0-\infty/t}$ and C_{max} values (Table 2). Given the absence of sex related differences in these parameters, values were averaged for both genders. Similarly, exposure ratios were determined for its cytotoxic component, DM1, based on animal:human plasma C_{max} , but not AUC due to the low plasma values obtained in both species and in humans (Table 3). Human reference values were obtained from clinical study TDM4370g/BO21977 in which patients were given 3.6 mg/kg intravenous trastuzumab emtansine every 3 weeks (for up to 4 doses), as proposed clinically. Protein binding for free DM1 was high in all species, with slightly greater binding in rats (~97%) than in monkeys and humans (92% in both species). Thus, while no corrections to account for protein binding were applied to exposure ratio calculations, it is noted that the exposure ratios for DM1 in rats compared to humans might actually be 2-3-fold less than predicted on this basis. Overall, rats and monkeys in toxicity studies were exposed to trastuzumab emtansine and DM1 levels above those anticipated therapeutically.

Table 2: Relative exposure to trastuzumab emtansine in pivotal acute and repeat dose toxicity studies.

Species	Study duration	IV Dose (mg/kg)	C_{max} (μ g/mL)	AUC* (ng·h/mL)	A:H Exposure ratio C_{max}	A:H Exposure ratio AUC
Rat (SD)	Single dose	6	165	431	1.9	0.9
		20	461	1425	5.4	3.0
		60#	1600	-.#	19	-
Monkey (Cynomolgus)	Single dose	3	82	199	1.0	0.4
		10	259	881	3.0	1.9
		30	748	2930	8.8	6.2
	4 doses (3 weeks apart)	3	77	192	0.9	0.4
		10	266	901	3.1	1.9
		30	782	3025	9.2	6.4
	8 doses (3 weeks apart)	1	28	40	0.3	0.1
		3	90	213	1.1	0.4
		10	257	973	3.0	2.0
Human [®] (patients)	4 doses (3 weeks apart)	3.6	85	475	-	-

Clinical Study TDM4370g/BO21977

* AUC = area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) or last measurable concentration or time of last observation (AUC_{all} or AUC_{0-t}); A:H = animal:human

Due to the deaths in the 60 mg/kg group at 3-4 days post-dose, only limited exposure parameters (AUC_{0-3d}) could be determined.

Table 3: Relative exposure to DM1 in pivotal acute and repeat dose toxicity studies.

Species	Study duration	IV Dose (mg/kg)	Equivalent DM1 dose† (µg/kg)	C _{max} (ng/mL)	A:H Exposure ratio
Rat (SD)	Single dose	6	102	10.7	2.1
		20	340	51.8	10
		60	1020	139	27
	Single dose (DM1 administered not TMD)	0.05[0.07*]	70	8.4	1.6
		0.1	100	12.7	2.5
		0.2	200	23.3	4.6
Monkey (Cynomolgus)	Single dose	3	51	7.3	1.4
		10	170	23.0	4.5
		30	510	63.3	12
	4 doses (3 weeks apart)	3	51	7.3	1.4
		10	170	23.7	4.6
		30	510	72.2	14
	8 doses (3 weeks apart)	1	18	1.9	0.4
		3	58	3.5	0.7
		10	193	11.2	2.2
Human ^ø (patients)	4 doses (3 weeks apart)	3.6	61	5.1	–

ø Clinical Study TDM4370g/BO21977

TMD = trastuzumab emtansine

* determined analytically; A:H = animal:human

† DM1 doses calculated by the sponsor and documented in the study reports

Acute toxicity

The acute toxicity of trastuzumab emtansine was examined in rats and monkeys given single intravenous doses up to 60 mg/kg and 30 mg/kg, respectively (equivalent to 6120 µg/m² DM1 for both species) and in rats given single free DM1 intravenous doses up to 1 mg/kg (equivalent to 6000 µg/m² DM1) in the pivotal studies.

In rats, 60 mg/kg intravenous trastuzumab emtansine doses (6120 µg/m² DM1) were lethal, with all animals either dying or sacrificed moribund at this dose. A single male death was observed at 20 mg/kg in the pivotal study; however, no deaths were observed at doses up to 50 mg/kg in non pivotal studies in females. Single doses of free DM1 to rats ≥0.4 mg/kg (≥2400 µg/m² DM1) were also lethal with all animals either dying or sacrificed moribund at this dose. In monkeys, there were no deaths or overt toxicity observed at the highest trastuzumab emtansine dose administered (30 mg/kg intravenous; equivalent to the 6120 µg/m² DM1 dose from 60 mg/kg trastuzumab emtansine given to rats).

In rats, clinical signs (generally limited to lethal doses), body weight loss and/or decreased food consumption, increased neutrophil counts, decreased lymphocyte counts, decreased platelet counts, increased liver enzymes, and target organs of toxicity including the liver, kidney, spleen, thymus, testis, epididymis, ovary, mammary gland and bone marrow were identified at trastuzumab emtansine doses ranging from 6-60 mg/kg. Similar findings were observed in rats given DM1 doses ranging from 0.1-1.0 mg/kg. In monkeys, similar effects on body weight gain, white blood cell parameters, platelet counts and hepatotoxic effects were observed at doses from 10-30 mg/kg intravenous trastuzumab emtansine as well as mild reductions in red blood cell parameters and increases in fibrinogen counts. In both species, there were also increased mitoses observed in multiple organs generally at all dose levels examined. All findings were resolved following the 3 week recovery period and were generally dose dependent in incidence and severity.

Overall, the acute toxicity of trastuzumab emtansine was moderate, with conjugation of DM1 in the antibody drug complex associated with greater than a 2 fold increase in tolerance in rats (based on body surface area dose of DM1). Moreover, rats appeared to be more sensitive to the toxicological effects of trastuzumab emtansine than monkeys. This may be due to differences in exposure (particularly C_{max} ; refer to 'Relative exposure') and/or the impact of antigen binding. Maximum tolerated single intravenous doses of trastuzumab emtansine of 20 mg/kg and 30 mg/kg in rats and monkeys, respectively were associated with trastuzumab emtansine exposure levels 3 and 6 times those anticipated clinically (based on AUC), respectively, and with free DM1 exposures 10 and 12 times that in patients (based on C_{max}).

Repeat dose toxicity

The toxicity of repeated intravenous doses of trastuzumab emtansine was examined in rats dosed weekly for 2 weeks in a single exploratory study and in several studies in monkeys dosed 3 weekly (as proposed clinically) for up to 5 months. Trastuzumab emtansine was given to rats at doses up to 52 mg/kg (3579 $\mu\text{g}/\text{m}^2$ DM1) and to monkeys at doses up to 30 mg/kg (approximately 6120 μg DM1/ m^2).

Rats

In the 2 week female rat study, a weekly intravenous dose of 52 mg/kg trastuzumab emtansine resulted in deaths or moribund sacrifice for all animals at this dose. Repeat dosing did not appear to markedly alter its toxicity profile, with reductions in body weight, increased white blood cell and neutrophil counts, decreased platelet counts, increased liver enzymes, and target organ effects in the liver (extramedullary haematopoiesis, increased mitoses, hepatocytes with reactive features), spleen (extramedullary haematopoiesis), thymus (atrophy) and bone marrow (sternal: hypocellular) at doses from 26-52 mg/kg. However, it is noted that a 2 week dosing period (3 doses over 2 weeks) with limited toxicological assessments performed in a small number of female rats only is insufficient to fully assess potential toxicological effects in this species. While only limited toxicokinetic data was determined in this study, exposure reported in acute toxicity studies suggest trastuzumab emtansine exposure is likely to be similar to and free DM1 exposure ~ 4 fold higher than that anticipated clinically at the 10 mg/kg dose. If not for the major study limitations, this would be considered the No Observed Adverse Effect Level (NOAEL).

Monkeys

Dose range finding and pivotal repeat dose toxicity studies were conducted in monkeys given intravenous trastuzumab emtansine every 3 weeks for 2, 4, or 8 doses followed by a 3 or 6 week recovery period. In the pivotal 4 and 8 dose studies, doses evaluated were 3, 10, and 30 mg/kg (approximately 612, 2040, and 6120 μg DM1/ m^2), and 1, 3, and 10 mg/kg (approximately 232, 695, and 2316 μg DM1/ m^2), respectively. All dose levels were generally well tolerated (with no deaths, only marginal effects on body weight and mild clinical signs, in addition to histological lesions discussed below). Some clinical pathology findings observed were suggestive of an inflammatory process (liver and/or nonspecific tissue injury) and included increased activated partial thromboplastin time, fibrinogen, triglycerides, globulin and decreased albumin and albumin to globulin ratio at doses from 10-30 mg/kg. These were generally resolved at the end of the recovery periods.

Target organs identified from these studies included the liver (increased liver enzymes, increased weight, hypertrophy (Kupffer/endothelial cells), mitotic figures, multinucleated hepatocytes, vacuolation, atrophy, increased sinusoidal leukocytes), haematologic/bone marrow effects (decreased red blood cell, white blood cell and platelet counts), the spleen (increased weight, hypertrophy (reticuloendothelial cells), increased cellularity of the red pulp, lymphoid depletion, mitotic figures), thymus (decreased weight, atrophy), lacrimal

glands (hypertrophy (epithelial cells), decreased mucous cells), sciatic nerve and spinal cord (axonal degeneration, hypertrophy/hyperplasia of Schwann cells) and occasionally at the intravenous injection site (mitotic figures, acanthosis, hyperkeratosis) at doses ranging from 3-30 mg/kg (from 1 mg/kg for axonal degeneration in males). Increased mitotic figures were also observed in multiple additional tissues, as observed previously in acute toxicity studies. With the exception of the sciatic nerve and/or spinal cord axonal degeneration and hyperplasia/hypertrophy of Schwann cells which were observed both during the treatment and recovery periods, all other findings generally resolved by the end of the treatment free period.

Peripheral neuropathy is a common adverse effect of anti tubulin drugs.¹⁰ The neurological findings of axonal degeneration were not associated with clinical effects during in-life observations or neurologic examinations in monkeys. This irreversible axonal degeneration has, according to the sponsor, “translated to patients as a low incidence of Grades 1 and 2 peripheral neuropathy” (Nonclinical Overview, Section 2.4, page 31, Volume 2, Module 2). While the sponsor has further stated that “clinical data to date, however, do not suggest that neurotoxicity, specifically peripheral neuropathy, is a significant safety risk”, the potential late onset and irreversibility of this finding at potential therapeutic exposure levels of trastuzumab emtansine and DM1 raise considerable safety concern and the need for clinical monitoring for potential neurotoxic effects.

Summary

Overall, the toxicity studies conducted in rats (while limited with respect to repeat dosing) and monkeys, adequately identified potential target organs of toxicity associated with trastuzumab emtansine administration primarily consisting of hepatic, bone marrow, lymphoid organ and neuronal effects (monkeys only). Rats were also observed with minor effects on the kidney and considerable adverse findings in the reproductive organs. The findings are consistent with toxicities of other tubulin targeting drugs. Chronic dosing did not result in cumulative toxicities. While these findings were generally observed at expected therapeutic exposure levels, raising cause for safety concerns with the proposed treatment regimen, the majority of the potential hepatotoxic and haematologic adverse effects observed appear to be manageable and reversible, provided adequate clinical monitoring protocols are put in place. It is noted that a safety warning for potential neurotoxic effects is included in the Product Information document. Effects of trastuzumab emtansine on male and female rat reproductive organs and relevant precautions in the draft PI statement are discussed under the ‘Reproductive Toxicity and Product Information’ sections.

Genotoxicity

Genotoxicity studies are not considered essential to support therapeutic products intended to treat patients with advanced cancer.¹¹ Nonetheless, DM1 (the cytotoxic component of trastuzumab emtansine) was examined for genotoxic potential *in vitro* (bacterial reverse mutation) and clastogenic potential *in vivo* (rat micronucleus test) in adequately performed GLP compliant studies. Trastuzumab emtansine was also examined for clastogenic effects *in vivo* (monkey micronucleus assay; incorporated into the 5 month monkey repeat dose toxicity study), and although this study was GLP compliant, it had considerable deficiencies in study design. Trastuzumab emtansine was not examined in

¹⁰ Wozniak KM, et al. (2011) Comparison of neuropathy-inducing effects of eribulin mesylate, paclitaxel, and ixabepilone in mice. *Cancer Res.* 71: 3952-3962.

¹¹ European Medicines Agency, “ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)”, December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

the Ames assay due to its large size (preventing it from binding or passing through the bacterial cell walls).

Trastuzumab emtansine was not clastogenic in monkey bone marrow *in vivo* after repeated exposure for 5 months, however the delayed timing of bone marrow collection may have contributed to this result. While plasma exposure was demonstrated by toxicokinetic data, bone marrow exposure was not confirmed and the limited reduction in the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) and (PCE/NCE ratio) for males only did little to clarify this. No positive controls were included to confirm the validity of this assay.

While DM1 did not demonstrate any evidence of mutagenicity *in vitro*, it was shown to be dose dependently clastogenic *in vivo* (significant increase in rat micronucleus frequency after an intravenous dose ≥ 0.05 mg/kg; associated with expected therapeutic DM1 exposure levels; refer to 'Relative exposure' section). These positive *in vivo* results are consistent with the mechanism of action of DM1 as a tubulin inhibitor and disruptor of the mitotic spindle apparatus and with findings of other anti tubulin drugs.

Carcinogenicity

Standard carcinogenicity studies were not performed and this is acceptable for a therapeutic product intended to treat patients with advanced cancer.¹²

Reproductive toxicity

Reproductive toxicology studies were not performed for trastuzumab emtansine or DM1. This is considered acceptable. Information available from general toxicology studies on the therapeutic product's effect on reproductive organs can be used as the basis of the assessment of potential impairment of fertility. Moreover, it is pointed out in the ICH guideline¹³ that embryofoetal development studies are not essential for therapeutics that are genotoxic and target rapidly dividing cells or belong to a class that has been well characterized as causing developmental toxicity.

The reproductive hazards of DM1, the cytotoxic and genotoxic component of trastuzumab emtansine, have been well characterised. DM1 is a microtubule inhibitory drug derived from maytansine. Based on animal studies of maytansine, DM1 is expected to be teratogenic and embryotoxic.

Reproductive toxicity of trastuzumab, the antibody component of trastuzumab emtansine has also been previously investigated in cynomolgus monkeys dosed twice weekly at 1, 5 and 25 mg/kg intravenous for 3 menstrual cycles (fertility study), on gestation days 20-50 (embryofoetal development study) or days 120-150 (late gestational toxicity study) associated with trastuzumab (conjugated and free) concentrations higher than those anticipated with the current proposed treatment regimen (3.6 mg/kg intravenous every 3 weeks). Trastuzumab had no effect on fertility, embryofoetal development or postnatal development despite being readily transferred through the placenta and with a small amount excreted in milk in this species. However, even though no embryofoetal toxicities were observed nonclinically, post marketing findings of oligohydramnios in the second and third trimesters of pregnancy, some associated with fatal pulmonary hypoplasia of the foetus have been reported (PI for Herceptin).

¹² European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

¹³ European Medicines Agency, "ICH Topic S 9 – Nonclinical Evaluation for Anticancer Pharmaceuticals: (EMA/CHMP/ICH/646107/2008)", December 2008, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

While no dedicated fertility studies were conducted with trastuzumab emtansine, acute toxicity studies in rats demonstrated adverse effects on reproductive organs. In a pivotal single dose intravenous toxicity study of trastuzumab emtansine in rats, males exhibited degeneration of seminiferous tubules in the testes and luminal debris in the epididymides, associated with increased organ weights at the severely toxic dose level of 60 mg/kg (approximately 9 fold anticipated clinical trastuzumab emtansine exposure at the proposed clinical dose, based on extrapolated $AUC_{0-\infty/all}$ and dose linearity, and 27 fold anticipated clinical free DM1 exposure based on C_{max}). At the same dose in female rats, haemorrhage and necrosis of the corpus luteum in ovaries and mammary gland degeneration/necrosis were observed. Mammary gland degeneration/necrosis was also observed in males at tolerated doses from 20 mg/kg (3 fold the anticipated clinical trastuzumab emtansine exposure at the proposed clinical dose, based on $AUC_{0-\infty}$, and 10 fold anticipated clinical free DM1 exposure based on C_{max}). On the basis of these findings, adverse effects on fertility may occur in patients.

Pregnancy classification

The sponsor has proposed Pregnancy Category D for trastuzumab emtansine. This is considered appropriate and is consistent with its high anticipated risk for embryotoxic, teratogenic and clastogenic effects in human pregnancy resulting from the actions of both the antibody and cytotoxic components of trastuzumab emtansine (refer to 'Reproductive toxicity' section above), and with the pregnancy category of other anti tubulin drugs (vinca alkaloids and taxanes).

Local tolerance

Specific local tolerance studies were not conducted. However, injection sites were examined both macroscopically and microscopically in toxicity studies in rats (following trastuzumab emtansine and DM1 administration) and monkeys (following single and multiple doses of trastuzumab emtansine).

In rats, no trastuzumab emtansine related macroscopic findings were observed at the site of injection, and microscopic findings were limited at terminal necropsy to the presence of basal cells of the epidermis and adnexal appendages arrested in mitotic metaphase, consistent with the pharmacologic activity of DM1 as an inhibitor of tubulin polymerisation. Similar findings were also observed in monkeys. However, following DM1 administration, severe tail lesions were observed due to extravasation of DM1 during dose solution administration. These findings suggest that there is a potential for toxicity at the injection site in the event of accidental delivery to the subcutaneous and/or dermal space. Therefore, extravasation should be avoided during trastuzumab emtansine administration.

Other toxicity studies

Tissue cross reactivity in cynomolgus monkey and human tissue sections was similar (in both distribution and intensity).

Acute toxicity studies conducted in rats and monkeys to evaluate the potential toxicity of trastuzumab emtansine with higher levels of free maytansinoids (5%-7% of the total drug) at identical dose levels (and similar trastuzumab emtansine exposure levels) to those in studies with lower levels of free maytansinoids, did not reveal any novel findings or significantly alter the toxicological profile of trastuzumab emtansine.

Impurities

Toxicity studies demonstrated that free maytansinoids levels at levels slightly above the proposed specification limits did not remarkably alter the safety profile of trastuzumab emtansine in rats or monkeys. However, free cytotoxic DM1 was rapidly and extensively distributed to many tissues, compared to limited tissue distribution of DM1 conjugated to trastuzumab, and the toxicity of trastuzumab emtansine is mainly attributable to the cytotoxic component, DM1. Specifications for trastuzumab emtansine-related impurities should be reduced to the lowest practicable level.

Paediatric use

Trastuzumab emtansine is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the safety specification of the risk management plan

Toxicity findings that were identified in the nonclinical studies, relevant to the clinical use of trastuzumab emtansine, and were not already reported to occur in humans, were presented in the sponsor's draft Risk Management Plan (RMP) (Version 1.0, 5 October 2012 and from updates provided in the Section 31 Response, 29 April 2013, Version 1.1), and are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

Summary

- The sponsor has applied to register a new chemical entity, trastuzumab emtansine (Kadcyla), as a single agent, for the treatment of patients with HER2 positive, unresectable locally advanced or metastatic (Stage IV) breast cancer who have received prior treatment with trastuzumab and a taxane. The proposed treatment regimen is 3.6 mg/kg, administered as an intravenous infusion every 3 weeks.
- Trastuzumab (Herceptin) alone is currently approved for the treatment of HER2 overexpressing breast cancer and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Recommended loading doses range from 4-8 mg/kg as an intravenous infusion, with subsequent 3 weekly intravenous infusions of 2-6 mg/kg.
- The submitted nonclinical data were generally acceptable and in accordance with ICH guidelines on the nonclinical evaluation of biotechnology products and anticancer drugs.
- Trastuzumab emtansine (trastuzumab-MCC-DM1) bound to its primary pharmacological target, the ECD of HER2 (HER2-ECD), with similar affinity to trastuzumab in vitro. DM1 is anti tubulin agent and an analogue of maytansine, which inhibits microtubule polymerisation and arrests cells in mitosis.
- Anti proliferative and anti tumour effects of trastuzumab emtansine were demonstrated in cancer cell lines in vitro. Trastuzumab emtansine caused cytotoxicity, decreased cellular proliferation and apoptosis in human tumour cell lines of breast cancer, ovarian cancer, gastric cancer, or NSCLC) expressing varying amounts of HER2 in vitro. These changes were not observed with trastuzumab and were attributable to its cytotoxic DM1 component. The cytotoxicity of trastuzumab emtansine increased with dose in cells expressing high levels of HER2. The IC₅₀ against cell proliferation of

breast cancer cell lines expressing HER2 were in the range of 5-150 ng/mL (compared to clinical C_{max} 85 µg/mL).

- Anti tumour activity of trastuzumab emtansine was also demonstrated in mouse models of HER2 positive breast cancers in vivo also following an intravenous bolus dose in the range of 10 to 30 mg/kg when administered once every 3 weeks, as proposed clinically. A dose of 10 mg/kg intravenous to mice every 3 weeks resulted in plasma trastuzumab emtansine exposure similar to that anticipated clinically (based on AUC).
- Limited GLP compliant safety pharmacology studies demonstrated no remarkable cardiovascular effects of DM1 (on hERG channel current) in vitro or trastuzumab emtansine (in monkeys) in vivo or haemolytic activity of trastuzumab emtansine in vitro at supra therapeutic concentrations. However, impaired megakaryocyte and platelet production were seen at clinically relevant trastuzumab emtansine concentrations.
- The pharmacokinetic profile of trastuzumab emtansine was broadly similar across all three nonclinical species (mice, rats and monkeys) examined and humans. Exposure increased with dose, no gender differences were apparent, and evidence of limited accumulation with repeat dosing was observed. Antibody responses to trastuzumab had no remarkable effect on trastuzumab emtansine pharmacokinetics. Free DM1 plasma levels were consistently low across studies in all species, including humans.
- Conjugation of trastuzumab did not appear to alter its distribution profile, while conjugation of DM1 limited its distribution to highly perfused organs. In contrast, free DM1 was rapidly and extensively distributed to many tissues. While no protein binding studies were provided for trastuzumab emtansine, DM1 was shown to be extensively bound to rat, monkey and human plasma proteins.
- The degradation pathways of trastuzumab emtansine were not expected to differ between nonclinical species and humans in the linear pharmacokinetic range. Following DM1 administration in rats, DM1 is extensively metabolised. There were no data on the metabolism of DM1 in monkeys, the species used in toxicity testing and this is considered a deficiency of the package. Nor were metabolism studies in humans in vivo, although three metabolites found in rats were detected in human liver microsome incubations in vitro. Similar toxicity findings in rats, monkeys and in clinical trials suggest that the rats and monkeys are appropriate animal models despite of the lack of metabolism studies in monkeys and humans.
- DM1 was shown to be a substrate of P-glycoprotein (P-gp), but did not inhibit P-gp activity at concentrations well above those anticipated clinically. Since DM1 and its metabolites are excreted mainly in the bile, P-gp inhibitors may decrease the elimination and excretion of DM1 and its metabolites. As for other anti-tubulin drugs (such as taxanes) that are also P-gp substrates, drug resistance to trastuzumab emtansine may develop as a result of increased P-gp expression in cancer cells with repeated administration.
- DM1 was metabolised by CYP450 enzymes CYP3A4 and to a lesser extent, CYP3A5, in vitro. However, DM1 does not induce or inhibit cytochrome P450 mediated metabolism at the highest concentration tested (600 ng/mL) in vitro. Plasma DM1 concentrations may be affected by CYP3A4/5 inhibitors or inducers.
- While the toxicology program for trastuzumab emtansine and/or DM1 was limited, pivotal studies were adequately conducted, sufficient to assess its toxicological profile and consistent with nonclinical ICH guidelines for an anticancer drug.

- The acute intravenous toxicity of trastuzumab emtansine in rats and monkeys was moderate. Conjugation of DM1 in the antibody drug complex was associated with increased tolerance in rats. Target organs identified in rats included the liver, kidney, spleen, thymus, testis, epididymis, ovary, mammary gland and bone marrow at doses ranging from 6-60 mg/kg. The liver was a target organ in monkeys at doses from 3-30 mg/kg. Maximum tolerated single intravenous doses of trastuzumab emtansine of 20 mg/kg and 30 mg/kg in rats and monkeys, respectively were associated with trastuzumab emtansine exposure levels 3 and 6 times those anticipated clinically (based on AUC).
- The toxicity of repeated intravenous doses of trastuzumab emtansine was examined in rats (at doses up to 52 mg/kg ; once weekly for 3 doses) and monkeys (at doses up to 10-30 mg/kg; once every 3 weeks for up to 8 doses). Target organs of toxicity primarily consisted of hepatic, bone marrow, lymphoid organ and neuronal effects (monkeys only). Rats were also observed with minor effects on the kidney and considerable adverse findings in the reproductive organs. The toxicity findings are consistent with toxicities of other tubulin targeting drugs. While these findings were generally observed at expected therapeutic exposure levels.
- A limited monkey micronucleus assay did not identify any clastogenic potential for trastuzumab emtansine. While DM1 did not demonstrate any mutagenic potential in vitro, it was shown to be dose dependently clastogenic in vivo at expected therapeutic DM1 exposure levels, consistent with the mechanism of action of DM1 and effects of other anti tubulin drugs.
- No standard carcinogenicity studies were performed for trastuzumab emtansine. This is acceptable.
- No reproductive toxicology studies were performed for trastuzumab emtansine or DM1. This is acceptable. However, adverse effects of trastuzumab emtansine on reproductive organs were observed in male and female rats at single intravenous doses from 20 and 60 mg/kg, respectively (3 and 9 fold anticipated clinical trastuzumab emtansine exposure, based on AUC). As an anti tubulin agent, DM1 is expected to be teratogenic and embryotoxic, suggesting trastuzumab emtansine. Cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus have been reported in pregnant women receiving trastuzumab.
- Specific local tolerance studies were not conducted. Rat and monkey intravenous toxicity studies with trastuzumab emtansine demonstrated the presence of basal cells of the epidermis and adnexal appendages arrested in mitotic metaphase at the injection site, consistent with the pharmacologic activity of DM1 as an inhibitor of tubulin polymerisation. In contrast, DM1 administration to rats was associated with severe tail lesions due to extravasation of DM1 during dose solution administration. These findings suggest that there is a potential for toxicity at the injection site in the event of accidental delivery to the subcutaneous and/or dermal space. Therefore, extravasation should be avoided during trastuzumab emtansine administration.
- Acute intravenous toxicity studies conducted with trastuzumab emtansine in rats and monkeys containing up to 2-3 fold increased levels of free maytansinoids, did not reveal any novel findings or significantly alter its toxicological profile.

Conclusions and recommendations

- The nonclinical submission for trastuzumab emtansine was generally acceptable and in accordance with ICH guidelines on the nonclinical evaluation of biotechnology products and anticancer drugs.

- Efficacy was demonstrated against HER2 expressing breast cancer cell lines in vitro and HER2 positive breast cancers in mouse models in vivo at expected clinical trastuzumab emtansine exposure levels.
- The toxicological profile of trastuzumab emtansine (and to a lesser extent, DM1, its cytotoxic component) was adequately characterised in rats and monkeys, identifying hepatic, bone marrow, lymphoid organ and neuronal effects. Rats also had minor effects on the kidney and adverse findings in the reproductive organs. These toxicities are generally consistent with that of other tubulin targeting drugs.
- DM1 was clastogenic in vivo at expected therapeutic DM1 exposure levels, consistent with effects of other anti tubulin drugs.
- Adverse effects of trastuzumab emtansine on reproductive organs were observed in male and female rats. The cytotoxic component, DM1, of trastuzumab emtansine is expected to be teratogenic and cytotoxic. Pregnancy category D is considered appropriate for trastuzumab emtansine.
- There are no nonclinical objections to the registration of Kadcylla provided an adequate safety monitoring program is implemented, as deemed appropriate by the clinical evaluator and delegate.
- The nonclinical section of safety specification in the RMP is acceptable.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The clinical submission contains full study reports from six clinical trials related to pharmacokinetics and pharmacodynamics. These include the Phase I Study TDM3569g, three Phase II Studies TDM4258g, TDM4374g, TDM4450g/B021976, a QTc Phase II Study TDM4688 and the Phase III pivotal Study TDM4370/B021977. Full study reports and appropriate summaries are provided.

Efficacy and safety data from the clinical submission is provided by full reports of the Phase III pivotal trial TDM 4370g/B021977 together with supporting efficacy and safety data from three Phase II studies for patients with HER2+ metastatic breast cancer, that is, Study TDM4450g, Study TDM4374g and Study TDM4258g. Further supportive safety data is also provided by one single arm Phase II Study TDM4688g and one Phase I Study TDM3569g as well as long term follow up safety data from 43 patients treated with Kadcylla in earlier Phase I and Phase II studies. These patients continued treatment in the extension Study TDM4529g. Full reports together with appropriate summaries are provided.

Pharmacokinetics/pharmacodynamics

These pharmacologic data have provided a comprehensive profile of trastuzumab emtansine conjugate with linear pharmacokinetics with predictable pharmacokinetic profile and no evidence of repeated dosing led to noticeable accumulation of the conjugate consistent with the observed half life of ~4 days. As concentrations of DM1 detected in the plasma were relatively low after the various infusions, this indicates that the linkage of trastuzumab to DM1 was stable. Various baseline tumour characteristics and baseline

renal and hepatic function do not appear to influence pharmacokinetic parameters. There is no evidence that age, race, geographic region or renal function influenced the pharmacokinetics of the conjugate and further assessment is being undertaken in relation to hepatic function.

Efficacy

Efficacy data from the pivotal study has clearly shown evidence of a statistically significant and clinically meaningful benefit for trastuzumab emtansine compared to lapatinib plus capecitabine in this patient population. The statistically significant improvement in progression free survival (PFS) was associated with a 35% reduction in the risk of progressive disease. It is also noted that interim overall survival (OS) data has a trend favouring trastuzumab emtansine. Secondary efficacy parameters and subgroup analyses all supported these results. The data from the pooled studies was more limited but nevertheless again demonstrated worthwhile efficacy for trastuzumab emtansine in both previously untreated advanced stage patients and those with heavy previous treatment.

Safety

These data have shown that, in general, trastuzumab emtansine was well tolerated with safety profile comparable to conventional chemotherapy regimen. It is noted that in the pivotal study trastuzumab emtansine treated patients had fewer at least grade III adverse events (AEs), serious adverse events (SAEs), and AEs leading to treatment discontinuation than those treated with lapatinib plus capecitabine. Those most frequently abnormal and at least grade III level for trastuzumab emtansine treatment included thrombocytopenia, increased liver enzymes, hypokalaemia and neutropenia. There were a small number of serious hepatic dysfunction events indicating a requirement for careful laboratory monitoring of these patients.

List of questions

Follow up analyses of overall survival data for the pivotal Study TDM4370g/B021977 would be of interest.

Clinical summary and conclusions

First round benefit/risk assessment

First round assessment of benefit

Data from the four studies presented in this submission to support efficacy for trastuzumab emtansine have all shown clear evidence of benefit for the patient populations treated. For the pivotal trial TDM4370g/B021977, there was a significantly prolonged PFS benefit (independent review committee [IRC] assessed) compared with those patients receiving the control arm of lapatinib plus capecitabine, with a median PFS of 9.6 months versus 6.4 months ($P < 0.0001$). All sensitivity analyses supported this result. It is also noted that there was a trend in favour of trastuzumab emtansine in relation to OS compared to the control arm with an Hazard Ratio (HR) = 0.621, $P = 0.0005$, and a one year survival rate of 84% versus 77%, and a two year survival rate of 65.4% versus 47.5%. These results are impressive also because of the nature of the patient population evaluated, namely those who had received considerable prior therapy including trastuzumab and a taxane. Also those patients who had relapsed within six months of receiving adjuvant trastuzumab demonstrated worthwhile benefits. It is to be noted that

these benefits in relation to the randomised trial were also pertinent, that is, the control arm was the only approved therapy presently available for patients with HER2+ locally advanced breast cancer and metastatic breast cancer who have failed on trastuzumab and a taxane.

These data were supported by the Phase II Study TDM4450g/BO21976 in which patients with previously untreated HER2+ metastatic breast cancer showed a statistically significant improvement in PFS when compared to the regimen of trastuzumab plus docetaxel. Again, the various sensitivity and subgroup analyses for these patients supported a significant primary efficacy endpoint of PFS. Two single agent Studies TDM4258g and TDM4374g in which heavily pre treated patients having received prior trastuzumab and a taxane also had an IRC assessed overall response rate of 30.2% and a median PFS of 6.2 months.

All of this data is substantial in terms of the level of efficacy for this patient population.

First round assessment of risks

The data provided in this safety evaluation (N = 882 patients, including 490 patients in the pivotal trial) demonstrated that trastuzumab emtansine was generally well tolerated with a safety profile comparable with conventional chemotherapy regimens. It is noted that in the pivotal study, trastuzumab emtansine treated patients had fewer grade III and higher AEs, SAEs, and AEs leading to treatment discontinuation than those treated with lapatinib plus capecitabine. The most frequent adverse effect of greater frequency in the trastuzumab emtansine arm was thrombocytopenia of at least grade III severity and followed by increased liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]), anaemia, fatigue, hypokalaemia, and neutropenia. The data from the supportive studies supported this adverse effect profile and its overall levels of severity.

Careful monitoring of patients receiving trastuzumab emtansine including appropriate regular laboratory evaluation would be important particularly in reference to the potential disturbance of hepatic function. Nevertheless, it is anticipated that any adverse effects likely to arise will be well managed with careful observation and early intervention as required.

First round assessment of benefit/risk balance

Taking into account the clearly efficacious results associated with the pivotal study, and supportive trials showing significant benefit for PFS compared to standard chemotherapy, together with a safety profile that appears manageable with appropriate careful monitoring and early intervention as required, the benefit-risk balance favours approval of trastuzumab emtansine for the proposed indication.

First round recommendation regarding authorisation

This evaluator considers that the data is adequate to support approval for the indication trastuzumab emtansine as a single agent as indicated for the treatment of patients with HER2+ unresectable, locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and ataxane.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns, which are shown at Table 4.

Table 4: Ongoing safety concerns as identified by the sponsor.

Important Identified Risks	Pneumonitis Hepatic toxicity (elevated transaminases) Nodular regenerative hyperplasia Infusion related reaction / Hypersensitivity Cardiac dysfunction (Left ventricular dysfunction) Thrombocytopenia Peripheral neuropathy
Important Potential Risks	ILD/ARDS Severe hepatic toxicity (DILI / Hy's Law cases) Congestive heart failure Foetal harm
Important Missing Information	Use in patients with hepatic impairment Use in patients with 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

OPR reviewer comment:

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification (SS), the above summary of the ongoing safety concerns is considered acceptable.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities, consistent with published guidelines,¹⁴ are proposed to monitor all the specified ongoing safety concerns. This includes the use of guided questionnaires for the important identified risks: 'Hepatic toxicity (elevated transaminases)' and 'Nodular regenerative hyperplasia'; and the important potential risk: 'Severe hepatic toxicity (DILI/Hy's Law cases)'. It would appear the sponsor has not provided copies of these guided questionnaires.

Furthermore a planned, international Phase IIb safety study entitled "A Multicentre, Single Arm Study of Trastuzumab Emtansine (T-DM1) in HER2 Positive Locally Advanced or Metastatic Breast Cancer Patients Who Have Received Prior Anti-HER2 and Chemotherapy-Based Treatment" is proposed to evaluate the safety and tolerability of trastuzumab emtansine. This study does not appear to be related to any specific Ongoing Safety Concern. Nevertheless, a corresponding Protocol M028231, Version 1, was provided in Annex 5 of the Australian RMP (AU-RMP). Subsequently, the sponsor's correspondence dated 19 March 2013 advised that this study is now ongoing (initiated November 2012) and has Australian patients enrolled.

An ongoing study: "Phase I, Open Lab, Parallel Group, Pharmacokinetic Study of Trastuzumab Emtansine in Patients With HER2 Positive Metastatic Breast Cancer and Normal or Reduced Hepatic Function" will assess the pharmacokinetics of trastuzumab emtansine and relevant catabolites and safety of trastuzumab emtansine in three patient cohorts: 1) patients with normal hepatic function, 2) patients with mild (Child-Pugh Class A) hepatic dysfunction, and 3) patients with moderate (Child-Pugh Class B) hepatic dysfunction. This additional pharmacovigilance activity will further monitor and

¹⁴ European Medicines Agency, "ICH Topic E 2 E Pharmacovigilance Planning (Pvp), Step 5: Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)", June 2005, Web, accessed 2 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf>.

characterise the important identified risks: 'Hepatic toxicity (elevated transaminases)' & 'Nodular regenerative hyperplasia'; the important potential risk: 'Severe hepatic toxicity (DILI /Hy's Law cases)'; and the important missing information: 'Use in patients with hepatic impairment'. A corresponding Final Protocol B025499, Version B, was provided in Annex 5 of the AU-RMP and the planned date for submission of final data is May 2013.

An ongoing study: "Multicentre, Multinational Phase II Study to Assess the Clinical Safety and Feasibility of T-DM1 Sequentially with Anthracycline Based Chemotherapy, as Adjuvant or Neoadjuvant Therapy for Patients with Early Stage HER2 Positive Breast Cancer" will further monitor and characterise the important identified risk: 'Cardiac dysfunction (Left ventricular dysfunction)' and the important potential risk: 'Congestive heart failure'. A corresponding Protocol B022857/TDM4874g, dated 24 November 2010, was provided in Annex 5 of the AU-RMP. However, no planned date for submission of final data was provided.

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

The sponsor should provide copies of the guided questionnaires for the specified Ongoing Safety Concerns and these should be included as an annex to the AU-RMP when this document is next updated. In addition this targeted follow up is considered to be a routine pharmacovigilance activity and should be categorised as such in the next revision of the AU-RMP.

The ongoing international Phase IIb safety Study M028231 should be categorised as an additional pharmacovigilance activity and preferably linked to specific Ongoing Safety Concerns to provide context. Updated information in relation to this study and to Study B022857/TDM4874g, particularly in regard to the planned date for submission of final data, should be included in Table 60: 'Overview of Study Protocols for the Pharmacovigilance Plan' in the next revision of the AU-RMP.

The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore, the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies as outlined in the AU-RMP, will be expected in future Periodic Safety Update Reports (PSURs) and RMP updates.

The sponsor should also provide compelling justification as to why the specified clinical studies required by the US FDA as post marketing commitments have not been included in the PP. Alternatively, if the sponsor decides to include these studies within the PP, the relevant sections of the AU-RMP will need to be updated accordingly, and at least draft protocols for these studies should be submitted to the TGA for review.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified Ongoing Safety Concerns.

OPR reviewer comment:

The sponsor's conclusion that no additional risk minimisation activities are needed is consistent with assessment of the US FDA and it is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities. Therefore, at this time the sponsor's conclusion is considered acceptable. Nevertheless, the nonclinical and clinical aspects of the SS remain subject to the evaluation by the TGA Office of Scientific Evaluation (OSE) and the Office of Medicines Authorisation (OMA), respectively.

In regard to the product being a new biological entity, the sponsor states that:

- Trastuzumab is manufactured using conventional large scale cell culture and purification techniques to produce and purify the secreted humanised protein.
- In general, the trastuzumab production process uses some raw materials derived from human and animal sources and these raw materials are controlled with regards to origin and source.
- Validated heat sterilisation processes or other validated sterilisation processes provide the primary defence against introduction of biologically derived adventitious agents into the manufacturing process.
- In addition to these precautions, the fermentation process includes in process controls for bioburden, mycoplasma, and viruses and the recovery process is validated for viral clearance.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the draft PI and Consumer Medicine Information (CMI) documents should *not* be revised until the Delegate's Overview has been received:

- Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
- The sponsor should provide copies of the guided questionnaires for the specified ongoing safety concerns and these should be included as an annex to the AU-RMP when this document is next updated. In addition, this targeted follow up is considered to be a routine pharmacovigilance activity and should be categorised as such in the next revision of the AU-RMP.
- The ongoing international Phase IIb safety study MO28231 should be categorised as an additional pharmacovigilance activity and preferably linked to specific Ongoing Safety Concerns to provide context. Updated information in relation to this study and to Study B022857/TDM4874g, particularly in regard to the planned date for submission of final data, should be included in Table 60: 'Overview of Study Protocols for the Pharmacovigilance Plan' in the next revision of the AU-RMP.
- The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore, the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies as outlined in the AU-RMP, will be expected in future PSURs and RMP updates.
- The sponsor should provide compelling justification as to why the specified clinical studies required by the US FDA as post marketing commitments have not been included in the PP. Alternatively, if the sponsor decides to include these studies within the PP, the relevant sections of the AU-RMP will need to be updated accordingly and at least draft protocols for these studies should be submitted to the TGA for review.
- The sponsor's conclusion that no additional risk minimisation activities are needed is consistent with assessment of the US FDA and it is agreed the specified Ongoing Safety Concerns would not appear to warrant additional risk minimisation activities.

Therefore, at this time the sponsor's conclusion is considered acceptable. Nevertheless, the nonclinical and clinical aspects of the SS remain subject to the evaluation by the OSE and the OMA, respectively.

- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows:
 - The currently approved US monograph contains key safety labelling recommendations in a boxed warning relating to potential for hepatotoxicity, cardiotoxicity, and embryofetal toxicity. No such boxed warning is proposed for the Australian PI. The sponsor should provide justification for such an omission.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft CMI document be revised as follows:
 - The currently approved US monograph contains the following information *inter alia* in relation to Patient Counselling:
 - Inform patients of the possibility of severe liver injury and advise patients to immediately seek medical attention if they experience symptoms of acute hepatitis such as nausea, vomiting, abdominal pain (especially right upper quadrant abdominal pain), jaundice, dark urine, generalised pruritus, anorexia, etc. (see 'Warnings and Precautions').
 - Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, palpitations, weight gain of more than 5 pounds in 24 h, dizziness or loss of consciousness (see 'Warnings and Precautions').

In the light of this information, the sponsor should include similar detail in the Australian CMI or provide justification for such omission.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR, and the OPR's evaluation of the sponsor's responses.

Table 5: Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor has reviewed the consolidated list of section 31 requests and has assessed that none of the questions raised have implications for the RMP.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
2. The sponsor was asked to provide copies of the guided questionnaires for the specified ongoing safety concerns and these should be included as an annex to the AU-RMP when this document is next updated. In addition this targeted follow-up is considered to be a routine pharmacovigilance activity and should be categorised as such in the next revision of the AU-RMP.	The sponsor has agreed to categorise the hepatobiliary events Guided Questionnaire as a routine pharmacovigilance activity in the next version of the AU-RMP. A copy of the single guided questionnaire used for the assessment of Kadcyła's hepatobiliary events (elevated transaminases, nodular regenerative hyperplasia and Hy's law for drug induced liver injury (DILI)) was provided.	This is acceptable.
3. The sponsor was advised that the ongoing international Phase IIIb safety study M028231 should be categorised as an additional pharmacovigilance activity and preferably linked to specific ongoing safety concerns to provide context. Updated information in relation to this study and to Study B022857/TDM4874g, particularly in regard to the planned date for submission of final data, should be included in Table 60: 'Overview of Study Protocols for the Pharmacovigilance Plan' in the next revision of the AU-RMP.	The sponsor agreed that additional pharmacovigilance activities should be linked to specific safety concerns. However, the sponsor states that although Study M028231 will enrich the overall safety database and provide supporting information, it is not designed to address any specific identified or potential risk. Consequently the sponsor proposes to remove this study as an additional pharmacovigilance activity in the next update of the RMP. The sponsor has also provided relevant milestones for Studies B025499, TDM4874g/B022857 and H4621g (MotHER).	Protocol M028231, Version 1, states that <i>inter alia</i> safety outcome measures will include the incidence of congestive heart failure (an important potential risk) and left ventricular ejection fraction decrease over the course of the study (an important identified risk). This would appear contradictory to the rationale for removing Study M028231 as an additional pharmacovigilance activity. Therefore the sponsor's proposal is unacceptable and it is reiterated this study should be categorised as an additional pharmacovigilance activity and linked to specific ongoing safety concerns to provide context.
4. The sponsor was advised that the ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies as outlined in the AU-RMP, will be expected in future PSURs and RMP updates.	The sponsor commits to update the TGA on the progress, results and analysis of the ongoing studies outlined in the AU-RMP, in future PSURs and RMP updates.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
5. The sponsor was asked to provide compelling justification as to why the specified clinical studies required by the US FDA as post-marketing commitments have not been included in the Pharmacovigilance Plan (PP). Alternatively, if the sponsor decides to include these studies within the PP, the relevant sections of the AU-RMP will need to be updated accordingly and at least draft protocols for these studies should be submitted to the TGA for review.	The sponsor has agreed to add the ongoing pregnancy registry for Herceptin and Perjeta, Study H4621g (MoTHER) as an additional pharmacovigilance activity for the important potential risk of 'foetal harm' and for the important missing information of 'use in pregnant women' in the next AU-RMP update. The sponsor has provided a corresponding draft synopsis and advised that the final protocol amendment is anticipated to be available by 31 May 2013. The final clinical study report for study B025499, an ongoing study being conducted in hepatic impaired patients, is included in the current AU-RMP for the important identified risks of 'hepatic toxicity (elevated transaminases)'; 'nodular regenerative hyperplasia'; the important potential risk of 'severe hepatotoxicity (severe DILI [Hy's Law cases]), and important missing information for 'use in patients with hepatic impairment'. In the next update of the AU-RMP, this study will be identified as an "additional" pharmacovigilance activity (currently routine).	This is acceptable.
6. The sponsor was advised that the conclusion that no additional risk minimisation activities are needed is consistent with assessment of the US FDA and it is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities. Therefore at this time the sponsor's conclusion is considered acceptable. Nevertheless the nonclinical and clinical aspects of the SS remain subject to the evaluation by the OSE and the OMA respectively.	The sponsor acknowledged that further questions may be raised by the nonclinical and/or clinical assessors.	N/A
7. In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft product information document be revised as follows: • The currently approved US monograph contains key safety	The sponsor has provided justification for not including such a boxed warning in the Australian PI.	The sponsor's justification would appear to be reasonable and therefore acceptable. Nevertheless ACSOM advised that similar information be added to the Australian PI,

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
labelling recommendations in a boxed warning relating to potential for hepatotoxicity, cardiotoxicity and embryo-foetal toxicity. No such boxed warning is proposed for the Australian PI. The sponsor should provide justification for such an omission.		however not necessarily in the form of a black box warning. The committee further advised that consideration be given to providing more detailed information in the CMI of the potential implications of treatment for future pregnancies.
8. In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine document be revised as follows: The currently approved US monograph contains the following information <i>inter alia</i> in relation to Patient Counselling: <i>Inform patients of the possibility of severe liver injury and advise patients to immediately seek medical attention if they experience symptoms of acute hepatitis such as nausea, vomiting, abdominal pain (especially RUQ abdominal pain), jaundice, dark urine, generalized pruritus, anorexia, etc. [see Warnings and Precautions (5.1)].</i> <i>Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [see Warnings and Precautions (5.2)].</i> In the light of this information the sponsor should include similar detail in the Australian CMI or provide justification for such omission.	The sponsor has added the following text to the Side Effects "After an infusion" section: "Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you notice any of the following: any of the side effects listed above - swelling of ankles or legs - weight gain of more than 2 kilograms in 24 hours - dizziness or fainting - increased cough - shortness of breath, especially when lying down or being woken from your sleep - abdominal pain - jaundice (your skin and whites of your eyes look yellow) - dark urine - rash, itching or hives on the skin - loss of appetite"	This is acceptable.

Summary of recommendations

Issues in relation to the RMP

The sponsor was advised that the ongoing international Phase IIIb safety Study M028231 should be categorised as an additional pharmacovigilance activity and preferably linked to specific ongoing safety concerns to provide context. The sponsor agreed that additional pharmacovigilance activities should be linked to specific safety concerns. However, the sponsor states that although this study will enrich the overall safety database and provide supporting information, it is not designed to address any specific identified or potential risk. Consequently, the sponsor proposes to remove this study as an additional pharmacovigilance activity in the next update of the RMP. This would appear contradictory to Protocol M028231, Version 1, which states that *inter alia* safety outcome

measures will include the incidence of congestive heart failure (an important potential risk) and left ventricular ejection fraction decrease over the course of the study (an important identified risk). Therefore, the sponsor's proposal to remove this study as an additional pharmacovigilance activity is unacceptable and it is reiterated this study should be categorised as an additional pharmacovigilance activity and linked to specific Ongoing Safety Concerns to provide context before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The committee noted that there are ethnic variations associated with the risk of thrombocytopenia, particularly in Asian patients compared with non Asian patients (48.2% compared with 17%) and advised that as this risk is significant, additional pharmacovigilance should be considered to monitor this. Currently, routine pharmacovigilance activities only are proposed to monitor the important identified risk: 'Thrombocytopenia'. The sponsor should adequately address the committee's concerns preferably before this application is approved.

In terms of risk minimisation activities, the committee noted that the US FDA has required the sponsor to include a black box warning in the PI, warning of the risk of hepatotoxicity, cardiotoxicity, and embryofetal toxicity. ACSOM advised that similar information be added to the Australian PI, but not necessarily in the form of a black box warning. ACSOM further advised that consideration be given to providing more detailed information in the CMI of the potential implications of treatment for future pregnancies. The Delegate is asked to consider this advice when negotiating the final PI and CMI.

ACSOM also noted that the FDA had recently required the sponsor to add an "ado" prefix to the name (that is, ado-trastuzumab emtansine) to distinguish the product from trastuzumab. ACSOM advised that there is clear potential for confusion between trastuzumab emtansine and trastuzumab and advised that consideration be given to adopting a similar naming convention in Australia. The committee advised that a prefix is likely to better mitigate the risk of medication errors than a suffix. Further measures to minimise the risk of product naming confusion, such as ensuring the outer packaging can be readily distinguished from trastuzumab, should also be considered. The Delegate is asked to consider this advice before this application is approved.

Comments on the safety specification of the RMP

Clinical evaluation report

The safety specification of the draft RMP is satisfactory.

Nonclinical evaluation report

Toxicity findings that were identified in the nonclinical studies, relevant to the clinical use of trastuzumab emtansine, and were not already reported to occur in humans, were presented in the sponsor's draft RMP (Section 1.13.1; Version 1.0, 5 October 2012 and from updates provided in the Section 31 Response, 29 April 2013, Version 1.1), and are in general concordance with those of the nonclinical evaluator.

Suggested wording for conditions of registration

RMP

The Australian RMP Version: 1.0 dated October 2012, to be revised as specified in the sponsor's correspondence dated 29 April 2013 with an amended Pharmacovigilance Plan satisfactory to the TGA, must be implemented.

PSUR

OMA to provide wording when finalised.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluation leader summarised key issues as:

- The issue of free maytansinoids levels during storage was raised by the PSC who supported the recommendation of the reduced shelf life for both the drug substance and drug product. The recommendations for the reduced shelf life storage were based upon the initial stability data submitted for evaluation. However, the company submitted further stability data outside the SSP requirements. If registered, it is recommended that the company submit a Category 3 to extend the shelf life.
- Free maytansinoid levels are controlled through release and shelf life specifications and the company complied with requests to tighten both the drug product and drug substance specifications during the evaluation process. In this evaluation, free maytansinoids levels are approached from a manufacturing aspect and do not consider their toxicological aspects. The level of the toxicity of the free maytansinoids in the drug product is best assessed in the clinical studies.

The recommendation was to approve the application. A drug product shelf life of 24 months at 2-8°C was recommended by the evaluator, upon registration. Batch release conditions of registration were proposed.

Nonclinical

The evaluator noted adverse effects of T-DM1 on male and female reproductive organs at clinically relevant levels.

DM-1 is expected to be both teratogenic and embryotoxic. Trastuzumab has been linked to cases of foetal renal growth retardation and functional impairment associated with oligohydramnios, in some cases associated with fatal pulmonary hypoplasia. Pregnancy category D was considered appropriate.

Primate toxicity studies of identical doses of T-DM1 but with higher free maytansinoid levels (5-7%, versus "not more than 3.0%" for Kadcyla) did not greatly alter the toxicological profile. The evaluator notes that study design does not allow full reassurance about the safety of these higher levels of free maytansinoids. Free DM1 was 2-5 fold more toxic in acute rat toxicity studies than when conjugated to trastuzumab; also, free DM1 is not confined to highly perfused organs, but is rapidly distributed to many tissues.

There was no objection to registration provided an adequate safety monitoring program is implemented.

Clinical

The clinical evaluator supports registration using the sponsor's proposed indication.

Overview of data

Pivotal efficacy and safety data were from:

- TDM4370g/B021977 (EMILIA): an ongoing, Phase III, open label, **randomised**, controlled trial in patients with HER2 positive, unresectable LABC or MBC. Patients

had previously received trastuzumab and a taxane. N = 495 received Kadcyla, N = 496 received the comparator regimen (capecitabine + lapatinib). Data cut off was 14 January 2012 (an update was to 31 July 2012). This trial has been published.¹⁵

Supportive efficacy and safety data were drawn from three Phase II studies in patients with HER2 positive, unresectable LABC or MBC:

- TDM4450g/BO21976: a Phase II, open label, **randomised**, controlled trial in patients with HER2 positive MBC who had not previously received treatment for metastatic or locally advanced disease. N = 67 received Kadcyla, and N = 70 received the comparator regimen trastuzumab + docetaxel.
- TDM4374g: a Phase II, open label, **single arm** study of HER2 positive LABC or MBC. Patients had received treatment with ≥ 2 lines of HER2 directed therapy in the metastatic setting. N = 110 patients were studied.
- TDM4258g: a Phase II, open label, **single arm** study of HER2 positive LABC or MBC. Patients had progressed on HER2-directed therapy and ≥ 1 chemotherapy for metastatic disease. N = 112 patients were studied.

Across those four studies, only the 3.6 mg/kg, q3wk regimen was used.

Further **safety** data were drawn from:

- TDM4688g (a QT study in 51 subjects with HER2 positive LABC or MBC, who had progressed on previous regimens).
- TDM3569g (a dose escalation study; 15 patients received 3.6 mg/kg q3wk).
- TDM4529g (long term follow up of 43 patients in earlier Phase I-II studies).

A Phase 1 study in Japanese patients was also provided (N = 10).

Pharmacokinetics

Pharmacokinetic and pharmacodynamic data were from: TDM3569g (where there was intensive sampling in Cycle 1, and peak-trough sampling subsequently); TDM4258g; TDM4374g; TDM4450/BO21976; TDM4688g; and TDM4370g. Studies other than TDM3569g used “frequent” sampling and peak/trough sampling.

A population pharmacokinetic analysis “Report 12-0489” used available data from those six studies. Its conclusions are outlined in the Clinical Evaluation Report.

Assessment of pharmacokinetics is complicated by the presence of monoclonal antibody, linker and DM1 components. The following were analysed: T-DM1 (‘conjugated’ trastuzumab); total trastuzumab (conjugated + unconjugated trastuzumab); and DM1. No assay was used to measure the linker in systemic circulation.

Absorption

Kadcyla is administered by intravenous infusion.

Distribution

Nonclinical studies found T-DM1’s distribution similar to trastuzumab’s. The population pharmacokinetic analysis estimated T-DM1’s central volume of distribution as 3.127 L, that is, similar to plasma volume. DM1 is distributed rapidly and extensively.

¹⁵ Verma S, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 367:1783-1791.

Metabolism

The sponsor writes:

*T-DM1 is expected to primarily undergo proteolytic degradation as is observed for other monoclonal antibodies. However, the DM1 component of T-DM1 is mainly metabolized by **CYP3A4** and, to a limited extent, by CYP3A5, based on microsomal incubations.*

T-DM1 and DM1 achieve steady state levels by Cycle 1, and total trastuzumab achieves steady state levels by Cycle 3.

Clearance of T-DM1 (7-13 mL/day/kg) was faster than clearance of total trastuzumab (3-6 mL/day/kg). In the Herceptin PI, clearance is quoted as 0.241 L/day for a 68 kg patient, that is, 3.5 mL/day/kg. One interpretation is that after deconjugation, trastuzumab returns to the circulation. Clearance was conceptualised as similar to that of other monoclonal antibodies, that is, target (HER2) antigen specific, and non specific (mediated in part by Fc) mechanisms, with an additional mechanism of T-DM1 clearance being deconjugation of DM1.

Half life of total trastuzumab (for example, in TDM4258g) was ~11 days. This compares with a 28-38 day half life of trastuzumab (from the Herceptin PI); this is of clinical relevance in the context of subsequent use of anthracyclines and development of heart failure. For Kadcyla, half life is shorter; and patients would be less likely to go on to anthracyclines.

Catabolites of T-DM1, including DM1, Lys-MCC-DM1 and MCC-DM1, were detected in plasma. In nonclinical studies, DM1, Lys-MCC-DM1 and MCC-DM1 are mainly excreted in the bile.

Excretion

The sponsor writes that "T-DM1 is expected to undergo catabolism by means of proteolysis in cellular lysosomes". DM1 is considered to be excreted in bile. No accumulation of T-DM1 was observed with repeat dosing.

The sponsor observed no change in the pharmacokinetics of T-DM1 or DM1 across cycles, and interpreted this as showing that tumour burden decreases did not affect T-DM1 or DM1 pharmacokinetics.

Drug interactions

The sponsor writes:

*T-DM1 is expected to primarily undergo proteolytic degradation as is observed for other monoclonal antibodies. However, the DM1 component of T-DM1 is mainly metabolized by CYP3A4 and, to a limited extent, by CYP3A5, based on microsomal incubations. Further, DM1 is not a potent inhibitor or inducer at clinically relevant concentrations (up to 600 ng/mL in vitro) and is a **P-gp substrate** but not an inhibitor.*

The sponsor found no evidence in the pivotal study (TDM4370g/B021977) that concomitant administration of CYP3A inhibitors or inducers or P-gp inhibitors with Kadcyla affects the pharmacokinetics of T-DM1, total trastuzumab or DM1.

The sponsor did not conduct formal drug-drug interaction studies, but relied on observations from clinical studies where patients were taking concomitant medicines:

Since the intended indication is for single agent trastuzumab no formal drug interaction studies have been performed; however, pharmacokinetic parameters have been analysed to assess the effect of co-administration of docetaxel, pertuzumab or paclitaxel with T-DM1 in ongoing Phase Ib/II clinical studies.

As T-DM1 is expected to undergo catabolism by means of proteolysis in cellular lysosomes, with no significant involvement of CYPs, and based on the preclinical and in vitro metabolism experiments conducted, T-DM1 pharmacokinetics are unlikely to be affected by concomitant medications.

One implication of DM1 excretion via bile and DM1 being a substrate for P-gp is that P-gp inhibitors may decrease DM1's elimination. The nonclinical evaluator also notes that increased P-gp expression in cancer cells has mediated drug resistance after repeat administration of other anti tubulin drugs.

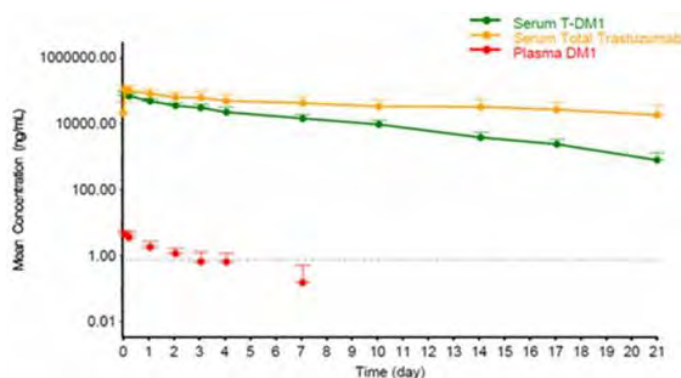
Free maytansinoids

Stability of the link between trastuzumab and DM-1 is relevant both during storage and in the circulation prior to reaching the intended site of action.

Maximum plasma levels of DM-1 were observed immediately after dosing (the first measurement was immediately after the end of infusion), which suggests deconjugation in the vial, and/or an immediate deconjugation step in the circulation. A threshold for free maytansinoids in vials is specified, and the sponsor notes that release of free maytansinoids from Kadcyra is temperature dependent and occurs during storage in the liquid state (the formulation is presented as a powder).

After Kadcyra administration (3.6 mg/kg), DM1 was detected in plasma with an average C_{max} of 6 ng/mL. The highest DM1 level in an individual after repeat dosing was 59.7 ng/mL. There was no evidence of accumulation in plasma with repeat dosing (for example, C_{max} at Cycle 1 in EMILIA was on average 4.61 ng/mL, and at Cycle 4 was 5.13 ng/mL). Figure 2 is taken from the one study with intensive sampling in Cycle 1 (TDM3569g).

Figure 2: Mean ($\pm$ SD) trastuzumab emtansine conjugate, serum total trastuzumab, and plasma DM1 concentration-time profiles for the trastuzumab emtansine 3.6 mg/kg q3w cohorts.



Note: N = 15 in the trastuzumab emtansine (T-DM1) 3.6/mg/kg every 3 week cohort. The dotted line represents the lower limit of quantitation (LLOQ) value of 0.737 ng/mL for the DM1 assay.

Although levels are low, toxicity of DM1 is high, and in nonclinical studies free DM1 was rapidly and extensively distributed to many tissues. Some AEs were attributed to DM1. The lower limit of quantitation for plasma DM1 was 0.737 ng/mL. Also, other catabolites were not routinely measured but in TDM4688g, exploratory assays revealed MCC-DM1 levels up to 122 ng/mL and Lys-MCC-DM1 levels up to 6.4 ng/mL.

Subgroups

No formal studies in hepatic or renal impairment were completed, although a study in hepatic impairment (B025499; including patients with mild to moderate impairment) is ongoing.

The sponsor used population pharmacokinetic analysis to evaluate effects of such intrinsic factors. The sponsor found no clinically relevant impact on pharmacokinetics in any single

included subgroup, for example, based on renal impairment; hepatic impairment; age; and race. Caveats are:

- The number of patients >75 yrs was low.
- There was only one patient with severe renal impairment (estimated creatinine clearance 15-29 mL/min), and N = 53 (7.9%) with moderate impairment (30-59 mL/min).
- Although single subgroups were not considered to impact meaningfully on pharmacokinetics, it is possible that individuals may have significant variation in pharmacokinetics because of some combination of characteristics such as body weight, target lesion dimensions, etc.

Efficacy

Study TDM4370g (EMILIA) - pivotal

This is an ongoing, Phase III, open label, randomised, controlled trial.

Enrolled patients had HER2 positive,¹⁶ unresectable LABC or MBC. They had received both: ≥1 trastuzumab containing regimen; and a taxane (alone or in combination with another agent). Two broad patient groups were enrolled, as the sponsor describes:

Patients must have progressed during or after treatment with their most recent regimen for advanced or metastatic disease or within 6 months of completing (neo)adjuvant therapy that included trastuzumab and a taxane.

This meant the study enrolled heavily pre treated patients (where the study regimen was at least third line) as well as patients who had never received systemic anti cancer therapy for metastatic disease and who had relapsed soon after (neo)adjuvant use of a trastuzumab containing regimen.

Patients who had asymptomatic treated brain metastases were eligible for inclusion. Patients who received recent (within 14 days) radiation therapy for brain metastases were eligible to participate. Approximately 10% of patients had brain metastases at enrolment. Excluded were patients with cardiac ejection fraction <50%, Eastern Cooperative Oncology Group (ECOG) performance status >1, inadequate organ function (hepatic, renal, haematopoietic), recent cardiopulmonary dysfunction, or inadequate contraception for women of child bearing potential. Prior treatment with lapatinib or capecitabine was also an exclusion criterion.

Randomisation was after stratification according to world region, visceral disease and number of prior chemotherapy regimens.

A total of N = 495 patients received Kadcylla, while N = 496 received the comparator regimen (capecitabine + lapatinib). The regimens were as follows:

- T-DM1 was administered at a dose of 3.6 mg/kg intravenous every 21 days (unless dose reduction and/or dose delays were required). The initial dose was administered over 90 minutes (± 10 minutes). Infusions could be slowed or interrupted for patients experiencing infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of T-DM1 were administered over 30 minutes (± 10 minutes), with a minimum 30 minute observation period after infusion.
- Lapatinib was given orally at a dose of 1250 mg (5 tablets) daily as continuous dosing and taken daily at least 1 h before or 1 h after a meal. Capecitabine was given as a total

¹⁶ IHC 3+ and/or gene-amplified by FISH ≥ 2.0.

daily dose of 2000 mg/m²/day (administered as two oral doses of 1000 mg/m² approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. Capecitabine was taken with food or within 30 minutes after the ingestion of food.

Demographics and baseline characteristics were well-balanced across arms. Median age was 53 yrs; median weight was 66-68 kg. Baseline ECOG was 0 (61-64%) to 1 (36-39%). Around 80% of patients had measurable disease, and 68% had visceral disease. 40.8% (Kadcyla) versus 45.2% (lapatinib + capecitabine) had ER- PR- tumours, respectively, while 35.6% and 31.3% had ER+ PR+ tumours, respectively. Patients had received a median of 5 agents for breast cancer, including a median of 3 for metastatic or locally advanced disease. About 88% of patients had already received prior systemic treatment in the metastatic setting; 118/991 had only received prior systemic treatment for early breast cancer but had relapsed within 6 months of completing treatment.

Median duration of follow up was 12.4-12.9 months (range, 0-34.7 months for both arms). Median dose intensity was 99.9% for Kadcyla, 93.4% for lapatinib, and 77.2% for capecitabine.

Progression free survival (PFS)

PFS, as assessed by IRC, was a co primary endpoint. Median PFS was **9.6 months for Kadcyla versus 6.4 months for lapatinib + capecitabine**. The HR was 0.65 (95% CI 0.55-0.77). Sensitivity analyses supported the main analysis. Investigator assessment was in agreement with IRC assessment.

PFS benefit was less apparent in: patients 65 to <75 yrs of age (HR 0.88); non visceral¹⁷ disease (HR 0.96); and non measurable disease (HR 0.91).

Patients ≥75 yrs of age had better PFS with lapatinib + capecitabine (HR 3.51, 95% CI 1.22-10.13).¹⁸ There were only 25 patients in this subgroup, but the HR was statistically significantly above 1. The difference was not due to worse tolerance, for example, there were no fatal AEs in patients 65+ yrs of age. There was no marked difference in the pharmacokinetics of T-DM1 according to age.

In patients who had received trastuzumab and taxane in the neoadjuvant setting, but who had relapsed within 6 months of treatment (N = 118), PFS HR was 0.52 (95% CI 0.30-0.88), similar to the PFS HR in the 873 patients with prior exposure in a metastatic setting (PFS HR 0.72, 95% CI 0.60-0.87).

PFS benefit was similar in subgroups based on line of therapy.

Overall survival (OS)

OS was a co primary endpoint. An **interim** analysis (14 January 2012 cut off) found a benefit for Kadcyla in terms of OS. The HR was 0.62 (95% CI 0.48-0.81). Minimum follow up at this point was 3 months, with a median of 12.4-12.9 months. Landmark 2 year survival was 65.4% for Kadcyla versus 47.5% for lapatinib + capecitabine. OS benefit was less apparent in, notably: patients 65 to <75 yrs old; and those with non visceral disease.¹⁹

The sponsor provided a clinical safety report addendum, with results of the second interim OS analysis (cut off 31 July 2012; as per Verma and colleagues²⁰). At this stage, the HR was 0.68 (95% CI 0.55-0.85); median duration of survival was 30.9 months for Kadcyla and 25.1 months for lapatinib + capecitabine. Median duration of follow up was ~19

¹⁷ Visceral disease was taken to mean disease in lungs or liver.

¹⁸ Described as "a less definitive benefit" for Kadcyla in Verma S, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 367:1783-1791.

¹⁹ Sponsor comment: "As designated by the investigator."

²⁰ Verma S, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 367:1783-1791.

months. Benefit was still less apparent in patients 65+ yrs of age (HR 1.05) and those with non visceral disease (HR 1.05), although re-analysis demonstrated that benefit was retained in patients with non visceral disease.

Final analysis of OS is expected in 2014.

Objective response rates

The objective response rate was 44% (Kadcyla) versus 31% (control).

Exposure-response analysis

An exposure-response analysis was performed in EMILIA; no impact of variability in exposure was found on PFS, OS, or overall response rate (ORR).

Quality of life

EMILIA assessed patient-reported outcomes including time to symptom progression. The FACT-B questionnaire was used. The sponsor notes:

The Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) score comprises a subset of the FACT-B and provides a summary measure of physical and functional well being and breast cancer specific symptoms. A decrease of at least 5 points in the TOI-PFB is considered to be clinically meaningful and thus defines symptom progression.

The Delegate notes the benefit for Kadcyla patients in this regard. Perhaps relevant, there was higher use of analgesics in the Kadcyla arm (for example, paracetamol, 30% versus 18%; NSAIDs, 28% versus 21%).

Studies TDM4374g and TDM4258g

Patients in these single arm studies were heavily pre treated, and stage of disease was more advanced, on average, than in the pivotal study. Median number of prior systemic treatments in the metastatic setting was 6. The sponsor conducted a pooled analysis. Median number of Kadcyla cycles was 7 (range 1-23), lower than in the pivotal study. IRC-assessed ORR was 30.2% (all partial responses). Median duration of PFS was 6.2 months (IRC), lower than for EMILIA and perhaps reflective of the more advanced state of disease in these Phase II trials.

Study TDM4450g/BO21976

This is an ongoing study in LABC/MBC patients with HER2 positive, unresectable disease who had **not received prior treatment** in the locally advanced or metastatic setting (prior hormone therapy for metastatic disease was allowed). Patients were required to have a disease free interval of ≥ 6 months from the end of (neo)adjuvant cytotoxic chemotherapy.

Patients were randomised to Kadcyla (N = 67) or to trastuzumab + docetaxel (N = 70) (8 mg/kg intravenous on Cycle 1 Day 1 then 6 mg/kg intravenous q3w; docetaxel 75 mg/m² or 100 mg/m² q3w based on investigator's discretion).

PFS was better in the Kadcyla group; the HR was 0.59 (95% CI 0.36-0.97). Median PFS was 14.2 months for Kadcyla, 9.2 months for trastuzumab + docetaxel. No differences in OS had been observed at the clinical data cut off of August 2011; few deaths had been reported (most subjects had received ≥ 1 anti cancer treatment after progression). The Kadcyla arm had delayed time to symptom progression (HR 0.59, 95% CI 0.38-0.91).

Immunogenicity

Antibodies to T-DM1 were measured in all clinical studies. A total of 44/836 patients (5.3%) developed antibodies, including 13/44 patients positive at baseline (indicative of the threshold used to declare positivity, which was chosen to minimise false negatives). In

the pivotal study, lower median PFS was seen in 20 patients with antibodies, compared to the ITT population (5.6 versus 9.6 months); ORRs were comparable and there was no great change in pharmacokinetic parameters. Based on immunodepletion studies, the contribution to these results from pre existing antibodies to trastuzumab is likely to be low.

Safety

Exposure

A total of 882 patients received single agent Kadcyla at the proposed dose. Safety results below are based on the initial EMILIA data, except where noted.

Overview of safety in EMILIA

Patients tolerated Kadcyla better than lapatinib + capecitabine, based on key results of the pivotal study (Table 6).

Table 6: Tolerance of Kadcyla compared with lapatinib + capecitabine.

EMILIA (TDM4370g) ^a	Kadcyla	Lapatinib + capecitabine
Deaths due to AEs	0.6% (n=3)	1.0% (n=5)
Grade ≥ 3 AEs	45%	60%
Serious AEs	18%	20%
Discontinuation due to AEs	7.1%	L: 8.8%; C: 11.1% ^b

a. Based on updated EMILIA data (cut off 31 July 2012)

b. 1.2% discontinued only lapatinib; 3.5% discontinued only capecitabine; 7.6% discontinued both

The clinical evaluation report notes AEs with different frequencies across arms. Patients in the Kadcyla arm had distinctly ($>10\%$ absolute, or >2 fold) more: thrombocytopenia; constipation; increases in AST and ALT; arthralgia; pyrexia; dry mouth; myalgia; chills; headaches; epistaxis; and urinary tract infections. Patients in the Kadcyla arm had less: diarrhoea; palmar plantar erythrodysesthesia syndrome; vomiting; rash; mucosal inflammation; stomatitis; dry skin; paronychia; nail disorder; hyperbilirubinaemia; and skin fissure AEs.

Overview of safety in TDM4450g/B021976

Kadcyla patients had many fewer grade ≥ 3 AEs (46.4% versus 90.9% in the trastuzumab + docetaxel arm); the difference was stark for grade ≥ 4 AEs (7.2% versus 59.1%), apparently due to the difference in grade 4 neutropenia (4.3% versus 51.5%). Febrile neutropenia was seen in 0% versus 13.6%. Docetaxel is very commonly associated with such neutropenia.

Kadcyla patients reported more grade ≥ 3 transaminase increases (ALT, 10.1% versus 0%; AST 8.7% versus 0%).

Kadcyla patients had to discontinue treatment less often.

Deaths

In EMILIA (based on updated data), for the 3 deaths attributed to AEs in the Kadcyla arm, the AEs were: pneumonia; neutropenic sepsis; and metabolic encephalopathy. For the 5 such deaths in the control lapatinib + capecitabine arm, the AEs were: acute respiratory distress syndrome (ARDS); coronary artery disorder; multi organ failure; coma; and hydrocephalus.

Cardiac effects

Heart failure and left ventricular systolic dysfunction

Trastuzumab is linked with congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF), especially if there is concurrent use of an anthracycline. In EMILIA, frequency of left ventricular (LV) dysfunction or cardiac failure was no higher in the Kadcyla arm than the control arm. One patient discontinued Kadcyla due to Grade 3 LV dysfunction. If there was a history of intolerance to trastuzumab (for example, cardiotoxicity), patients were excluded from EMILIA.

In the other randomised Study TDM4450g/BO21976, events were also balanced across arms. Data for Kadcyla in trastuzumab naive patients are limited.

The proposed PI includes instructions for dose modification/discontinuation in case of symptomatic CHF or falls in LVEF. A Precaution proposes LVEF assessment at baseline and "at regular intervals (for example, every three months)".

Arrhythmias

A QT Study TDM4688g was conducted; there, no significant effect of T-DM1 was found on the QT interval (the beginning of the QRS complex to the end of the T wave).

Hypokalaemia grade ≥ 3 occurred in 2.7% (Kadcyla) versus 4.5% (control) in EMILIA.

There was one report of sudden death in the total Kadcyla database.

Haematological toxicity

Thrombocytopenia

Thrombocytopenia (AE and/or laboratory test result) grade ≥ 3 (that is, $<50\,000/\text{mm}^3$) occurred in 12.8% (Kadcyla) versus 0.2% (lapatinib + capecitabine) in EMILIA. While severe platelet decreases did not return to baseline levels by the next treatment cycle in most cases, recovery was deemed sufficient to allow continued treatment. Bleeding events were more common in the Kadcyla arm (29.8% versus 15.8%). One patient with grade 1 thrombocytopenia had grade 4 gastrointestinal haemorrhage in the Kadcyla arm. Patients homozygous for the FcγR IIa A allele (that is, genotype AA) had a 21.7% frequency of severe thrombocytopenia; patients with heterozygous AG genotype had an 11.3% frequency; and patients with homozygous GG genotype had an 8% frequency. Asian patients had more grade 3 thrombocytopenia: 51.1% for Kadcyla versus 1.2% for control. Note that these are the figures for total; grade 3 thrombocytopenia was 33.7% versus 0.0%. Any link with FcγR IIa polymorphisms is unclear. In *in vitro* studies, clinically relevant concentrations of T-DM1 impaired megakaryocyte and platelet production.

Anaemia

Anaemia was very commonly observed. In EMILIA, 2% of Kadcyla patients (7/352) versus 0.6% of control arm patients (2/360) had a significant drop in Hb on study.

Neutropenia

In EMILIA, 3.3% of Kadcyla patients (15/450) versus 7.0% of control arm patients (33/473) had a significant drop in neutrophils on study. Several deaths were infection related in EMILIA.

Hepatotoxicity

Trastuzumab is not strongly associated with hepatotoxicity (for example, in breast cancer, grade 3-4 hepatic AEs in 7% with trastuzumab + paclitaxel versus 15% with paclitaxel alone).

DM1 and maytansine are associated with hepatotoxicity, but also not strongly.

Pre clinical studies of T-DM1 found dose dependent effects on the liver, but these were mild/moderate and reversible after 3-6 wks. The sponsor notes:

The similarities in liver toxicity observed between rats (a non binding species for HER2 directed antibodies) and cynomolgus monkeys (a binding species for HER2 directed antibodies) administered either T-DM1 or DM1 indicate that the toxicities are primarily antigen independent and consistent with the mechanism of action and pharmacologic activity of DM1.

In EMILIA, ALT elevation >3x ULN (Upper Limit of Normal) occurred in 18.6% (Kadcyla) versus 7.8%, although elevation >8x ULN occurred in 1.2% versus 1.0%. No cases of Hy's Law²¹ were observed, but 4 Kadcyla and 2 control patients developed elevated bilirubin (>2xULN) after developing elevated ALT (>3x ULN). Also, several deaths were considered related to hepatotoxicity.²²

In TDM4450g/BO21976, ALT elevation >3x ULN occurred in 17.3% (Kadcyla) versus 12.9% (trastuzumab + docetaxel).

The sponsor conducted a review of hepatotoxicity (trial data cut off December 2011, and global safety database data cut off March 2012). Of note from this review:

- Nodular regenerative hyperplasia has been pathologically documented after Kadcyla use (N = 5 cases as of 2011). This condition is characterised by widespread benign transformation of hepatic parenchyma into small regenerative nodules; it may lead to non cirrhotic portal hypertension. The 5 cases were identified out of only 7 with biopsy results, of 30 patients with serious hepatic AEs in the sponsor's global safety database (size ~2200). In 4/5 cases, exposure was for 15+ months; in the other case, 2.5 months. NRH was interpreted by the sponsor's hepatic expert as caused by Kadcyla, "which may be related to vascular/endothelial injury within the spectrum of veno occlusive disease (VOD) of an effect on growth factors".
- The global safety database included two patients with fatal liver disease, in one of whom the main confounder was only use of trazodone. There were three cases of encephalopathy, plus a late breaking fatal case.
- In the clinical trial database of 1211 subjects across 10 studies, by 18 weeks of Kadcyla treatment, ~14.9%, 4.7% and 1.3% of patients experienced ALT elevations >3x ULN, >5x ULN, and >8x ULN, respectively. Only 2.4% of additional patients had ALT elevations >3x ULN after 18 weeks.
- In the same database, 8 patients had ALT >3x ULN followed within 21 days by bilirubin >2xULN. In the randomised studies TDM4370g/BO21977 and TDM4450g/BO21976 (both with 1:1 randomisation), there were 4 patients from TDM4370g/BO21977 (2 Kadcyla patients versus 2 control patients) versus 1 control patient.

No relationship between level of exposure to T-DM1 or DM1 and liver toxicity has been observed. In patients who developed hepatotoxicity after T-DM1 treatment, exposures of T-DM1, total trastuzumab and/or DM1 were not consistently high.

In summary, Kadcyla causes asymptomatic transaminitis commonly, and there are rare cases of severe hepatotoxicity, including fatal cases.

²¹ US Food and Drug Administration, "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation", July 2009, Web, accessed 29 November 2013 <www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>; the sponsor used only ALT in its analyses.

²² Sponsor comment: "There was 1 death reported as 'metabolic encephalopathy' in EMILIA."

The proposed PI includes recommendations about dose modification/discontinuation with elevated liver function tests (LFTs), and a Precaution recommending LFT monitoring at baseline and at each dose.

Infusion reactions

In EMILIA, 3.9% of Kadcyła patients developed infusion-related reactions; all events were mild or moderate in severity. Slowing the infusion helped in some cases.

Separately, extravasation at the injection site may be predicted to cause toxicity on the basis of severe tail lesions (presumably in rats) after extravasation. Clinically, reactions were usually mild.

Neurotoxicity

Maytansine is linked with peripheral neuropathy. In EMILIA, grade ≥ 3 peripheral neuropathy was seen in 2.9% of Kadcyła patients, versus 0.4% of controls. Where specified, it was commonly sensory (as per maytansine). In TDM4450g/BO21976, there were more and more severe events in the control arm (grade ≥ 3 in 1.4% versus 6.1%), but numbers were lower than in EMILIA.

Vision disorders were reported in 6.3% (Kadcyła) versus 1.6% (control) in EMILIA; all were mild to moderate, for example, blurred vision. One case of optic neuropathy was reported in the Kadcyła arm.

In primates, T-DM1 caused irreversible sciatic nerve/spinal cord axonal degeneration.

Pneumonitis

Pulmonary AEs have been seen with trastuzumab. In EMILIA, pneumonitis was seen in 1.6% of Kadcyła patients versus 0.8% of control arm patients (based on updated data); there were no severe cases. Across all studies, 9 patients (1.0%) developed pneumonitis, and 1 case (interstitial lung disease) was fatal. Two deaths from respiratory failure were also reported.

Exposure-safety analysis

Variability in T-DM1 AUC and $C_{\max}$ and DM1 $C_{\max}$ did not influence risk of hepatic or thrombocytopenia AEs: no correlation was seen between exposure and platelet counts, ALT, AST, or total bilirubin.

Risk management plan

The RMP evaluator consulted the ACSOM for advice about this submission. The committee drew attention to the increased risk of thrombocytopenia in Asian recipients. ACSOM also advised that the PI draw attention to risks of hepatotoxicity, cardiotoxicity and embryofetal toxicity (noting the US PI includes black box warnings about these risks).

A proposed condition of registration about the RMP was:

The Australian RMP Version: 1.0 dated October 2012, to be revised as specified in the sponsor's correspondence dated 29 April 2013 with an amended Pharmacovigilance Plan satisfactory to the TGA, must be implemented.

A condition of registration for PSURs was also recommended.

Risk-benefit analysis

Efficacy: choice of comparator

In the study that assessed lapatinib + capecitabine in advanced breast cancer,²³ dosing in the combination arm was lapatinib 1250 mg per day plus capecitabine 1000 mg/m² BD on Days 1-14 of a 21 day cycle. This is consistent with dosing in the comparator arm in EMILIA.

The sponsor notes:

Virtually all patients with HER2 positive MBC will eventually develop progressive disease (PD) on or following trastuzumab based therapy for their metastatic disease. In clinical practice, subsequent lines of therapy often consist of a HER2 directed agent (for example, lapatinib or trastuzumab) with chemotherapy. However, there is only one regimen that is approved specifically for patients with HER2 positive MBC whose tumours have progressed following trastuzumab and a taxane: the combination of lapatinib and capecitabine.

NCCN guidelines address preferred regimens for trastuzumab exposed HER2 positive tumour patients. The recommendation is to continue HER2 blockade for patients with HER2 positive MBC that progresses on first line trastuzumab containing regimens. Setting aside Kadcyra itself, options canvasses are: pertuzumab + trastuzumab, with or without a taxane or vinorelbine; or, capecitabine + lapatinib.

It could be argued that the comparator arm should have included, as well, trastuzumab, but this would not reflect approved use. It could also be argued that in the subset of patients with disease progression in the (neo)adjuvant setting, the comparator regimen is not 'first-line' for metastatic disease.

On balance, choice of the comparator arm in EMILIA is appropriate.

Efficacy: elderly patients

Patients in the age range 65 to <75 yrs had an attenuated PFS benefit (point estimate of HR, 0.88) and also an attenuated OS benefit (HR = 0.94).

Patients of age ≥75 yrs had no PFS benefit (point estimate of HR, 3.51, 95% CI 1.22-10.13) and no OS benefit (HR 4.22, 95% CI 0.97-18.30) (the HR was 3.45 [0.94-12.65] at the second interim analysis).

There were no patients 85 yrs of age or over.

It may be that the fraction of target patients >75 yrs of age in the community would be higher than in this study (2.5%).

Although the PFS and OS outcomes both pointed to lack of benefit in the elderly, to the extent that differences were often statistically significant despite the low number of subjects involved, the Delegate considers this issue would be best managed by inclusion of text as a Precaution in the PI.

Pharmaceutical chemistry free maytansinoids

The shelf life limit for free maytansinoids is an issue. Free maytansinoids consist mainly of MCC-DM1 and minor amounts of DM1, DM1 dimer and the methyl ester of MCC-DM1. There will be batch release testing.

²³ Geyer CE, et al. (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 355: 2733-2743 (correction published 2007; 356:1487).

Name

The US FDA has issued a drug safety communication warning prescribers not to confuse “ado-trastuzumab emtansine” with “trastuzumab”. The warning specifies that use of the term “trastuzumab emtansine” may result in confusion with “trastuzumab”. This issue was picked up by ACSOM; advice was to consider whether a similar naming convention should be adopted here (and to ensure that outer packaging distinguishes Kadcyra from trastuzumab products). The Delegate proposes inclusion of a black box warning.

CNS disease

Patients with active CNS disease were excluded from study.

Indication

The sponsor’s proposed indication is:

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

The sponsor’s proposed indication could be interpreted as equating to second line use. In the US indication, the target population is clearer (“patients with HER2 positive MBC who previously received trastuzumab and a taxane, separately or in combination”). The US indication is restricted to metastatic disease. In the pivotal study, a wide range of patients were included, including some who had not received treatment for metastases (but who had relapsed early after [neo]adjuvant use of trastuzumab + taxane).

The indication does not reflect the fact that the subset of 118 EMILIA patients who had only previously received (neo)adjuvant trastuzumab + taxane had early progressive disease. Thus, the indication could be taken to include patients who had only received (neo)adjuvant trastuzumab + taxane, who perhaps even responded for a considerable time, but who developed MBC. This group, or at least an overlapping group, of patients has been assessed in randomised study TDM4450g/B021976. On balance, the Delegate supports the wording proposed by the sponsor.

Overall risk-benefit

Kadcyla has a strongly positive benefit-risk profile relative to lapatinib + capecitabine in the proposed target population. Not only is efficacy demonstrably better (to the extent that OS is improved by a clinically significant amount), but tolerability is better (admittedly in large part due to the absence of docetaxel’s effect on neutrophil count) and patients seems to experience a better quality of life.

Proposed action

The Delegate proposes to approve the application using the sponsor’s proposed indication.

The advice of the Advisory Committee on Prescription Medicines (ACPM) is requested. Specifically:

- What is the ACPM’s view of the benefit-risk balance of Kadcyla?
- What is the ACPM’s view of the indication wording proposed by the sponsor (for example, in comparison with the US PI indication)?
- Does the ACPM have any suggestions to improve the PI or CMI (for example, in relation to information about hepatotoxicity, cardiotoxicity and/or embryofoetal toxicity; and in relation to the proposed black box warning about distinguishing Kadcyla from Herceptin)?
- Does the ACPM favour re-naming trastuzumab emtansine as, for example, ado-trastuzumab emtansine, to minimise medication errors?

Response from sponsor

Sponsor comment on the benefit-risk balance

The sponsor agrees with the TGA Delegate that the data supports a favourable benefit-risk balance for Kadcyla as a treatment for HER2 positive, unresectable locally advanced or metastatic breast cancer patients.

Kadcyla is the first single agent therapy for metastatic breast cancer that has shown greater efficacy together with improved tolerability and quality of life compared with conventional combination therapies. Kadcyla has demonstrated a statistically significant and clinically meaningful OS benefit in HER2 positive, unresectable locally advanced or metastatic breast cancer patients. At the second OS interim analysis (cut off date 31 July 2012), a HR of 0.682 (95% CI: 0.548, 0.849; $p = 0.0006$) was observed and this result crossed the efficacy stopping boundary. The median duration of survival was 25.1 months in patients treated with lapatinib plus capecitabine, compared with 30.9 months in patients treated with trastuzumab emtansine. The OS benefit of Kadcyla was consistent across the majority of patient subgroups studied, and across all lines of therapy. The clear OS benefit is consistent with the results of the primary analysis of the other co primary endpoint PFS by independent review, for which there was a significant improvement in PFS associated with Kadcyla (HR = 0.65, $p < 0.0001$; median 9.6 versus 6.4 months).

The sponsor acknowledges that there are important identified risks associated with Kadcyla treatment that must be monitored. However, the sponsor believes the significant benefit observed with Kadcyla outweighs the risks in support of the proposed indication.

Sponsor comment on the indication

The sponsor proposes to align the Australia indication with the FDA approved indication:

Kadcyla, as a single agent, is indicated for the treatment of patients with HER2 positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- *Received prior therapy for metastatic disease, or*
- *Developed disease recurrence during or within six months of completing adjuvant therapy.*

The TGA Delegate “on balance” supported the proposed indication wording; however, noted that, “the target population is clearer in the US indication (patients with HER2+ MBC who previously received trastuzumab and a taxane, separately or in combination)”. Based on similar feedback from US prescribers, and to better align with the proposed Pharmaceutical Benefits Scheme (PBS) restriction (concurrent submission under evaluation: Pharmaceutical Evaluation Branch (PEB) had no major objections), the sponsor proposes to adopt the FDA approved indication.

Furthermore, the indication will be harmonised with New Zealand as Medsafe requested the sponsor adopt the FDA approved indication (consent expected July 2013).

Comment on the Delegate’s specific request: PI, CMI and black box warning

Does the Committee have any suggestions to improve the PI or CMI (for example, in relation to information about hepatotoxicity, cardiotoxicity and/or embryofoetal toxicity; and in relation to the proposed black box warning about distinguishing Kadcyla from Herceptin)?

Sponsor comment:

As per the sponsor’s response to a similar question regarding justification of the omission of black box warnings for hepatotoxicity, cardiotoxicity and/or embryofoetal toxicity from

product labelling, the sponsor does not believe black box warnings are necessary for the Australian PI. This was deemed acceptable by the TGA Delegate and OPR (RMP) evaluator.

The sponsor acknowledges the ACSOM recommendation that similar information contained in the USPI black box warnings be added to the Australian PI. To address this request, the sponsor has proposed additional text for the 'Precautions' section in addition to the Delegate's proposed edits. Additionally, the sponsor has proposed further information to the CMI about the potential implications for future pregnancies in accordance with the Delegate's recommendation.

With regards to the proposed black box warning to distinguish Kadcyra from Herceptin, the sponsor does not believe that this is warranted. As per ACSOM (ref: TGA website):

"a black box warning on medicines is the most extreme warning available to the TGA to alert people to the possible side effects of a medicine".

Black box warnings are typically associated with very SAEs or precautions; however, the proposed black box for medication errors is a risk minimisation activity proposed for a potential risk (not an identified risk). While the sponsor confirms that six cases of medication error occurred with trastuzumab emtansine during clinical trials, it should be noted that these medication errors occurred with product labelled for clinical trials. Product labelled for clinical trials does not contain the trade name or specific distinguishing features to differentiate between the medicines as is described in the Kadcyra RMP.

In light of the distinctive packaging and precautionary statements included in the PI as outlined below, the sponsor does not agree that the addition of the proposed boxed warning is warranted for the Kadcyra PI.

Dosage and Administration section:

"In order to prevent medication errors it is important to check the vial labels to ensure the medicine being prepared and administered is Kadcyra (trastuzumab emtansine) and not trastuzumab (Herceptin)."

In addition, to improve traceability of AEs, but also to reinforce the distinct trade name of the prescribed product:

"In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record."

Comment on the Delegate's specific request: Re-naming trastuzumab emtansine

Does the Committee favour re-naming trastuzumab emtansine as, for example, ado-trastuzumab emtansine, to minimise medication errors?

Sponsor comment:

The sponsor does not support re-naming trastuzumab emtansine as a measure to reduce medication errors.

The FDA issued a Drug Safety Communication (DSC) on 6 May 2013 regarding the potential for confusion between the US Adopted Name (USAN) for Herceptin (trastuzumab) and Kadcyra (trastuzumab emtansine). Whilst the FDA issues Drug Safety Communications to inform health care providers, patients, and consumers about newly observed potential risks of FDA approved medicines, the FDA confirmed that this communication was part of the Agency's ongoing efforts to help proactively avoid potential medication errors; and was not a reaction to a new issue.

As outlined in the dossier, six cases of medication error occurred with trastuzumab emtansine during clinical trials. However, it should be noted that these medication errors occurred with product labelled for clinical trials, which had no trade name or specific

distinguishing features to differentiate the various products. The sponsor has taken proactive measures, such as distinctive packaging of Kadcyla and the precautionary statements included in the PI, to prevent any potential medication errors caused by name confusion post-approval. The sponsor believes the commercial packaging adequately distinguishes between Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab) as well as between the two strengths of Kadcyla and Herceptin.

The sponsor also wishes to note to ACPM that the TGA has proposed to Industry (as per consultation document entitled: "International Harmonisation of Ingredient Names - Consultation paper" released May 2013, closed for consultation July 10, 2013) that the Australian nomenclature (ABN/AAN) be aligned with the International Non-proprietary Name (INN). The sponsor confirms that the INN for Kadcyla is trastuzumab emtansine, including in the US where the ado prefix has been implemented on the packaging but the USAN remains trastuzumab emtansine.

Further sponsor comment for ACPM: Thrombocytopenia in Asian patients

As noted by ACSOM, there are ethnic variations associated with the risk of thrombocytopenia, particularly in Asian patients compared with non-Asian patients (48.2% compared with 17%). ACSOM advised that additional Pharmacovigilance activities should be considered to monitor this risk 'Thrombocytopenia'. The sponsor should adequately address the committee's concerns preferably before this application is approved.

Sponsor comment:

The sponsor acknowledges the higher incidence of thrombocytopenia observed in Asian patients as compared to non-Asian patients. While additional Pharmacovigilance activities are not planned to specifically address thrombocytopenia in Asian patients, the sponsor performs cumulative assessments of thrombocytopenia, stratified by race, when such data are available.

As recommended by the Delegate, the sponsor has added additional information to quantify the risk of Grade ≥ 3 thrombocytopenia in Asian versus non-Asian subjects. The sponsor considers these measures to be adequate to monitor and communicate this important risk to prescribers.

Conclusion

In response to the Delegate's overview and recommendation, the sponsor has proposed to align the Australian indication with the FDA approved indication to clarify the patient population and to add text to the 'Precautions' section and CMI as recommended. However, alternative views have been provided on points in which the sponsor did not agree; namely, the addition of a black box warning or re-naming trastuzumab emtansine as measures to prevent medication error. Overall, the sponsor agrees with the Delegate's assessment that the magnitude of efficacy benefit, the improvements in patient reported outcomes, and the consistent favourable safety profile reported for patients who received trastuzumab emtansine combine to give a positive benefit-risk ratio in support of the proposed indication.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Kadcyla powder for injection containing 100 mg and 160 mg of trastuzumab emtansine to have an overall positive benefit-risk profile for the indication as proposed:

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

The ACPM advised that from a toxicity standpoint, trastuzumab emtansine (T-DM1) must not be given concurrently with trastuzumab. The drug name was modified to ado-trastuzumab emtansine by US regulators to reduce the risk of prescribing and dispensing errors. The ACPM advised that if the sponsor decides not to modify the name of the drug substance, the only alternative that could be acceptable, given the risk, is a black box warning.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI, and specifically advised on the inclusion of the following:

- A statement in the 'Precautions' section of the PI and relevant sections of the CMI to reference the liver toxicity to ensure close monitoring is undertaken.
- Suitable statements in the PI and CMI to warn of CYP3A4 interactions including:
 - antidepressants which are CYP3A4 inhibitors
 - dietary products such as supplements, grapefruit and noni fruit, the juice of which is popular among cancer patients. Goji fruit and juice is likely to fall into a similar category. All of which may not be mentioned to their treating doctor.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Kadcyla powder for intravenous infusion containing trastuzumab emtansine 100 mg and 160 mg, indicated for:

Kadcyla, as a single agent, is indicated for the treatment of patients with HER2 positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- *Received prior therapy for metastatic disease or,*
- *Developed disease recurrence during or within six months of completing adjuvant therapy.*

Specific conditions of registration applying to these therapeutic goods

- The Australian Risk Management Plan Version: 1.0 dated October 2012, or subsequent versions, accepted by the TGA's Office of Product Review, must be implemented.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>