CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125427Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA	125427
Submission Date:	August 23, 2012
Brand Name:	Kadcyla®
Generic Name:	Trastuzumab emtansine (T-DM1)
Formulation:	160 mg lyophilized single use vial (20 mg/ml after reconstitution) for intravenous infusion
OCP Reviewer:	Sarah J. Schrieber, PharmD
OCP Team Leader:	Qi Liu, PhD
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Pharmacometrics Team Leader:	Nitin Mehrotra, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	DOP1
Sponsor:	Genentech
Submission Type; Code:	NME/0000/1
Dosing regimen:	T-DM1 3.6 mg/kg IV every 3 weeks.
Indication:	For the treatment of patients with HER2-positive, (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane

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1 Executive Summary

Trastuzumab emtansine (T-DM1, xxx-trastuzumab emtansine) is a HER-2-directed antibody-drug conjugate (ADC). T-DM1 is comprised of an anti-HER2 monoclonal antibody (trastuzumab) linked to the small molecule emtansine (DM1). The applicant seeks approval for T-DM1 as a single agent for the treatment of patients with HER2-positive (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

One phase 3 trial TDM4370g was conducted to support the proposed indication at a dose of 3.6 mg/kg T-DM1 given as an intravenous infusion over 30 minutes once every three weeks (q3w). It was a randomized (1:1), open-label, active-control, multi-center trial in patients with HER2+ metastatic breast cancer after prior trastuzumab and taxane treatment (N=951). Overall survival (OS) and progression free survival (PFS) were significantly longer in the T-DM1 arm compared to the active control arm (lapatinib plus capecitabine). After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with better efficacy (OS, PFS, and objective response rate (ORR)). Exposure-response relationships for safety identified an inverse trend for Grade 3 or worse hepatotoxicity, but no significant exposure-response relationships were identified for thrombocytopenia.

A population PK analysis estimated the T-DM1 clearance and terminal elimination half-life as 0.68 L/day and ~4 days, respectively. Statistically significant covariates for T-DM1 PK parameters identified included: sum of longest diameter of target lesions by RECIST, albumin, HER2 extracellular domain (ECD) concentrations, baseline trastuzumab concentrations, AST, and body weight. However, the magnitude of effect for these covariates on T-DM1 exposure indicates that no dose adjustment is required. Based on the population PK analysis, as well as analysis of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments are not needed for mild or moderate renal impairment. The influence of hepatic impairment on the PK of T-DM1 or DM1 has not been determined. *In vitro* studies indicate that DM1, the cytotoxic component of T-DM1, is metabolized mainly by CYP3A4. Concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity. No large changes in the mean QT interval (i.e., >20 ms) were detected at the proposed T-DM1 dosing regimen.

The overall incidence of positive anti-therapeutic antibody (ATA) to T-DM1 was determined to be 5.3% in the studies included in the BLA with the assays used.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in BLA 125427. This BLA is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

Phase IV Requirements
The Office of Clinical Pharmacology recommends one Post Marketing Requirements (PMR) and one Post Marketing Commitments (PMC).

PMR #1: Evaluate the impact of hepatic impairment on KADCYLA (xxx-trastuzumab emtansine conjugate, total trastuzumab, and DM1 containing catabolites) pharmacokinetics; consequently update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment.

PMC #1: To conduct xxx-trastuzumab emtansine conjugate exposure-response analyses for progression free survival, final overall survival, and safety endpoints utilizing data from trial BO25734/TDM4997 (TH3RESA). Evaluation of the results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will determine the need, or otherwise, for a postmarketing trial to optimize the dose in metastatic breast cancer patients with lower xxx-trastuzumab emtansine conjugate exposure at the approved dose (3.6 mg/kg q3w).

1.2 Summary of Clinical Pharmacology Findings

Trastuzumab emtansine (T-DM1, xxx-trastuzumab emtansine) is a HER-2-directed antibody-drug conjugate (ADC) consisting of trastuzumab, a humanized anti-HER2 IgG1 isotype monoclonal antibody, emtansine (DM1), an anti-microtubule agent derived from maytansine, and SMCC, a linker molecule used to conjugate DM1 to trastuzumab.

Mechanism of Action: The mechanism of action of T-DM1 consists of a multi-step process. T-DM1 binds to HER2 then undergoes receptor-mediated internalization, which results in the intracellular release of DM1 and subsequently cell death.

Efficacy: The proposed indication is for the treatment of patients with HER2-positive, (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane. One phase 3 randomized (1:1), open-label, active-control trial was conducted to support the proposed indication at a dose of 3.6 mg/kg T-DM1 given as an intravenous infusion over 30 minutes once every three weeks. Overall survival (OS) and progression free survival (PFS) were significantly longer in the T-DM1 arm compared to the active control arm (lapatinib plus capecitabine).

Exposure-Response (Efficacy and Safety): After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with better efficacy (OS, PFS, and objective response rate (ORR)). Exposure-response relationships for safety identified an inverse trend for Grade 3 or worse hepatotoxicity, but no significant exposure-response relationships were identified for thrombocytopenia.

Pharmacokinetics (PK): Data on the PK of T-DM1, total antibody, and DM is available from one phase 1 trial, four phase 2 trials, and one phase 3 trial. A population PK analysis estimated the T-DM1 clearance and terminal elimination half-life as 0.68 L/day and ~4 days, respectively; inter-individual variability of CL is 19.1%. T-DM1 accumulation was not observed following multiple dosing. No dose adjustments are required for significant covariates (sum of longest diameter of target lesions by RECIST, albumin, HER2 ECD concentrations, baseline trastuzumab concentrations, AST, and body weight). Based on the population PK analysis, as well as analysis

of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments are not needed for mild or moderate renal impairment. The influence of hepatic impairment on the PK of T-DM1 or DM1 has not been determined. *In vitro* studies indicate that DM1, the cytotoxic component of T-DM1, is metabolized mainly by CYP3A4. Concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity.

Immunogenicity: With the immunogenicity assays used, the overall incidence of positive anti-therapeutic antibody (ATA) to T-DM1 was determined to be 5.3% in the studies included in the BLA. The presence of T-DM1 in patient serum at the time of ATA sampling can interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-T-DM1 antibody development. In addition, neutralizing activity of anti-T-DM1 antibodies has not been assessed.

QT: No large changes in the mean QT interval (i.e., >20 ms) were detected at the proposed T-DM1 dosing regimen.

Signatures:

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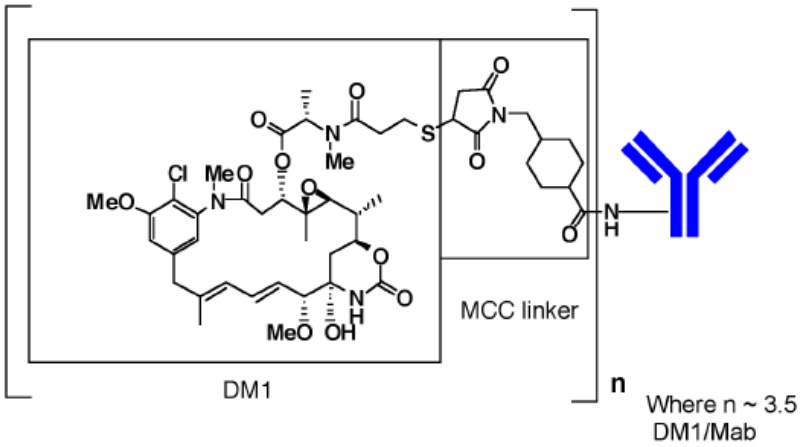
2 QUESTION BASED REVIEW
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Trastuzumab emtansine (T-DM1) is a HER-2-directed antibody-drug conjugate (ADC) consisting of three components:

- Trastuzumab, a humanized anti-HER2 IgG1 isotype monoclonal antibody
- Emtansine (DM1), an anti-microtubule agent derived from maytansine
- SMCC, a linker molecule used to conjugate DM1 to trastuzumab.

Figure 1. Structural Formula of T-DM1.



Note: The bracketed structure is DM1 plus MCC. The n is on average 3.5 per trastuzumab molecule.

The average drug-to-antibody molar ratio (DAR) is 3.5 (range: 0 - 8). The molecular weight (MW) of DM1 is 737.5 Da, and the MW of T-DM1 is ~148,781 Da.

T-DM1 is a sterile, preservative-free, white to off-white, lyophilized cake supplied in 100 mg and 160 mg single-use vials. T-DM1 drug product (DP) is reconstituted with the volume of Sterile Water for Injection to yield a solution containing 20 mg/mL and is further diluted for intravenous (IV) infusion. The reconstituted T-DM1 DP is clear to slightly opalescent colorless solution with no visible particulate matter. Each vial contains T-DM1 and the excipients sodium succinate, sodium hydroxide, sucrose, and polysorbate 20. The pH of the reconstituted product is 5.0.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

The mechanism of action of T-DM1 is a multi-step process. T-DM1 inhibits shedding of the HER2 extracellular domain (ECD), inhibits signaling of the HER2 receptor, and mediates antibody-dependent cell-mediated cytotoxicity in human breast cancer cells that overexpress HER2. Upon binding to HER2, T-DM1 undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which induces cell cycle arrest and apoptotic cell death.

The proposed indication is for T-DM1 as a single agent, for the treatment of patients with HER2-positive, [redacted] (b) (4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes a T-DM1 dosing regimen of 3.6 mg/kg as an intravenous (IV) infusion over 30 minutes once every 3 weeks (q3w).

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A summary of completed clinical trials with T-DM1 to support the BLA application is shown in Table 1.

Table 1. Summary of completed clinical trials with T-DM1 to support the BLA application.

Study Number	Study Design	Primary Objectives	No of Subjects	Treatment Regimen
TDM3569g	Open-label, phase 1 study of T-DM1 in patients with HER2-positive MBC	Safety and tolerability (incidence of DLTs), PK	52	Three-weekly dosing: 0.3, 0.6, 1.2, 2.4, 3.6, 4.8 mg/kg IV Weekly dosing: 1.2, 1.6, 2.0. 2.4, 2.9 mg/kg IV
TDM4258g	Open-label, single-arm, phase 2 study of T-DM1 in patients who have progressed while receiving HER2-directed therapy	Safety, efficacy (ORR, PFS, DoR), PK	112	3.6 mg/kg IV q3w until PD or unacceptable toxicity
TDM4374g	Open-label, single-arm, phase 2 study of T-DM1 in patients with HER2-positive MBC	Safety, efficacy (ORR, PFS, DoR), PK	110	3.6 mg/kg IV q3w until PD or unacceptable toxicity
TDM4450g / BO21976	Open-label, randomized, 2-arm, phase 2 study to evaluate efficacy and safety of T-DM1 vs. trastuzumab and docetaxel	Efficacy (PFS, ORR, DoR, CBR), Safety	137	Arm A: T-DM1 3.6 mg/kg IV q3w Arm B: trastuzumab 8 mg/kg IV (loading dose) then 6 mg/kg IV + docetaxel 75 or 100 mg/m^2 IV q3w
TDM4688g	Open-label, single-arm, phase 2 study of T-DM1 in patients with HER2-positive LABC or MBC. Patients with early progression may then receive pertuzumab with T-DM1	Effect of T-DM1 on corrected QT interval, Safety and tolerability, Efficacy (ORR, PFS, DoR, CBR)	51	T-DM1 (as single agent or combined with pertuzumab): 3.6 mg/kg IV q3w Pertuzumab: 840 mg/kg IV (loading dose) then 420 mg/kg IV q3w

Study Number	Study Design	Primary Objectives	No of Subjects	Treatment Regimen
TDM4370g / BO21977	Open-label, randomized, 2-arm, phase 3 study of T-DM1 vs. capecitabine + lapatinib in patients with HER2-positive LABC or MBC	Efficacy (PFS, OS, ORR, DoR), Safety	991	Arm A: T-DM1 3.6 mg/kg IV q3w Arm B: Lapatinib 1250 mg/day po qd and capecitabine 1000 mg/m^2 po bid on days 1−14 of a 21-day cycle

2.2.1.1 Registration Clinical Trial

A single phase 3 trial in patients with HER-2 breast cancer was conducted to support the efficacy and safety of T-DM1.

The trial was a phase 3 randomized (1:1), open-label, multi-center study in patients with HER2+ MBC after prior trastuzumab and taxane treatment (N=951).

- Treatment Arm A included T-DM1 3.6 mg/kg IV q3w monotherapy.
- Treatment Arm B included Lapatinib 1250 mg/day po qd and capecitabine 1000 mg/m^2 po bid on days 1−14 of a 21-day cycle.

The co-primary efficacy endpoints of the study were progression-free survival (PFS) based on tumor response assessments by an independent review committee (IRC), and overall survival (OS)., Additional endpoints included PFS (based on investigator tumor response assessments), objective response rate (ORR), duration of response and time to symptom progression. The sponsor's reported primary results are as follows:

- PFS results: T-DM1 9.6 mo; cap/lap 6.7 mo
  - HR 0.650 [95% CI (0.55, 0.77); 1-sided p<0.0001]
- OS results: T-DM1 30.9 mo; cap/lap 25.1 mo
  - HR 0.682 [95% CI (0.548, 0.849); 1-sided p<0.0006]

2.2.1.2 Clinical Pharmacology Studies

Data on the pharmacokinetics of T-DM1 is available from one phase 1 trial, four phase 2 trials, and one phase 3 trial, as listed in Table 1. Trials enrolled patients with HER-2 positive metastatic breast cancer. The clinical pharmacology program characterized the PK of three analytes using traditional and population methods:

- ADC- T-DM1 ADC
- TAb: Total antibody (ADC plus unconjugated trastuzumab)
- DM1: Released small molecule drug

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoints in the clinical trial used to support the BLA application were progression free survival (PFS) and overall survival (OS).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Three analytes were measured to characterize the PK of T-DM1: ADC, DM1, and Tab. ADC and Tab were measured in serum by enzume-linked immunosorbant assays (ELISA). DM1 was measured in plasma by liquid chromatography and tandom mass spectrometry (LC-MS/MS).

2.2.4 Exposure Response

2.2.4.1 Does the exposure-response relationship for efficacy identify a subgroup of patient population that may benefit from dose optimization?

Yes, patients with lower exposures may benefit from an increase in dose. After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with better efficacy in terms of overall survival (OS) and progression free survival (PFS) (co-primary endpoints), as well as the secondary endpoint objective response rate (ORR) (trial TDM4370g).

Overall survival (OS)

OS was a co-primary efficacy endpoint of the phase 3 trial TDM4370g, where T-DM1 was dosed 3.6 mg/kg IV q3w. Population PK predicted T-DM1 trough concentration on Day 21 in Cycle 1 ($C_{min,C1D21}$) was available for 68.2% patients (N=334) in the T-DM1 arm (N=490). Kaplan-Meier survival analysis was performed with these patients stratified according to quartiles of $C_{min,C1D21}$ (≤1.29, 1.29–1.99, 1.99–2.75 and >2.75 µg/mL) or median value and the result is shown in Figure 2. The survival curve of patients without PK data lies between the less than median and greater than median exposure group indicating that the population used for exposure-response analysis is representative of the overall patient population (Figure 1, Panel B).

A significant difference in survival was observed for patient groups divided according to quartiles of $C_{min,C1D21}$ (log rank test P<0.0001). The median [95% CI] survival time for patients within the lowest quartile of concentrations was 15.3 months [5.6–10.1 months], which is 8 months shorter than the median survival time for patients treated with lapatinib plus capecitabine. The median survival for patients with trough concentrations within other quartiles could not be estimated since these quartiles did not cross 50% survival cutoff. Since Kaplan Meier is a univariate analysis and the difference in survival in these exposure quartiles may be confounded by other covariates, cox-proportional hazard analysis was conducted.

Figure 2. Kaplan-Meier curve of overall survival (OS) for the T-DM1 arm (N=490) by quartiles (Panel A) or median (Panel B) of $C_{min, C1D21}$ and for the active control arm (N=488) of the study TDM4370g/BO21977.
The numbers in the right figure shows the median survival with 95% confidence interval.

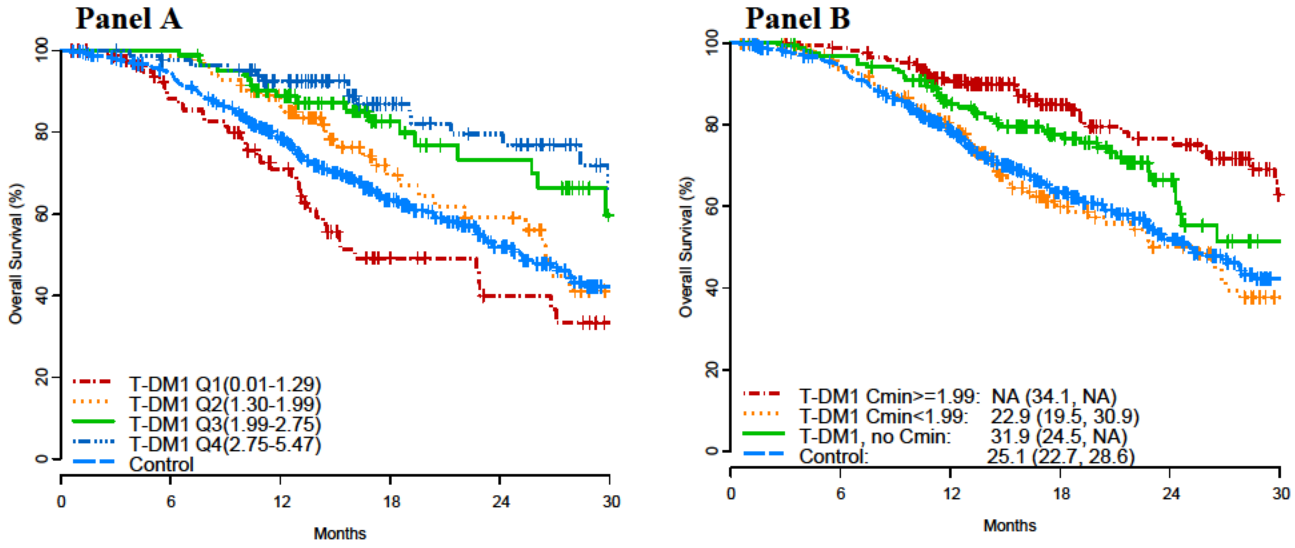


Table 2 shows the comparison of distribution of these risk factors between each quartile group and the comparator group. Comparing the key covariates at baseline of quartiles, it appears that Quartile 1 and Quartile 2 are imbalanced with higher HER2 ECD shed antigen concentration, worse ECOG score, more measurable disease, more visceral disease, and higher tumor burden (Table 2), which may, along with low T-DM1 exposure, account for the less improved efficacy within the Q1 and Q2.

Table 2. Summary of covariates and exposure for patients per quartile of predicted T-DM1 trough concentration on Day 21 in Cycle 1 ($C_{min,C1D21}$).
Standard of care (SOC) is the lapatinib plus capecitabine.

Parameter	SOC	TDM1	Q1	Q2	Q3	Q4
N	488	490	84	83	83	84
PK Patient (Yes/No)	0/488	307/183	76/8	74/9	77/6	79/5
Age (yr)	53 [11]	52 [11]	53 [10]	53 [13]	51 [10]	51 [11]
Weight (kg)	71 [19]	69 [14]	67 [15]	70 [16]	69 [12]	71 [13]
Race (White/Asian/Other)	367/85/36	355/92/43	58/18/8	48/24/11	62/16/5	65/10/9
HER2 ECD (ng/mL)	60 [121]	86 [248]	227 [517]	63 [90]	33 [50]	38 [56]
ECOG (0/1)	308/172	248/159	43/41	51/32	55/28	61/23
Prior Chemo (<=1/>1/NA)	18/404/66	15/409/66	4/71/9	3/74/6	2/70/11	1/66/17
Liver metastasis (Yes/No)	190/292	207/280	49/34	35/47	23/60	36/48
Measurable Disease (Yes/No)	386/102	392/98	75/9	72/1	52/31	64/20
Visceral Disease (Yes/No)	328/160	329/161	63/21	59/24	45/38	49/35
Tumor burden (cm)	14.77 [12.24]	14.54 [10.93]	19.75 [12.35]	14.57 [9.66]	15 [10]	10.47 [10.31]

Parameter	SOC	TDM1	Q1	Q2	Q3	Q4
Albumin (g/L)		41.3 [4.32]	39.79 [4.91]	41.12 [4.19]	41 [4]	42.13 [3.83]
Trastuzumab baseline (ug/mL)		10.79 [19.31]	4.8 [8.64]	8.04 [14.4]	8 [14]	19.29 [25.37]
AST (U/L)		28.76 [14.55]	36.17 [20.98]	28.94 [12.62]	25.1 [9.84]	24.73 [8.33]

Cox regression analysis identified four significant baseline risk factors for survival status:

- Baseline HER2 ECD (>=median, < median)
- ECOG performance status (>=1 vs. 0)
- Measurable disease (Yes vs. No)
- Tumor burden (>= median, < median).

Hazard ratio (HR) for each quartile of $C_{min,C1D21}$ vs. the control arm was estimated using a Cox proportional hazards model adjusted by the following baseline covariates:

- ECOG (0 vs. 1)
- Number of disease sites (< 3 vs. ≥3)
- Prior anthrocycline use (yes vs. no)
- Prior transtuzumab treatment (yes vs. no)
- Visceral disease (yes vs. no)
- Measuable disease (yes vs. no)
- Tumor burden
- HER2 shed antigen.

HRs decreased with increasing T-DM1 exposure (Table 3). However, it is noted that even the lowest quartile of $C_{min,\ C1D21}$ demonstrated a comparable OS with the active treatment arm (capecitabine + lapatinib).

Table 3. Hazard ratio (HR) for each of $C_{min,C1D21}$ quartiles vs. the active control arm (capecitabine + lapatinib) after adjusting baseline covariates including ECOG, number of disease sites, prior anthracycline use, prior transtuzumab treatment, visceral disease, measurable disease, HER2 ECD and tumor burden.

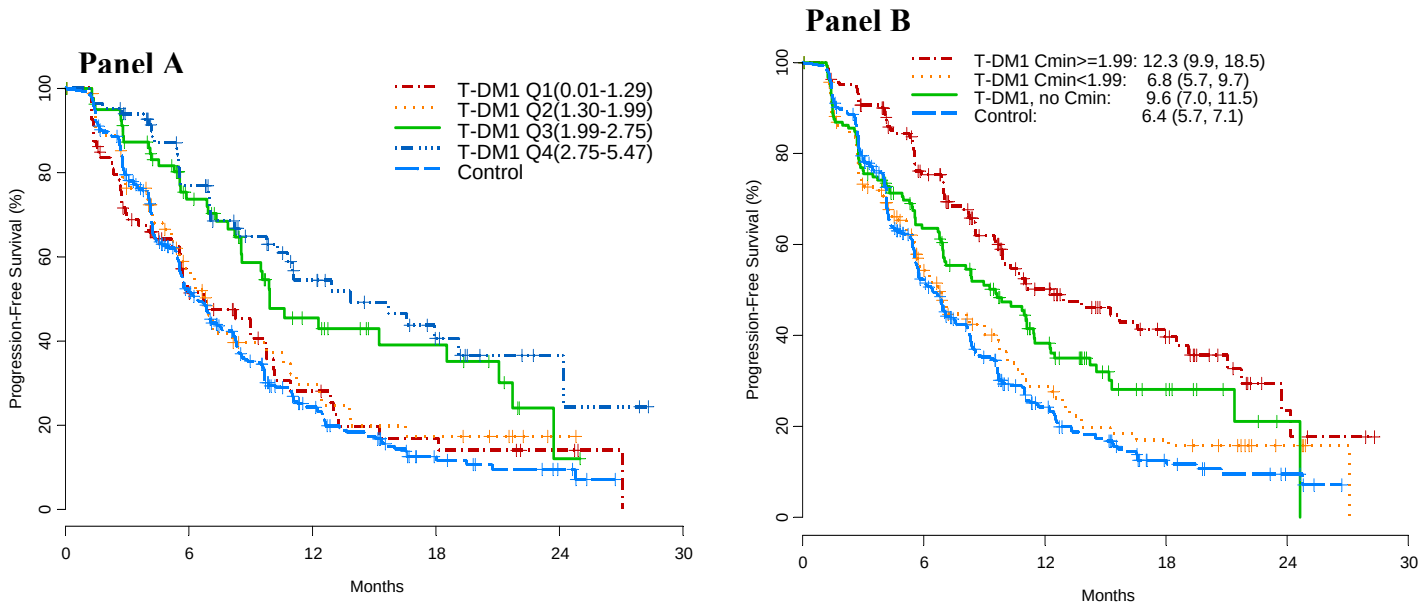
Efficacy Endpoint		HR (95% CI)	P-value
PFS	TDM1 Q1 vs. Control	0.82 (0.57, 1.16)	0.25
	TDM1 Q2 vs. Control	0.73 (0.52, 1.02)	0.066
	TDM1 Q3 vs. Control	0.57 (0.39, 0.83)	0.0032
	TDM1 Q4 vs. Control	0.36 (0.24, 0.53)	< 0.0001
OS	TDM1 Q1 vs. Control	0.97 (0.65, 1.46)	0.89
	TDM1 Q2 vs. Control	0.68 (0.44, 1.05)	0.080
	TDM1 Q3 vs. Control	0.40 (0.22, 0.72)	0.0024
	TDM1 Q4 vs. Control	0.35 (0.20, 0.63)	0.0005

Progression free survival (PFS)

Similar to the OS analysis described above, Kaplan-Meier survival analysis for PFS, the other co-primary efficacy endpoint in trial TDM4370g, was also performed with these patients stratified according to quartile of trough TDM1 concentrations in cycle 1 (≤1.29, 1.29–1.99, 1.99–2.75 and >2.75 µg/mL) or median value. The result is shown Figure 3. A significant difference in survival was observed for patient groups divided according to quartiles of $C_{min,C1D21}$

(log rank test P<0.0001). The median [95% CI] survival time for patients within the lowest quartile of $C_{min,C1D21}$ was 6.7 months [5.6–10.1 months], which is 3.2 months shorter than the median survival time for patients with concentrations within other quartiles. The median [95% CI] survival time for patients within less than median concentrations was 6.8 months [5.7–9.7 months], which is 5.6 months shorter than the median survival time for patients with concentrations within other quartiles. The PFS difference is not, however, attributed only to low concentrations but is also due to confounding risk factors in this subgroup. A similar trend was observed using steady state trough concentrations as the stratification factors in the Kaplan-Meier analysis.

Figure 3. Kaplan-Meier curve of PFS for the T-DM1 arm (N=490) by quartiles (Panel A) or median (Panel B) of $C_{min, C1D21}$ and for the active control arm (N=488) of the trial TDM4370g**.** The numbers in the right figure shows the median survival with 95% confidence interval.



A stepwise Cox regression model identified three significant baseline risk factors (p<0.01) for survival status:

- ECOG performance status (>=1 vs. 0)
- Measurable disease (Yes vs. No)
- Tumor burden (>= median, < median).

Hazard ratios (HR) were estimated for each of $C_{min,C1D21}$ quartiles vs. the control arm using a Cox proportional hazards model adjusted by the following baseline covariates:

- ECOG (0 vs. 1)
- Number of disease sites (< 3 vs. ≥3)
- Prior anthracycline use (yes vs. no)
- Prior trastuzumab treatment (yes vs. no)
- Visceral disease (yes vs. no)
- Measurable disease (yes vs. no)
- Tumor burden

HRs of PFS decreased with increasing exposure (Table 2). However, it is noted that even the

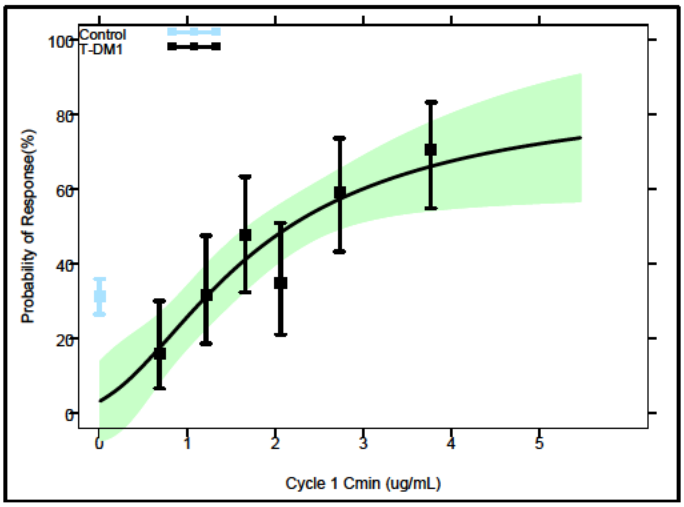
lowest quartile of $C_{min,\ C1D21}$ demonstrated a comparable PFS with the active treatment arm (capecitabine + lapatinib).

Objective Response Rate (ORR)

ORR was the secondary efficacy endpoint in trial TDM4370g. T-DM1 exposure $C_{min,C1D21}$ is significantly related with objective response rate ($P<0.01$) indicating higher exposures are related to better response rates (Figure 4).

A significant logistic regression relationship was identified between $C_{min,C1D21}$ and ORR using an E_{max} model. E_{max} logistic regression model were used as it appeared to reasonably describe the data (Figure 4). The objective response rates increases with exposure. Based on the model, the typical response rate for the median C_{min} of 1.98 µg/mL is 47% (95% CI: 40% to 54%). The EC50 is estimated ~1.5 µg/mL. This ORR analysis provides supportive evidence for a significant exposure-response relationship as it shows the same direction as OS and PFS.

Figure 4. The logistic regression analysis between ORR and T-DM1 $C_{min,C1D21}$ using an E_{max} model.
Solid black squares represent the proportion of responders grouped by quantiles of T-DM1 Cmin,C1D21 and plotted at the median for the groups. Solid blue square represents the response treated with active control (lapatinib plus capecitabine). Centered curves and shaded area represent predicted values and 95% of model predicted response probability, respectively.



Overall, the exposure-response analysis for efficacy indicated that the higher the T-DM1 exposure, the greater the OS or PFS improvement. Furthermore, T-DM1 exposure ($C_{min,C1D21}$) was significantly related to objective response rate (ORR, $P<0.01$), using a logistic regression analysis of an E_{max} model.

Refer to Appendix 4.1 for more information.

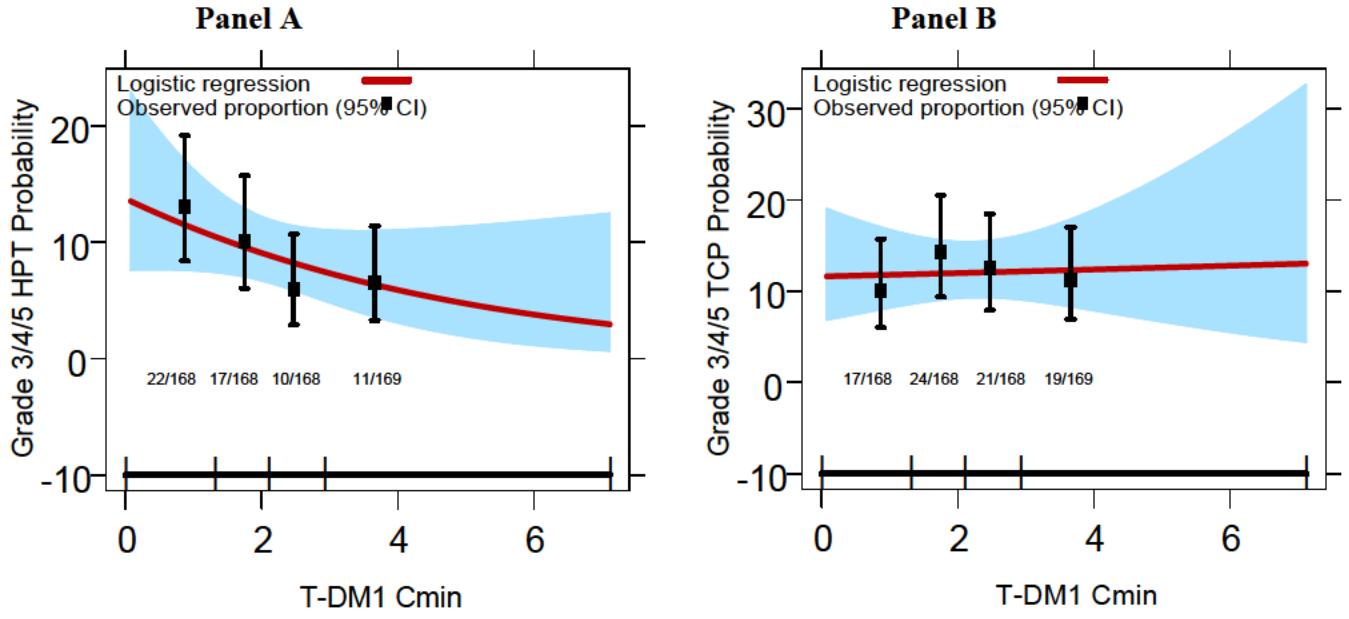
2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure-response relationships for safety identified an inverse trend for Grade 3 or worse (Grade 3+) hepatotoxicity (Figure 5, Panel A), but no significant exposure-response relationships were identified for thrombocytopenia (Figure 5, Panel B). The $C_{min, C1D21}$ were available in 673 patients including 334 patients in the phase 3 trial TDM4370g. The incidence of Grade 3 or worse adverse events (Grade 3+ AEs) in patients with low exposure (< median $C_{min, C1D21}$) is slightly higher than that in patients with high exposure (> median $C_{min, C1D21}$). The dose adjustments (including dose interruption, dose discontinuation, dose reduction) are similar across quartiles of $C_{min, C1D21}$. Compared to the control arm (capecitabine + lapatinib), T-DM1 treated patients has lower incidence of Grade 3+ AEs and lower rate of dose adjustments.

Individual toxicities

The most common adverse events leading to dose adjustments (including dose interruption, discontinuation, and reduction) were thrombocytopenia and hepatotoxicity (increased AST/ALT) in either the phase 3 trial TDM4370g, or all trials submitted in this BLA combined except for trial TDM4688g. Exposure-response analysis using a logistic regression model with $C_{min,C1D21}$ as the exposure variable were conducted for these individual toxicities. Results suggested that an inverse trend was identified for hepatotoxicity (Figure 5, Panel A), but not for thrombocytopenia (Figure 5, Panel B).

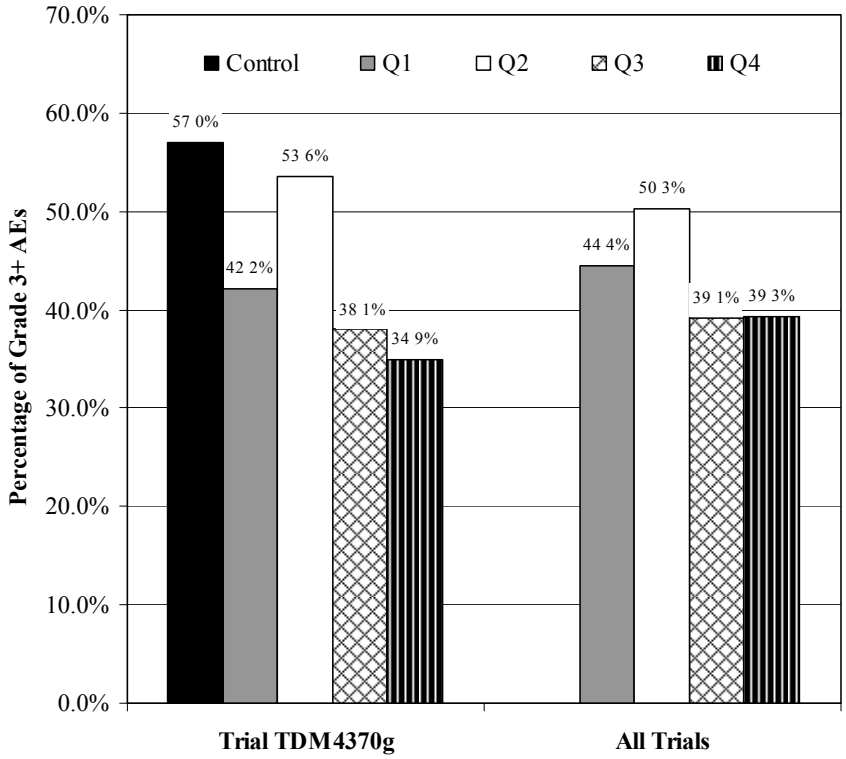
Figure 5. The relationship between Cmin, C1D21 and the incidence of ≥ Grade 3 hepatotoxicity (HPT) (Panel A) or thrombocytopenia (TCP) (Panel B) using logistic regression model.
Solid black symbols represent the observed proportion of patients experiencing ≥ Grade 3 AE in each quartile of $C_{min,C1D21}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 3 AE. The exposure range in each quartile of $C_{min,C1D21}$ is denoted by the horizontal black line along with the number of patients with AE/total number of patients in each quartile.



Grade 3+ AEs

Exposure-response analyses using $C_{min, C1D21}$ as the exposure variable were conducted for Grade 3+ AEs to evaluate whether the high exposure is related to the higher incidence of Grade 3+ AEs. A slightly higher incidence of Grade 3+ AEs was observed in patients with low exposure quartiles (Q1 and Q2), rather than in patients with high exposure (Q3 and Q4) (Figure 6). A plausible explanation is that the poorer baseline prognostic factors in these patients leads to more AEs. The incidence of Grade 3+ AEs in the control arm (capecitabine and lapatinib) is higher than that in T-DM1 arm.

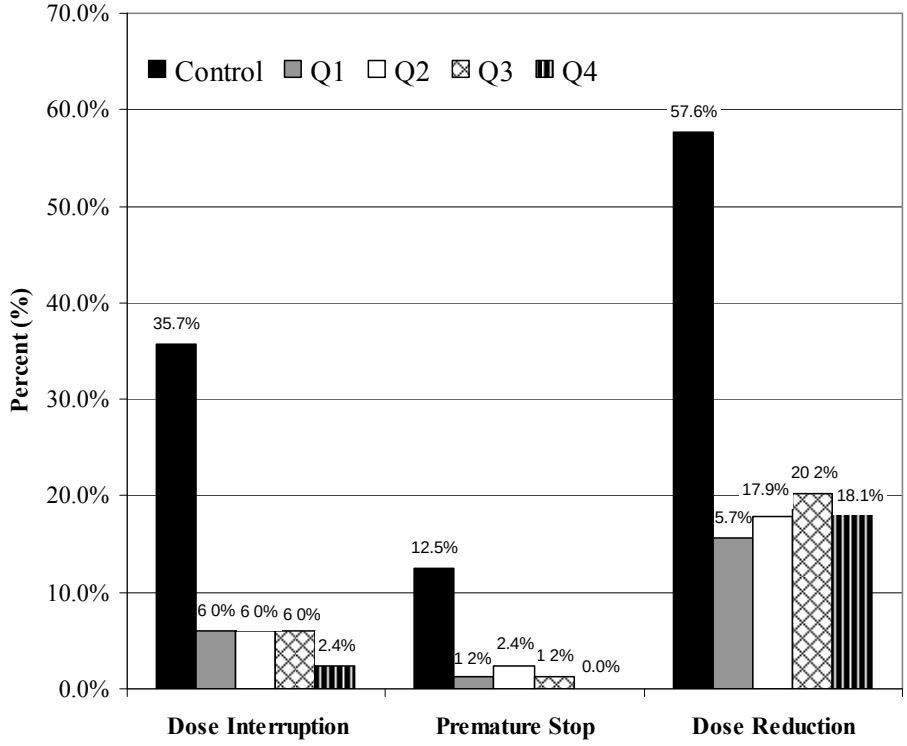
Figure 6. Incidence of Grade 3+ AEs in patients in trial TDM4370g (n=334) or in T-DM1 treated patients (n=673) with $C_{min, C1D21}$ available.



Dose adjustments

Actual dose adjustments in trial TDM4370g were stratified by the T-DM1 $C_{min, C1D21}$ to evaluate whether higher actual dose adjustments (dose interruption, early discontinuation, and dose reduction) are related with higher exposure. Results suggest that actual dose adjustments were similar across the quartiles of T-DM1 exposure (Figure 7). The dose adjustments occurred more frequently in the active control arm with capecitabine and lapatinib than T-DM1 arm.

Figure 7. Dose adjustments including dose interruption, premature stop, or dose reduction in patients in the trial TDM4370g.



See Appendix 4.1 for more information.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Study TDM4688g was an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer that assessed the effect of multiple doses of T-DM1 (3.6 mg/kg q3w) on the QTc. 12-lead ECGs were performed in triplicate and obtained at: screening (between Day -21 to Day -3); Cycle 1 Day 1: 30 and 15 minutes pre-dose, and 15 and 60 minutes post-dose; Cycle 1 Day 8 and Cycle 3 Day 1: 15 minutes pre-dose and 15 and 60 minutes post-dose. No large changes in mean QTc intervals (i.e. >20 ms) were detected following the treatment of T-DM1 administered by IV infusion every 3 weeks at a dose of 3.6 mg/kg. The largest upper bound of the 2-sided 90% CI for the mean QTc change from baseline was 7.73 ms observed 60 minutes post-dose on Day 1 of Cycle 3.

Further details can be found in the QT-Interdisciplinary Review Team Memo.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The following support the selection of the T-DM1 3.6 mg/kg IV q3w dose regimen:

- The maximum tolerated dose (MTD) was determined to be 3.6 mg/kg IV q3w in the phase 1 trial (Study TDM3569g).

- The safety and efficacy was demonstrated in the phase 3 trial (TDM4370g), as well as in supporting phase 2 trials.

The reviewers found that the body weight based dose of 3.6 mg/kg every 3 week is considered acceptable:

- Baseline body weight was identified as the significant covariate impacting T-DM1 steady state AUC and Cmax. The figures below show the covariate assessment of the impact of body weight on inter-individual random effects of PK parameters (Figure 8) and the expected T-DM1 exposures simulated from post-hoc PK parameters of patients using body weight based dosing regimen (Figure 9)
- Based on reviewer's model using power function, the exponential values of body weight effects on T-DM1 CL and central volume of distribution (V_c) using the power model were estimated to be 0.490 and 0.596, respectively.
- Considering that the T-DM1 MTD was established based on body weight-based dosing, and it has been used in clinical trials, the current body weight-based dosing of T-DM1 is acceptable.

Figure 8. Plots of CL vs. body weight (left) and V_c vs. body weight (right).

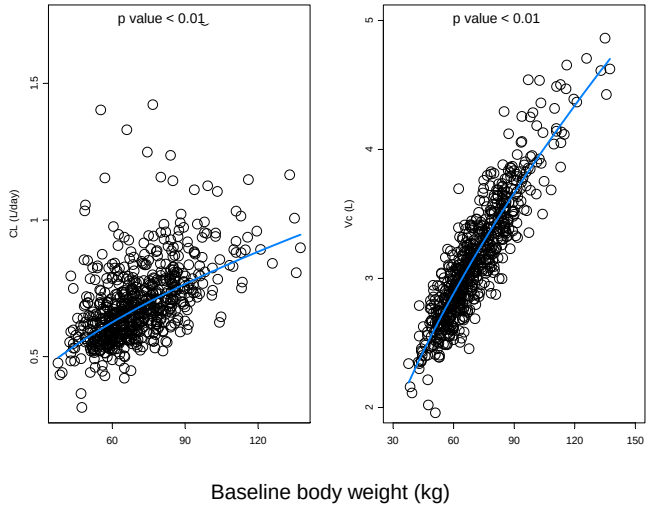
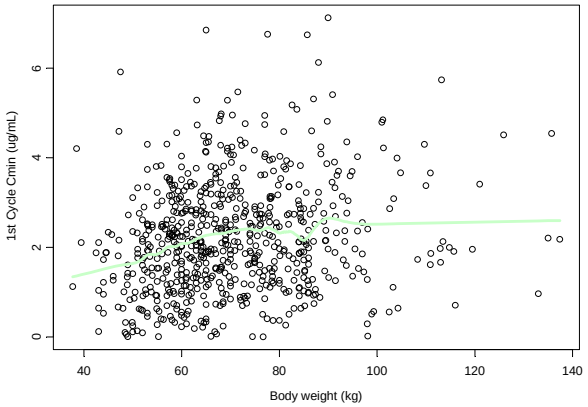


Figure 9. Cycle 1 T-DM1 Cmin vs. body weight.
The plot indicates that body weight based dosing is appropriate since random scatter of exposures across the body weight range is observed.



See Appendix 4.1 for more information.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

The PK of T-DM1 at 3.6 mg/kg q3w, the proposed dose, was characterized by noncompartmental methods in each of the studies included in the application. Population PK analyses were also conducted and a linear two-compartment model with first-order elimination from the central compartment adequately described the ADC concentration-time profile. PK parameters for ADC, TAb, and DM1 have been presented separately. Figures 10 and 11 depict time vs. concentration time-profiles following T-DM1 3.6 mg/kg infusions.

Figure 10. Phase 2 trial TDM4450g mean (SD) serum T-DM1, serum TAb, and plasma DM1 concentration vs. time profiles following T-DM1 3.6 mg/kg IV q3w.

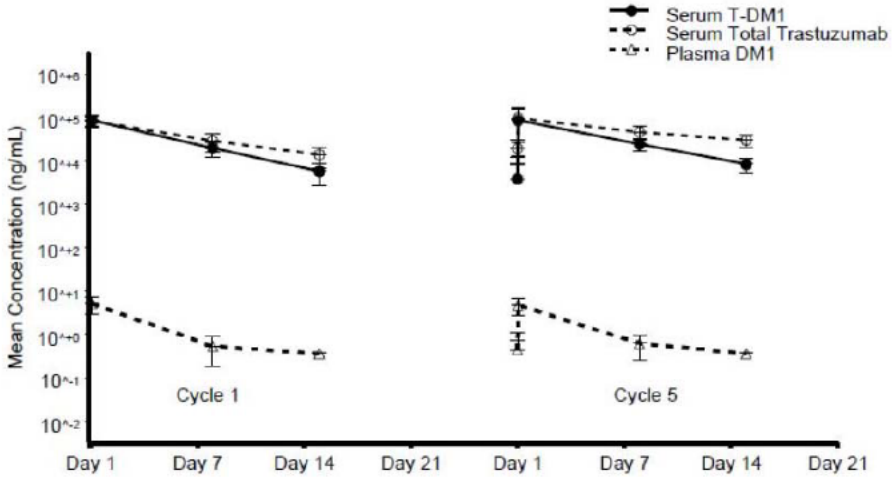
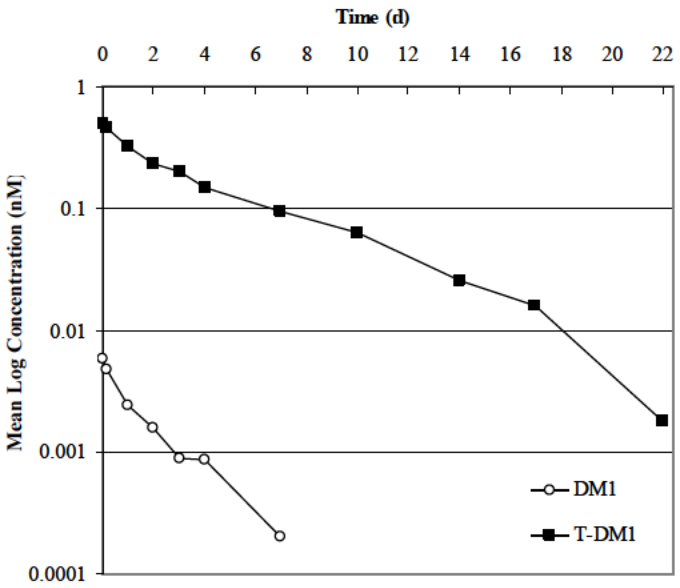


Figure 11. Phase 1 trial TDM3569g mean serum T-DM1 and plasma DM1 molar mass concentration (nM) vs. time profiles following a single dose of T-DM1 3.6 mg/kg IV q3w.



2.2.5.1 What are the single dose and multiple dose PK parameters?

Antibody-drug conjugate

Maximum concentrations of ADC were observed close to the end of infusion (Figures 10 and 11). Based on population PK analysis, the CL of ADC was 0.676 L/day and the t½ was ~4 days. Accumulation was not observed with the q3w dose regimen (Table 5, Figure 10).

Table 4. Phase 1 trial TDM3569g mean (SD) T-DM1 PK parameters following the first dose of T-DM1 q3w.

		T-DM1 Mean (SD) PK Paramters				
Dose (mg/kg)	**N**	**Cmax (µg/mL)**	**AUCinf (µg*d/mL)**	**t½ (d)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
0.3	3	9.6 (1.7)	14.5 (3.4)	1.3 (0.2)	21.1 (4.5)	35.7 (7.5)
0.6	1	13.3 (-)	24.5 (-)	1.3 (-)	24.5 (-)	43.8 (-)
1.2	1	20.3 (-)	42.9 (-)	1.3 (-)	27.8 (-)	51.8 (-)
2.4	1	76.3 (-)	330 (-)	2.2 (-)	7.2 (-)	30.7 (-)
3.6	15	76.2 (19.1)	300 (66)	3.1 (0.7)	12.7 (3.6)	58.4 (12.4)
4.8	3	130.3 (7.8)	673.00 (12.17)	4.1 (0.7)	7.1 (0.1)	41.2 (6.2)
Cycle 1 PK Sampling scheme: 0, 0.5, 4, 24, 48, 72 hrs post-dose, and Day 7, 10, 14, and 18 post-dose, and Cycle 2 predose.						

Table 5. Mean (SD) T-DM1 PK parameters following single and multiple doses of T-DM1 3.6 mg/kg q3w.

			T-DM1 Mean (SD) PK Paramters				
Study Number	**Cycle**	**N**	**Cmax (µg/mL)**	**AUC* (µg*d/mL)**	**t½ (d)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
TDM3569g	1	15	76.2 (19.1)	300 (66)	3.1 (0.7)	12.7 (3.6)	58.4 (12.4)
TDM4258g	1	101	80.9 (20.7)	457 (129)	3.5 (0.7)	8.5 (2.7)	28.4 (12.9)
	4	69	68.9 (21.8)	461 (136)	4.4 (1.7)	8.4 (4.3)	45.2 (43.0)
TDM4374g	1	105	79.5 (21.1)	486 (141)	4.0 (1.0)	8.0 (3.0)	31.2 (10.9)
	4	82	78.3 (25.6)	456 (162)	4.3 (0.8)	7.3 (2.5)	39.3 (32.8)
TDM4450g / BO21976	1	62	84.2 (30.6)	495 (158)	3.5 (0.7)	8.2 (4.0)	30.2 (21.3)
	5	39	79.1 (23.7)	473 (141)	4.2 (0.6)	6.7 (1.6)	33.6 (12.4)
TDM4688g	1	51	75.6 (21.9)	431 (126)	4.0 (0.9)	9.2 (3.0)	41.2 (24.5)
	3	47	80.7 (18.1)	475 (150)	4.5 (0.9)	7.9 (3.3)	43.6 (40.7)
TDM4370g /	1	292	83.4 (16.5)	489 (122)	3.7 (0.9)	7.8 (2.2)	29.5 (14.6)

			T-DM1 Mean (SD) PK Paramters				
Study Number	**Cycle**	**N**	**Cmax (µg/mL)**	**AUC* (µg*d/mL)**	**t½ (d)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
BO21977	4	257	85.0 (33.4)	475 (127)	4.2 (0.7)	7.1 (1.9)	33.3 (11.4)
*AUC = AUCinf for Cycle 1 and AUC =AUC to last sampling time for Cycles 3, 4, or 5.							

Total antibody

TAb exhibited greater exposures and a longer t½ as compared to T-DM1 (Tables 6, 7), and has a similar PK profile as the ADC (Figure 10). There was minimal accumulation of total trastuzumab following q3w dosing (Table 7, Figure 10).

Patients enrolled in the trials had received prior trastuzumab treatment. For example, to demonstrate this point, in trial TDM3569g, 11 of 15 patients had measurable trastuzumab concentrations before the T-DM1 3.6 mg/kg IV infusion. At the 3.6 mg/kg dose, the predose trastuzumab levels (C0) ranged from 0 - 73 µg/mL (Table 7), which was between 0 - 66% of the Cmax values after the first T-DM1 dose. The presence of trastuzumab in serum prior to T-DM1 dosing was identified as a statistically significant covariate for T-DM1 PK parameters (see section 2.3.1).

Table 6. Phase 1 trial TDM3569g mean (SD) TAb PK parameters following the first dose of T-DM1 q3w.

		TAb Mean (SD) PK Paramters				
Dose (mg/kg)	**N**	**Cmax (µg/mL)**	**AUCinf (µg*d/mL)**	**t½ (d)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
0.3	3	26.2 (30.0)	234 (371)	4.8 (3.2)	10.1 (8.4)	32.2 (23.2)
0.6	1	18.0 (-)	105 (-)	8.1 (-)	5.7 (-)	51.1 (-)
1.2	1	25.1 (-)	61 (-)	1.8 (-)	19.7 (-)	43.7 (-)
2.4	1	61.3 (-)	412 (-)	5.2 (-)	5.7 (-)	44.0 (-)
3.6	15	110.4 (40.3)	1144 (857)	9.1 (4.9)	4.9 (3.2)	50.7 (19.7)
4.8	3	164.7 (18.0)	1993 (838)	8.9 (2.1)	2.72 (1.2)	32.8 (4.5)
Cycle 1 PK Sampling scheme: 0, 0.5, 4, 24, 48, 72 hrs post-dose, and Day 7, 10, 14, and 18 post-dose, and Cycle 2 predose.						

Table 7. Mean (SD) TAb PK parameters following single and multiple doses of T-DM1 3.6 mg/kg q3w.

				TAb Mean (SD) PK Paramters				
Trial Number	**Cycle**	**N**	**C0 range[+] (µg/mL)**	**Cmax (µg/mL)**	**AUC* (µg*d/mL)**	**t½ (d)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
TDM3569g	1	15	0 - 72.9	110.4 (40.3)	1144 (857)	9.1 (4.9)	4.9 (3.2)	50.7 (19.7)
TDM4258g	1	101	0 - 66.9	88.0 (30..2)	1040 (1030)	9.2 (10.9)	5.6 (6.3)	46.5 (58.4)
	5	69	-	85.7 (24.7)	888 (294)	11.2 (6.3)	3.5 (2.2)	46.1 (19.9)
TDM4374g	1	105	0 - 122	89.9 (31.3)	1150 (852)	9.4 (4.9)	4.6 (2.6)	43.2 (16.3)
	4	82	-	89.2 (29.1)	700 (280)	10.0 (4.8)	3.3 (1.7)	39.6 (13.3)
TDM4450g / BO21976	1	60	0 - 27.3	83.3 (20.5)	700 (260)	5.8 (2.0)	6.2 (4.3)	38.6 (11.8)
	5	38	-	108 (71.0)	788 (323)	8.3 (2.1)	3.1 (0.9)	34.8 (10.5)
TDM4688g	1	51	0 - 148	95.9 (32.3)	1420 (1390)	10.3 (6.8)	4.2 (2.4)	41.9 (16.2)
	3	47	-	98.6 (26.1)	958 (394)	12.0 (6.2)	3.1 (1.7)	43.7 (15.4)
TDM4370g / BO21977	1	291	0 - 124	86.3 (20.1)	816 (422)	7.8 (4.0)	5.4 (2.3)	45.2 (15.6)
	4	556	-	87.4 (30.7)	604 (166)	6.9 (2.2)	4.7 (1.9)	41.4 (14.5)

[+]C0 represents the pre-dose (baseline) TAb concentration range.
-, not applicable.
* AUC = AUCinf for Cycle 1 and AUC =AUC to last sampling time for Cycles 3, 4, or 5.

DM1

Following administration of T-DM1 3.6 mg/kg, plasma DM1 concentrations were measurable at the first post-infusion sampling time (0.5 hr post-dose), but not measurable at the day 7, 14 and 22 sampling time for the majority of patients. For example, in trial TDM4370g, only one-third of patients had measurable DM1 concentrations at Day 7 post-dose, and only 1 of 270 patients had a measurable DM1 concentration at Day 14 post-dose. No accumulation of DM1 was detected following multiple dosing. Figure 10 above is a representative example of the time vs. concentration time-profile for DM1 following T-DM1 3.6 mg/kg infusions. Additionally, when taking into account the molecular weight and plotting the molar mass drug concentrations for both T-DM1 and DM1, DM1 concentrations are ~2 log less than T-DM1 concentrations (Figure 11).

Table 8. Phase 1 trial TDM3569g mean (SD) DM1 PK parameters following the first dose of T-DM1 q3w.

		DM1 Mean (SD) PK Paramters			
Dose (mg/kg)	**N**	**Cmax (ng/mL)**	**AUCinf (ng*d/mL)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
0.3	3	0 (0)	-	-	-

		DM1 Mean (SD) PK Paramters			
Dose (mg/kg)	**N**	**Cmax (ng/mL)**	**AUCinf (ng*d/mL)**	**CL (mL/d/kg)**	**Vd (mL/kg)**
0.6	1	0.74 (-)	-	-	-
1.2	1	0.89 (-)	-	-	-
2.4	1	3.41 (-)	6.64 (-)	-	-
3.6	15	4.57 (1.33)	9.11 (5.21)	-	-
4.8	3	5.66 (0.94)	16.03 (8.26)	-	-
Cycle 1 PK Sampling scheme: 0, 0.5, 4, 24, 48, 72 hrs post-dose, and Day 7, 10, 14, and 18 post-dose, and Cycle 2 predose.					

Table 9. Mean (SD) DM1 PK parameters following single and multiple doses of T-DM1 3.6 mg/kg q3w.

			Mean (SD)	
Study Number	**Cycle**	**N**	**Cmax (ng/mL)**	**AUCinf (ng*d/mL)**
TDM3569g	1	15	4.57 (1.33)	9.11 (5.21)
TDM4258g	1	105	5.35 (2.03)	-
	4	83	5.89 (2.23)	-
TDM4374g	1	104	5.36 (2.56)	-
	4	81	5.07 (1.92)	-
TDM4450g / BO21976	1	63	5.11 (2.34)	-
	5	50	4.71 (2.25)	-
TDM4688g	1	51	5.42 (1.62)	-
	3	47	5.46 (1.87)	-
TDM4370g / BO21977	1	287	4.61 (1.61)	-
	4	267	5.13 (4.09)	-
-, not reportable due to limited/sparse sampling				

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. Due to its safety profile, T-DM1 has not been administered to healthy volunteers. For information on drug metabolism, refer to section 2.2.5.6.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. T-DM1 is administered as an IV infusion. No studies of drug absorption have been performed.

2.2.5.4 What are the characteristics of drug distribution?

Plasma Protein Binding

The mean binding of DM1 to proteins in human plasma was 93% (Study 05-1047-1459).

Tissue Distribution

Based on population PK analysis, following a 3.6 mg/kg T-DM1 IV dose, the mean (95% CI) central volume of distribution (V_c) is 3.13 (3.08, 3.18) L, which suggests that T-DM1 is primarily limited to the vascular space.

No radiolabeled tissue distribution studies for T-DM1 have been performed in humans. It is not characteristic to have human tissue distribution studies for biologic agents. However, the tissue distribution study of Herceptin-MCC-[^{3}H] DM1 in normal Sprague-Dawley rats revealed that total radioactivity (intact ADC, linker with DM1, free DM1, or its metabolites) was highest in the plasma compartment (12% injected dose per gram of tissue (ID/g) at 1 hr post-dose) during the study compared with the distribution of radioactivity to other tissues (e.g., liver: 3% ID/g at 1 hr post-dose) (Study 04-1022-1459).

Transporter Proteins

DM1 is a substrate for P-glycoprotein (P-gp) *in vitro*. DM1 is not an inhibitor of P-gp *in vitro* (concentrations $\leq$ 0.5 μM (369 μg/mL)) (Study 10-1207). No studies have been conducted with other transporter proteins. See section 2.4.2.4.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No radio-labeled mass balance study of T-DM1 has been preformed in humans. Mass balance studies are not generally performed for biologic products such as monoclonal antibodies because they are proteins which are degraded into amino acids that are recycled into other proteins. However, a mass balance study was performed for [^{3}H]-DM1 in rats (Study 08-1136) for which the cumulative radioactivity recovery in feces and urine at 120 hours was 126 ± 29.8% and 4.88 ± 2.36%, respectively. Similar findings were observed in a rat study performed for Trastuzumab-MCC-[^{3}H]-DM1 (study 09-1060).

2.2.5.6 What are the characteristics of drug metabolism?

In vitro studies in human liver microsomes (HLM) showed that DM1 undergoes metabolism by CYP3A4/5, for which three metabolites (M2, M3, and M7) were detected (Study 09-2416). Table 10 summarizes the relative percent of DM1 remaining following incubation with HLM in the presence and absence of CYP inhibitors. Of note, the human recombinant CYP results mirrored the findings of the HLM study, where the percent DM1 remaining in incubations containing rCYP3A4 and rCYP3A5 decreased to 21.7% and 54.5%, respectively, compared to time 0 minutes (100%).

Table 10. Relative Percent of DM1 (± SD) Remaining after 60-Minute Incubation with HLMs in the Presence of CYP Inhibitors Compared with No Inhibitors.

CYP Inhibitor	Assay Condition	Inhibitor (μM)	Relative Percentage of DM1 Remaining [a]
NA	+N	NA	26.8±3.37
NA	–N	NA	82.6±16.1
All	+N+ABT [b]	1000	81.2±10.2
1A2	+N+furafylline [b]	10	25.7±2.78
2A6	+N+TCP	1	24.8±4.61
2B6/2C19	+N+ticlopidine	10	26.5±2.68
2C8	+N+quercetin	10	27.9±6.23
2C9	+N+sulfaphenazole	10	24.6±5.19
2D6	+N+quinidine	1	22.0±6.80
3A4/5	+N+ketoconazole	1	76.5±17.1
3A4/5	+N+TAO [b]	20	84.2±8.99

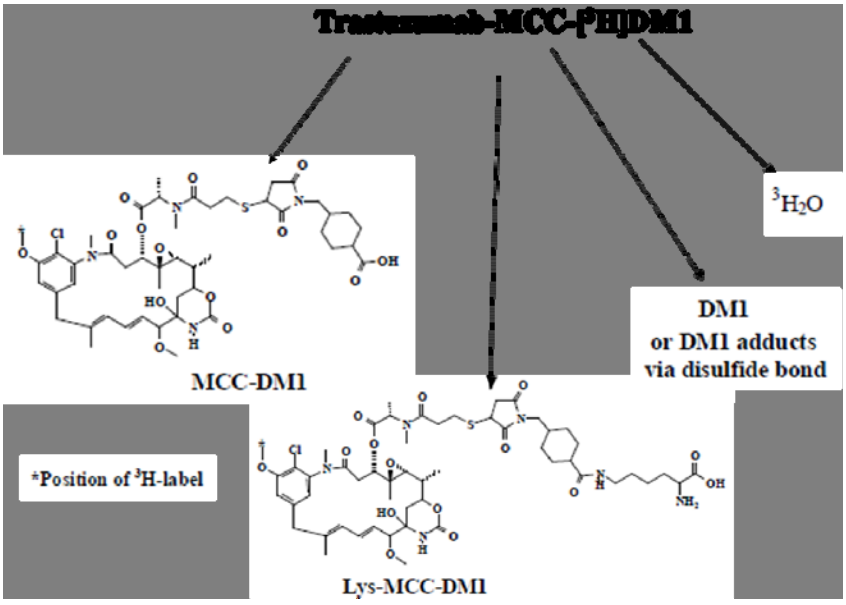
+ N=plus NADPH; - N=without NADPH; ABT=1-aminobenzotriazole; CYP=cytochrome P450; HLM=human liver microsome; NA=not applicable; TAO=troleandomycin; TCP=tranylcypromine.

[a] Percentages (n=3; ±SD) were calculated by setting the amount present at time 0 minutes at 100%.

[b] ABT, furafylline, and TAO were pre-incubated for 15 minutes.

In human plasma, T-DM1 catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels; the maximum concentrations achieved during the study were 122 ng/mL, 6.38 ng/mL, and 9.72 ng/mL, respectively. (Study TDM4688g). Of note, these catabolites were previously identified in nonclinical studies. Figure 12 below depicts the proposed catabolic pathways of Tmab-MCC-[^{3}H]DM1.

Figure 12. Proposed catabolic pathways of Tmab-MCC-[^{3}H]DM1.



No metabolism study has been conducted for the antibody portion of T-DM1 or for the ADC itself in humans. Metabolism studies are not generally performed for antibodies because they are degraded into amino acids which are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion?

Elimination

A mass balance study was performed for [^{3}H]-DM1 in rats (Study 08-1136) for which the cumulative radioactivity recovery in feces and urine at 120 hours was 126 ± 29.8% and 4.88 ± 2.36%, respectively. In rats, the primary route of excretion of DM1 appears to be via feces (Study 08-1136 and 09-1060).

Clearance

Based on population PK analysis, following a 3.6 mg/kg T-DM1 IV dose, the mean (95% CI) CL is 0.676 (0.661, 0.691) L/d. Refer to section 2.2.5.1 above for more information.

Volume of Distribution

Based on population PK analysis, following a 3.6 mg/kg T-DM1 IV dose, the mean (95% CI) V_c is 3.13 (3.08, 3.18) L. Refer to section 2.2.5.1 and 2.2.5.4 above for more information.

Half-life

Based on population PK analysis, following a 3.6 mg/kg T-DM1 IV dose, the t½ is ~4 days. Refer to section 2.2.5.1 above for more information.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Single doses of 0.3, 0.6, 1.2, 2.4, 3.6, and 4.8 mg/kg q3w and single doses of 1.2, 1.6, 2.0, 2.4, and 2.9 mg/kg qw were evaluated in the phase 1 trial TDM3569g. The PK exposure (Cmax and AUC) of T-DM1 appears to increase with an increase in dose. Based on the phase 1 data, for the q3w dose regimen, T-DM1 PK appears to be greater than dose proportional within the dose range of 3.6 - 4.8 mg/kg q3w. However, the assessment of linearity is limited by small sample sizes at most of the dose levels in the q3w dose cohorts (Table 4).

Based on the population PK analysis for the pooled data from five trials in patients with breast cancer, a linear two-compartment model with first-order elimination from the central compartment adequately described the ADC concentration-time profile. The majority of the T-DM1 administered doses were in the range of 3.6 - 4.8 mg/kg. There were only a few individuals who received low doses of 0.3, 0.6 and 1.2 mg/kg q3w; the Bayesian post-hoc clearance estimates of those individuals were suggestive of a faster clearance. However, the population PK analysis using non-linear elimination was tested and the model did not improve the fit of observed data.

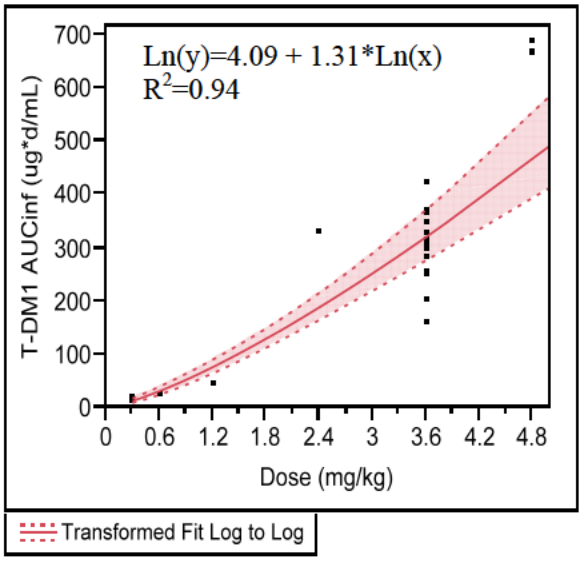
Single dosing for the q3w cohorts: Using AUCinf data from single dosing for the q3w dose cohorts, a power model was applied to test dose proportionality for each component of T-DM1 (Figure 13 Panels A-C).

- For T-DM1, the slope for the power model on logarithmic scale is 1.31 for AUCinf with a 90% confidence interval of (1.17, 1.45) (Figure 13, Panel A).
- For TAb, the slope for the power model on logarithmic scale is 1.18 for AUCinf with a 90% confidence interval of (0.78, 1.59) (Figure 13, Panel B).
- For DM1, the slope for the power model on logarithmic scale is 1.38 for AUCinf with a

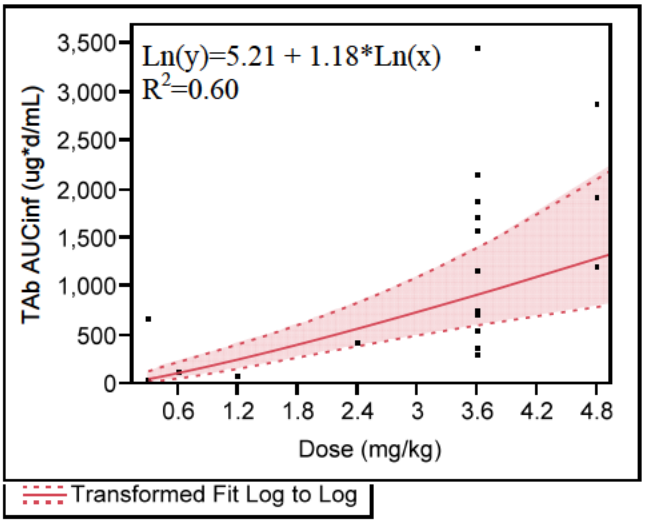
90% confidence interval of (-0.33, 3.09) (Figure 13, Panel C).

Figure 13. Single dose log AUCinf (ng*h/mL) vs. log of dose (mg) in the dose proportionality Study TDM3569 in the dose range of 0.3 to 4.8 mg/kg q3w.
The shaded area represents the 90% confidence interval of the slope. Panel A: T-DM1; Panel B: TAb; Panel C: DM1.

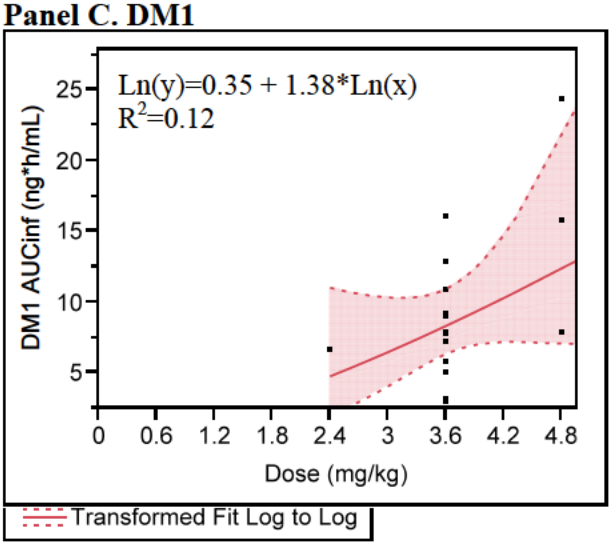
Panel A: T-DM1



Panel B: TAb



Panel C. DM1



The CL of T-DM1 at lower doses (≤1.2 mg/kg) in the q3w cohorts was observed to be ~2-fold greater than the CL at doses between 2.4 - 4.8 mg/kg (Table 11). However, similar trends in CL changes were not observed in the qw dose cohorts. Conclusions can not be made about linearity at doses lower than 3.6 mg/kg q3w due to small sample sizes (N=1) in many of the dose cohorts.

Table 11. Summary statistics for single dose T-DM1 CL (mL/d/kg) for the q3w and qw dose cohorts.

Dose (mg/kg)	N	Mean (SD) CL (mL/d/kg)
q3w Cohorts		
0.3	3	21.1 (4.5)
0.6	1	24.5
1.2	1	27.8
2.4	1	7.16
3.6	15	12.7 (3.6)
4.8	3	7.1 (0.1)
qw Cohorts		
1.2	3	15.9 (2.4)
1.6	3	13.0 (3.4)
2.0	3	11.8 (2.4)
2.4	16	13.1 (4.1)
2.9	3	14.0 (2.6)

Overall, the assessment of linearity is limited by the small sample sizes at most of the dose levels, as is clearly summarized in Table 4 and Figure 13.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.9.1 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the population PK modeling, after adjusting for significant covariates, inter-individual variability for CL and V_c was 19.1% and 11.7%, respectively. See Appendix 4.1 for more details.

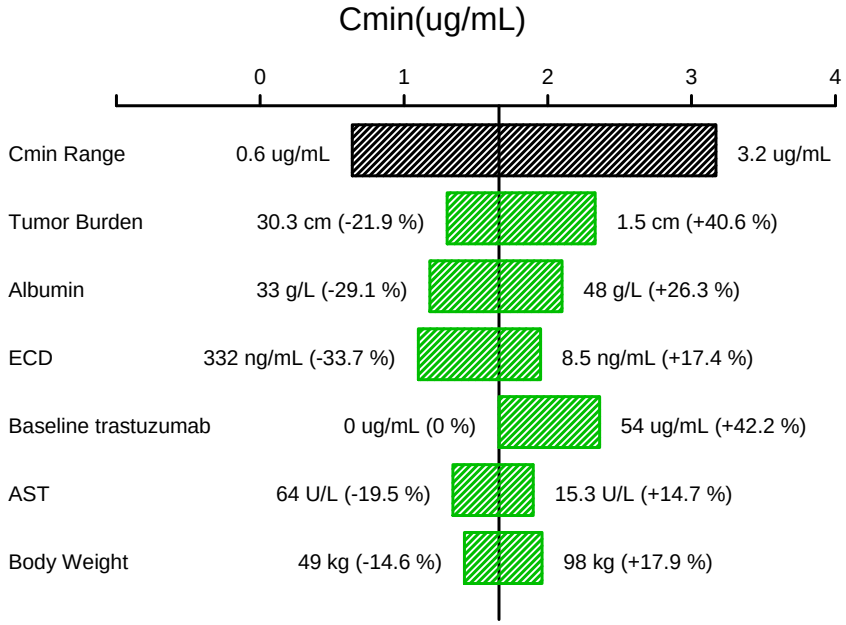
2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, race, gender, weight, height, genetic polymorphism, or organ impairment on T-DM1 PK.

Population PK analysis evaluated the impact of age, race, sum of longest diameter of target lesions by RECIST (tumor burden), albumin, HER2 ECD concentration, baseline trastuzumab concentrations, AST, and body weight on the PK of T-DM1. The following were identified as statistically significant covariates for T-DM1 PK parameters: sum of longest diameter of target lesions by RECIST, albumin, HER2 ECD, baseline trastuzumab concentrations, AST, and body weight. A summary of the covariate effects on T-DM1 PK is shown in Figure 14.

Figure 14. Effect of covariates on T-DM1 steady state exposure.



See Appendix 4.1 for more information.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The magnitude of effect for the identified statistically significant covariates on T-DM1 exposure indicates that no dose adjustments are required. Refer to section 2.3.1 above and Appendix 4.1 for more information.

2.3.2.1 Pediatric patients

Safety and effectiveness of T-DM1 have not been established in pediatric patients. Breast cancer is rare in children.

2.3.2.2 Body weight

Body weight was identified as a significant covariate in the population PK analysis. Refer to section 2.2.4.4 above and Appendix 4.1 for more information on the body weight covariate.

2.3.2.3 Age

Age was not identified as a significant covariate in population PK analysis. See Appendix 4.1 for more information.

2.3.2.4 Race

Race was not identified as a significant covariate in population PK analysis. See Appendix 4.1 for more information.

2.3.2.5 Renal Impairment

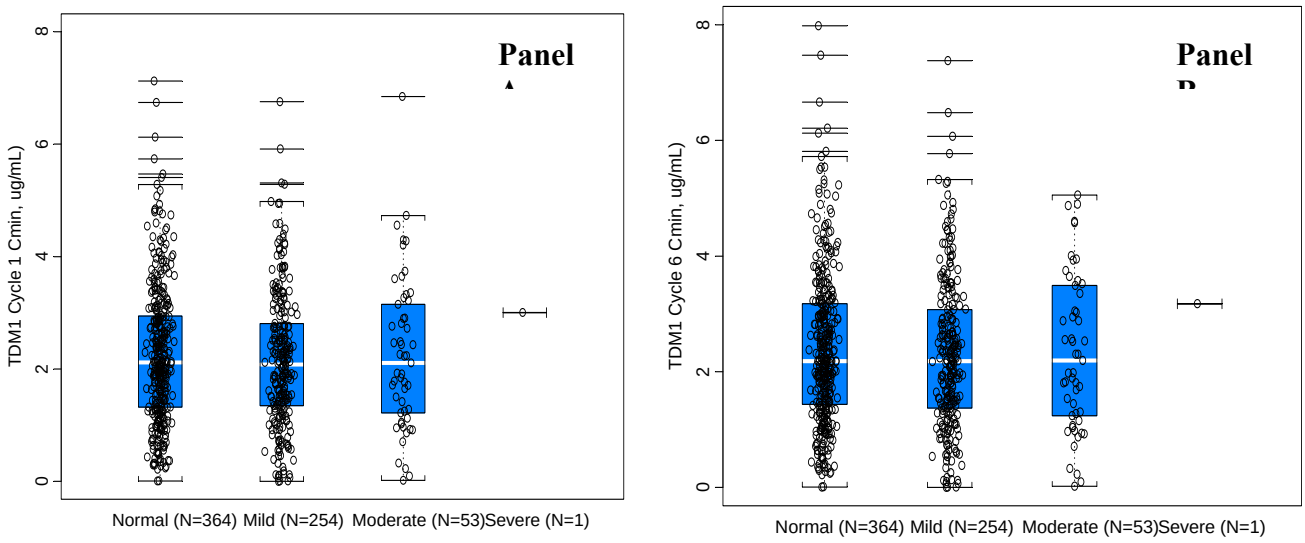
Mild to moderate renal impairment does not appear to affect the PK or safety of T-DM1, which indicates that dose adjustment in patients with mild to moderate renal impairment may not be necessary. No dose adjustments can be recommended for patients with severe or end-stage renal impairment due to insufficient data.

The applicant did not conduct a dedicated organ impairment trial to assess the effect of renal impairment on T-DM1 exposure. Based on the population PK analysis, baseline renal function (creatinine clearance estimated using Cockroft-Gault equation) did not have a significant effect on the C_{min} of T-DM1 in Cycle 1 or 6 (Figure 15). The baseline renal function data included in the analysis comprised of 364 patients with normal renal function (CrCL ≥ 90 mL/min), 254 patients with mild (CrCL 60 - 89 mL/min), 53 patients with moderate (CrCL 30 – 59 mL/min), and 1 patient with severe (CrCL 15 – 29 mL/min) pre-existing renal impairment, respectively.

PK:

Based on the covariate assessment of the impact of serum creatinine clearance on inter-individual random effects of PK parameters (data not shown, see Appendix 4.1) and the comparison of expected T-DM1 exposure simulated from post-hoc PK parameters of patients with different renal functions (Figure 15), mild or moderate impaired renal function appears to have no effect on T-DM1 exposure. No conclusions can be drawn for patients with severe renal impairment and end stage renal disease, as the assessment was limited to only 1 patient with severe renal impairment.

Figure 15. Plots of renal function vs. Cycle 1 (Panel A) and Cycle 6 (Panel B) C_{min} for TDM1.



The effect of renal function on PK of DM-1 could not be evaluated based on the data submitted, as the PK sampling of DM-1 was not adequate to capture its AUC in most of the patients.

Safety

Safety analyses for renal impairment cohorts revealed that renal impairment does not appear to

affect the incidence of Grade 3+ AEs or dose adjustments. Data in Table 12 are presented for the phase 3 trial TDM4370g, as well as all trials combined.

Table 12. Incidence of Grade 3 and above (G3+) AEs) and dose adjustments in patients with various degrees of renal function.

Renal Function Category	Trial TDM4379g			
	Total # Patients per group	Grade 3+ AEs (%)	Total # Patients per group	Dose Adjustments* (%)
Normal (CrCL ≥ 90 mL/min)	169	37.9	169	24.9
Mild (CrCL 60 – 89 mL/ min)	122	51.6	122	23.0
Moderate (CrCL 30 – 59 mL/min)	17	23.5	17	0
Severe (CrCL < 30 mL/min)	1	100	0	0

*Dose adjustments include: dose interruption, discontinuation, or reduction. Also, dose adjustment information was missing in some patients.

Renal Function Category	All Trials			
	Total # Patients per group	Grade 3+ AEs (%)	Total # Patients per group	Dose Adjustments* %
Normal (CrCL ≥ 90 mL/min)	324	40.1	279	30.5
Mild (CrCL 60 – 89 mL/ min)	233	52.8	202	27.7
Moderate (CrCL 30 – 59 mL/min)	42	47.6	34	17.7
Severe (CrCL < 30 mL/min)	3	66.7	1	0

*Dose adjustments include: dose interruption, discontinuation, or reduction. Also, dose adjustment information was missing in some patients.

See Appendix 4.1 for more information

2.3.2.6 Hepatic Impairment

The applicant is currently conducting a dedicated trial to assess the effect of mild and moderate hepatic impairment on T-DM1 exposure.

Of note, while AST was identified as a significant factor for T-DM1 clearance (see section

2.3.1), the magnitude of its effect on T-DM1 Cmin is less than 20%. The study population did not include sufficient numbers of patients with hepatic impairment and the range of AST values may not be wide enough to draw any meaningful conclusions. Therefore, the effect of hepatic impairment on T-DM1 pharmacokinetics could not be determined from the population PK analysis.

2.3.2.7 What pregnancy and lactation use information is there in the application?
The safety and effectiveness of the T-DM1 have not been established in pregnancy and in lactating women.

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Patients were tested for anti-product antibodies (APAs) against all components of the ADC, including the antibody, linker, drug, or potential neo-epitopes, in all clinical trials. Serum samples that screened positive in the screening bridging immunoassay assay were further analyzed by competitive binding immunodepletion with T-DM1 and with trastuzumab to confirm and characterize the detected positive response. Confirmed positive samples were serially diluted to establish titer values for the APA response. Neutralizing activity of anti-ADC antibodies was not assessed.

In trials TDM3569g, TDM4258g, and TDM4374g, the APA positive patients were defined as those with pre-dose (baseline) negative and post-dose positive samples.

In trials TDM4688g, TDM4450g, and TDM4370g, the APA positive patients were defined as those with a positive APA response at any time-point post-treatment, irrespective of their APA status at baseline, which accounts for all post-treatment positive samples.

Immunogenicity sampling schedule in the trials was adequate. The following is the sampling time points for each trial:

- *TDM3569g* (both qwk & q3wk dose cohorts): Baseline (Cycle 1 pre-dose), every cycle thereafter (pre-dose, Day 1), and at the follow-up visit.
- *TDM4258g* and *TDM4374g*: Baseline (Cycle 1 pre-dose), Cycles 2, 3, 4 (pre-dose, Day 1), and at the follow-up visit.
- *TDM4450g*: Baseline (Cycle 1 pre-dose), Cycles 3, 5 (pre-dose, Day 1), and at the follow-up visit.
- *TDM4688g*: Baseline (Cycle 1 pre-dose) and Cycle 3 (pre-dose, Day 1).
- *TDM4370g*: Cycles 2, 3, 4 (pre-dose, Day 1) and at the follow-up visit.

In the case of trials TDM3569g and TDM4258, the APA status at baseline did not change the positive APA rates, and was only slightly different for trial TDM4374g. Therefore, the overall immunogenicity rate for each trial was calculated using data from patients who demonstrated a positive APA response at any time-point post-treatment, irrespective of their baseline status.

The presence of ADC in patient serum at the time of APA sampling can interfere with the ability of this assay to detect anti-ADC antibodies. As a result, data may not accurately reflect the true incidence of anti-ADC antibody development.

Table 13. Summary of the total number of APA evaluable and APA positive patients for each trial.

Study Number	Study Phase	Number of Patients with Evaluable ATA Result [a]	Number of Patients with Positive ATA Response [b,c]
TDM3569g [c]	I	48	1
TDM4258g [c]	II	108	8
TDM4374g [d]	II	108	6
TDM4688g	II	47	0
TDM4450g/BO21976	II	65	9
TDM4370g/BO21977	III	460	20
Total		836	44 (5.3%)

ATA = anti-therapeutic antibody.

[a] Number of patients with at least one post-dose (post–trastuzumab emtansine treatment) ATA timepoint available for analysis.

[b] Number of patients with at least one post-dose timepoint with confirmed positive response after trastuzumab emtansine treatment.

[c] At the time of the clinical study report publication of the studies TDM3569g, TDM4258g, and TDM4374g, the ATA positive patients were defined as those with pre-dose (baseline) negative samples and post-dose positive samples.

[d] For TDM4374g, the rate reported in this integrated table with the new conservative interpretation differs from the value reported in the CSR, The reported immunogenicity rate in the clinical study report was calculated with 5 of 108 ATA positive patients, as 1 other patient was excluded from the rate due to a positive baseline sample.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

The impact of immunogenicity on T-DM1 PK is not evaluable. Data for a direct comparison of T-DM1 PK at time of positive ATA samples is not available.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Samples confirmed to be APA positive were not tested for the presence of neutralizing antibodies. Neutralizing activity of anti-ADC antibodies has not been assessed.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The impact of immunogenicity on T-DM1 efficacy was assessed in the phase 3 TDM4370g trial. As indicated in table 13 above in section 2.3.3.1, the immunogenicity incidence rate in trial TDM4370g was 4.3% (20 of 460 evaluable patients). Analyses revealed an ~70% lower median PFS in the 20 APA positive patients compared to the ITT population (5.6 vs. 9.6 months), while objective response rates (ORR) were comparable (38.9 vs. 43.6%). There were 8 deaths and the estimated median OS [95% CI] was 26.8 mo [13.4 mo, NE]. While there appears to be a negative trend on PFS and OS in APA positive patients, the impact of APA on clinical efficacy is limited due to the low number of APA positive patients and uncertainty related to the immunogenicity assay (see section 2.3.3.1).

2.3.3.5 What is the impact of anti-product antibodies on clinical safety? *(e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)*?

The impact of APA on clinical safety is limited due to the low incidence rate of APA following

T-DM1 treatment and uncertainty related to the immunogenicity assay (see section 2.3.3.1).

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, smoking, and alcohol use on the dose-exposure and/or dose-response for T-DM1 have not been assessed in formal clinical studies.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

See other sections in 2.4.2 below for more information.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Several *in vitro* non-GLP studies were conducted to characterize the metabolism of DM1. The *in vitro* metabolism of DM1 in human liver microsomes (HLM) showed that it undergoes metabolism by CYP3A4/5, for which three metabolites (M2, M3, and M7) were detected (Study 09-2416).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

DM1 (concentrations ≤ 1000 nM (737.5 ng/mL)) did not induce CYP 1A2, 2B6, or 3A4/5 in cultured human hepatocytes (Study 09-2382).

DM1 (concentrations ≤ 678 nM (500 ng/mL)) did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 in HLM. However, pre-incubation of DM1 in HLM for 0.5 hour resulted in inhibition of CYP 3A4 (midazolam 1'hydroxylase) activity (IC50 = 155 nM (114 ng/mL)), which suggests that DM1 may be a time-dependent inhibitor of CYP3A4 (Study 09-1344).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

DM1 is a substrate for P-gp *in vitro*. DM1 is not an inhibitor of P-gp *in vitro*. See section 2.2.5.4.

2.4.2.5 Are other metabolic/transporter pathways important?

No studies have been conducted with other transporter proteins.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No. The proposed dosing regimen involves the use of T-DM1 as a monotherapy.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

None. The current proposed use of T-DM1 is as a monotherapy. Additional medications may be given concomitantly to alleviate symptoms arising from adverse events.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No dedicated drug-drug interaction studies have been conducted. DM1 is mainly metabolized by CYP3A4 (see section 2.2.5.6). Therefore, when strong CYP3A4 inhibitor(s) are concomitantly administered with T-DM1, there is a potential for an increase in DM1 exposure and toxicity. Of note, ADC exposures are not expected to be affected by the CYP3A4 inhibitor(s). This taken in conjunction with the ADC exposure-response relationship for efficacy described in section 2.2.4.1, a T-DM1 dose reduction to mitigate possible increased toxicities related to increased DM1 exposures may result in unacceptable efficacy loss and does not appear to be a clinically acceptable approach to deal with this drug-drug interaction.

The sponsor conducted an exploratory analysis of the effect of concomitant medications through the use of pooling drug classes (inhibitors and inducers of CYP3A and P-gp) on Cycle 1 and Cycle 4 T-DM1, TAb, and DM1 PK within the phase 3 trial TDM3470g.

Table 14 summarizes the individual patient cases of strong CYP3A4 concomitant medication identified within the TDM3470g drug-drug interaction dataset. Six patients who had received strong CYP3A4 inhibitor concomitant medications were identified. The timing of T-DM1 dosing and administration days of strong CYP3A4 inhibitor concomitant medication does not allow for a meaningful evaluation of the drug interaction potential (Table 14).

Table 14. Timing of strong CYP3A4 concomitant medication use and T-DM1 dosing day information.

Patient	Strong CYP3A4 Inhibitor	Days after T-DM1 Dose #1 to ConMed Use Start	Days after T-DM1 Dose #1 to ConMed Use End	ConMed Use Duration (d)	T-DM1 Dosing Days^	Cycle #^
A	Itraconazole	171	185	14	170*	9
B	Itraconazole	160	166	6	150*	8
C	Clarithromycin	5	19	14	1, 23	1, 2
D	Clarithromycin	55	61	6	43, 64	3, 4
E	Clarithromycin	85	Not specified	n/a	64*	4
F	Clarithromycin	9	15	6	1, 22	1, 2

^Only T-DM1 dosing days and treatment cycle #'s around the time of conmed use are listed.
*Final dose received in the trial.

Overall, the drug-drug interaction analysis is not informative due to multiple limitations. For example, the sponsor's analysis did not account for timing of concomitant medication use relative to T-DM1 dosing and PK sampling. Another concern is regarding the sponsor's approach to pooling the medications; pooling of drugs within each class assumes similar potency for each drug. Additionally, the sponsor's drug-drug interaction dataset included topical concomitant medications and also did not account for compliance of concomitant medication use.

Given the limitations to the available drug-drug interaction data and concerns for clinical safety, concomitant use of strong CYP3A4 inhibitors with T-DM1 should be avoided. An alternate medication with no or minimal potential to inhibit CYP3A4 should be considered. However, if concomitant use of strong CYP3A4 inhibitors is unavoidable, practitioners may consider delaying T-DM1 treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and T-DM1 treatment can not be delayed, patients should be closely monitored for adverse reactions.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

2.4.3 What issues related to dose, dosing regimens, or administration is unresolved and represents significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the composition of the to-be-marketed formulation, which was used in the pivotal clinical trial?

Three different processes have been used to manufacture T-DM1. (b) (4)

Table 15 below shows the changes in the manufacturing processes for T-DM1. Nonclinical monkey PK studies were conducted to assess comparability of the process changes. Additionally, human cross-study PK comparisons were conducted to use as supporting data. The three processes were found to be comparable (results are not presented in the review).

Table 15. Summary of manufacturing process changes for T-DM1 used in clinical studies.

(b) (4)

2.5.2 What is the relationship of the proposed to-be-marketed formulation used in the pivotal clinical trial with previous clinical trial formulations in terms of comparative exposure?

The to-be-marketed formulation (b) (4) is the formulation used in the phase 3 trial

TDM4370g. Two other formulations [redacted] were used during development; see section 2.5.1. The comparability of the formulations was assessed in animal (monkey and rat) studies with parallel designs. Monkey and human cross-study PK comparisons were also conducted as exploratory analyses.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

In order to characterize the PK and disposition of T-DM1, the concentrations of three analytes were measured: ADC, DM1, and TAb. ADC and TAb were measured in serum by ELISA immunoassays. DM1 was measured in plasma by liquid chromatography and tandem mass spectrometry (LC-MS/MS).

2.6.2 Which metabolites have been selected for analysis and why?

In addition to the ADC, TAb and DM1 have been measured. The metabolites of DM1 that were formed are present in very small amounts and do not warrant further characterization.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For the ADC, the assay measures only intact conjugate. The assay is not able to differentiate between the conjugates with different drug to antibody ratios. For total antibody, both conjugated and unconjugated antibody was measured.

For DM1, the assay was designed to measure DM1 and any disulfide-bound forms of DM1 (e.g., dimers, glutathione, cysteine, and albumin adducts). It was designed to exclude measurement of DM1 conjugated to lysine residues of trastuzumab via MCC-DM1.

2.6.4 What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

ADC Serum ELISA: The concentration of T-DM1 containing one or more covalently-bound DM1 was quantified using an indirect sandwich ELISA method. The ELISA used an anti-DM1 monoclonal antibody as the coat capture reagent and biotinylated recombinant HER2 ECD and horseradish peroxidase–conjugated streptavidin for detection. See Table 16 for assay performance details.

The minimum dilution for neat serum samples was 1/100, resulting in a minimum quantifiable concentration (MQC) of 40 ng/mL for human serum samples at Genentech. No limit was identified for the maximum dilution. The validated assay for human serum samples was transferred to [redacted]; the MQC for human serum samples established [redacted] was 60 ng/mL.

Total Antibody Serum ELISA: The concentration of total trastuzumab (conjugated and unconjugated trastuzumab) was quantified using an indirect sandwich ELISA method. Two different assay versions were used. The first ELISA (4.HERc.1_AVR_3) used recombinant HER2 ECD as capture reagent and horseradish peroxidase-conjugated goat F(ab')2 anti-human IgG Fc for detection. The second ELISA (BA.MET.HERc.009 AVR_1), which replaced the first assay, used an anti-idiotypic antibody against trastuzumab as capture reagent and a biotinylated monoclonal anti-human IgG antibody (10C4), followed by horseradish peroxidase-avidin D for detection. See Table 16 for assay performance details.

The MQC for the first and secondary assays were 40 and 60 ng/mL, respectively. No limit was identified for the maximum dilution.

DM1 Plasma LC-MS/MS: The assay measures all disulfide-bound forms of DM1. DM1 contains a free sulfhydryl and when released from T-DM1 it is likely to dimerize or react with other thiol-containing molecules in plasma. Therefore, to avoid under-quantification of released DM1, lithium–heparin plasma samples were treated with a reducing agent (Tris (2-carboxyethyl) phosphine (TCEP)) to release disulfide-bound DM1. The free thiol was then blocked with N-ethyl maleimide (NEM) to prevent any further reactions. Following solid-phase extraction, samples underwent LC-MS/MS detection; the LC-MS/MS assay quantified DM1-NEM.

The assay LLOQ and ULOQ upon TCEP reduction were 1.00 and 500 nM, respectively. See Table 16 for assay performance details.

Other:
For **MCC-DM1** the LLOQ and ULOQ were 3.00 and 500 nM, respectively. The overall precision (CV%) of the MCC-DM1 method was ≤6.8% at all concentrations and the intra-batch precision (CV%) was ≤9.0% at all concentrations.

For **Lys-MCC-DM1** the LLOQ and ULOQ were 1.00 and 500 nM, respectively. The overall precision (CV%) of the Lys-MCC-DM1 method was ≤6.8% at all concentrations and the intra-batch precision (CV%) was ≤8.7% at all concentrations.

Table 16. Assay performance of validated PK assays used in clinical trials.

PK Assay	Validation Report No.	Validation and Sample Analysis Site	Standard Curve Range	MQC [a] or LLOQ	Accuracy	Intra-assay Precision (% CV)	Inter-assay Precision (% CV)	Studies
Trastuzumab Emtansine Conjugate	4.HERc.2_ AVR_4	Genentech	0.16 to 20 ng/mL	MQC: 40 ng/mL	% Recovery: 91 to 127	2 to 10	5 to 6	TDM3569g, TDM4258g, TDM4374g, TDM4450g, TDM4688g, TDM4370g [d]
		(b) (4)	0.16 to 20 ng/mL	MQC: 60 ng/mL				
Total Trastuzumab (First Assay)	4.HERc.1_ AVR_3	Genentech	0.16 to 20 ng/mL	MQC: 40 ng/mL	% Recovery: 90 to 118	3 to 7	4 to 8	TDM3569g, TDM4258g, TDM4374g, TDM4450g, TDM4688g
Total Trastuzumab (Second Assay)	BA.MET.HERc.009 AVR_1	Genentech [d], (b) (4)	0.16 to 20 ng/mL	MQC: 60 ng/mL	% Recovery: 92 to 101	2 to 9	0 to 10	TDM4370g [d]
DM1 [c]	05-1360 /VR377	(b) (4)	1.00 to 500 nM (0.737 to 369 ng/mL)	LLOQ: 1.00 nM (0.737 ng/mL)	% Bias: 0.8 to 14.9	6.2 to 9.1	8.8 to 17.7	TDM3569g, TDM4258g, TDM4374g, TDM4450g, TDM4688g, TDM4370g

LLOQ = lower limit of quantification; PK = pharmacokinetic.

[a] MQC is minimum quantifiable concentration in neat serum samples, which incorporates the minimum required dilution of samples.

[b] The validated assay was transferred to (b) (4) for analysis of samples from study TDM4370g/BO21977. Analysis of samples from all other studies was performed at Genentech. Transfer validation was conducted prior to sample analysis at (b) (4) and its data are appended to the Genentech validation report. LLOQ was established at 60 ng/mL at (b) (4) during the transfer validation as the acceptability criteria was not met for the LLOQ sample at 40 ng/mL.

[c] DM1 concentrations were determined in plasma samples.

[d] Initial assay validation was performed at Genentech, followed by the transfer validation at (b) (4) Study sample analysis was performed only at (b) (4)

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

ADC Serum ELISA: The standard curve range was 0.16 - 20 ng/mL. With the LLOQ of 0.4 ng/mL and 1/100 minimum dilution for samples, the MCQ was 40 ng/mL with the Genentech assay. With the (b) (4) assay, the MQC was 60 ng/mL. Serum samples were diluted 1/100-1/800, 1/1000-1/8000, 1/3000-1/24000, or 1/10000-1/80000 in four serial dilutions into the working range of the assay. Data of the unknown human serum samples were processed by using a four-parameter logistic fit of the standard curve (Watson LIMS, version 7.2.0.04).

Total Antibody Serum ELISA: The standard curve range was 0.16 - 20 ng/mL. With the LLOQ of 0.4 ng/mL and 1/100 minimum dilution for samples, the minimum quantifiable concentration was 40 ng/mL. Serum samples were diluted 1/100-1/800, 1/1000-1/8000, 1/3000-1/24000, or 1/10000-1/80000 in four serial dilutions into the working range of the assay. Data of the unknown human serum samples were processed by using a four-parameter logistic fit of the standard curve (Watson LIMS, version 7.2.0.04).

DM1 Plasma LC-MS/MS: The standard curve range was 1.00 - 500 nM and contained nine non-zero samples (1.00, 2.50, 5.00, 10.0, 25.0, 75.0, 200, 400 and 500 nM). The calibration curve was calculated by linear regression with weighting factor 1/xx and correlation coefficients were ≥0.9982.

Other:

For **MCC-DM1** the standard curve range was 3.00 - 500 nM. The calibration curve was calculated by linear regression with weighting factor 1/xx and the correlation coefficients were ≥0.9957.

For **Lys-MCC-DM1** the standard curve range was 1.00 - 500 nM. The calibration curve was calculated by linear regression with weighting factor 1/xx and the correlation coefficients were ≥0.9968.

2.6.5 What is the QC sample plan?

ADC Serum ELISA: Two different control lot preparations were used and with each preparation, three levels of quality control samples were made: lower, middle and upper QC levels. Each control level was assayed in two replicates on each plate. Assay acceptability was assessed by the controls on each plate. Assays were acceptable if at least four of the six single measurements for the three controls were within ± 20% of the established mean value for the low, mid, and high controls, but no two measurements at the same control level were out of the acceptable range. Additionally, assays must have maximum optical density (OD) ≥1.0.

Total Antibody Serum ELISA: The same as described above for ADC Serum ELISA.

DM1 LC-MS/MS: Three levels of quality control samples were made: lower (3.00 nM), middle (100 nM), and upper (350 nM) QC levels. Each control level was assayed in two replicates on each plate. Assay acceptability was assessed by the controls on each plate. Assays were acceptable if at least two of the six single measurements for the three controls were within ± 15% of the established mean value for the low, mid, and high controls, and one of the measurements at the same control level were in the acceptable range.

2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

Six clinical trials in patients with breast cancer included immunogenicity analysis. Two of these trials (TDM3569g and TDM4258g) used a human serum electrochemiluminescence (ECL) immunogenicity assay, while the remaining four (TDM4374g, TDM4450g, TDM4688g, and TDM4370g) used a human serum ELISA immunogenicity assay. The assay performance of the two validated anti-therapeutic antibody assays is described in Table 17. The ECL method was slightly more robust with regard to interference from the T-DM1 levels in the sample, with a 3-fold higher drug tolerance level than the ELISA method.

The relative sensitivity of the two assays using affinity-purified, anti-T-DM1 antibodies were estimated to be 115 ng/mL for the ECL method and 52 ng/mL for the ELISA method. The drug tolerance of the two assays were demonstrated with detection limits of 1580 ng/mL antibodies in the presence of 100 µg/mL T-DM1 for the ECL method and 500 ng/mL in the presence of 100 µg/mL T-DM1 for the ELISA method.

Table 17. Assay performance of the validated anti-therapeutic antibody assays.

Assay	Validation Report	Validation and Sample Analysis Site	Relative Sensitivity Using Anti-Trastuzumab Emtansine Antibodies [a]	Relative Sensitivity Using Anti-DM1 Monoclonal Antibody [a]	Trastuzumab Emtansine Interference [b]	Studies
Anti-Trastuzumab Emtansine ECLA	4.HERc.7_AVR_1	Genentech	115 ng/mL	240 ng/mL	1580 ng/mL	TDM3569g, TDM4258g
Anti-Trastuzumab Emtansine ELISA	BA.MET.HERc.008.AVR_1	Genentech, (b) (4)	52 ng/mL	219 ng/mL	500 ng/mL	TDM4374g, TDM4450g. TDM4688g, TDM4370g

ECLA = electrochemiluminescence assay; ELISA = enzyme-linked immunosorbent assay.

[a] Relative sensitivity was established using polyclonal antibodies to trastuzumab emtansine and a monoclonal antibody to DM1 to demonstrate the assay's capacity to measure all antibodies to trastuzumab emtansine with acceptable sensitivity.

[b] Trastuzumab emtansine interference: In the presence of high level of trastuzumab emtansine (100 µg/mL), the assays demonstrated good tolerance to therapeutic interference, with the assay's relative sensitivity estimated to be approximately 1580 ng/mL for the ECLA and 500 ng/mL for the ELISA using polyclonal antibodies to trastuzumab emtansine.

Data from a panel of serum samples (64 samples for the ECLA and 100 for the ELISA) from T-DM1-naïve and trastuzumab-naïve breast cancer patients were used to establish the assay decision thresholds, or screening cut-points. The cutpoint value is the product of the multiplication factor (defined as 1.23 for ECL and 1.87 for ELISA) and the negative control mean signal of each plate. Samples were considered positive if the sample signal was greater than or equal to the cutpoint value.

The minimum dilution for samples was 1/50, resulting in a minimum reportable titer value of 1.7 titer units ($\log_{10} 50$).

Refer to the CMC review for further details.

2.6.7 What is the performance of the binding assay(s)?

The performance of the binding assays has been reviewed in detail in the CMC review. Table 17

describes the assay performance of the two validated anti-therapeutic antibody assays. Refer to the CMC review for further details.

2.6.8 What is the performance of the neutralizing assay(s)?

A neutralizing assay was not used.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included.

APPLICANT PROPOSED PACKAGE INSERT	FDA RECOMMENDED PACKAGE INSERT
6.2 Immunogenicity As with all therapeutic proteins, there is the potential for an immune response to KADCYLA. A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to KADCYLA. Following KADCYLA dosing, 5.3% (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. (b) (4) Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. (b) (4)	**6.2 Immunogenicity** As with all therapeutic proteins, there is the potential for an immune response to KADCYLA. A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to KADCYLA. Following KADCYLA dosing, 5.3% (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. The presence of KADCYLA in patient serum at the time of ATA sampling can interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-KADCYLA antibody development. In addition, neutralizing activity of anti-KADCYLA antibodies has not been assessed. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to KADCYLA with the incidence of antibodies to other products may be misleading. Clinical significance of anti-KADCYLA antibodies it not known.
7 Drug Interactions No formal drug-drug interaction studies with KADCYLA in humans have been conducted. (b) (4)	**7 Drug Interactions** No formal drug-drug interaction studies with KADCYLA have been conducted. *In vitro* studies indicate that DM1, the cytotoxic component of KADCYLA, is metabolized mainly by CYP3A4, and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with KADCYLA should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying KADCYLA treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and KADCYLA treatment can not be

	delayed, patients should be closely monitored for adverse reactions.
8.5 Geriatric Use (b) (4)	**8.5 Geriatric Use** Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine [see Clinical Pharmacology (12.3)].
8.7 Renal Impairment (b) (4)	**8.7 Renal Impairment** No dedicated renal impairment trial for KADCYLA has been conducted. Based on the population pharmacokinetics, as well as analysis of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments of KADCYLA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited data available [see Clinical Pharmacology (12.3)].
8.8 Hepatic Impairment (b) (4)	**8.8 Hepatic Impairment** *In vitro* studies in human liver microsomes indicate that DM1 is metabolized by CYP3A4/5. The influence of hepatic impairment on the pharmacokinetics of trastuzumab emtansine conjugate (ADC) or DM1 has not been determined.
	n/a
12.3 Pharmacokinetics ***Distribution*** (b) (4)	**12.3 Pharmacokinetics** The pharmacokinetics of KADCYLA was evaluated in a phase 1 study and in a population pharmacokinetic analysis for the trastuzumab emtansine conjugate (ADC) using pooled data from 5 trials in patients with breast cancer. A linear two-compartment model with first-order elimination from the central compartment adequately describes the ADC concentration-time profile. In addition to ADC, the pharmacokinetics of total antibody (conjugated and unconjugated trastuzumab), DM1 were also determined. The pharmacokinetics of KADCYLA are summarized below.

(b) (4)	***Distribution*** Maximum concentrations (Cmax) of ADC and DM1 were observed close to the end of infusion. In Study 1, mean (SD) ADC and DM1 Cycle 1 Cmax following KADCYLA administration was 83.4 (16.5) µg/mL and 4.61 (1.61) ng/mL, respectively. *In vitro*, the mean binding of DM1 to human plasma proteins was 93%. In vitro, DM1 was a substrate of P-glycoprotien (P-gp). Based on population pharmacokinetic analysis, the central volume of distribution of ADC was 3.13 L.
Metabolism (b) (4)	***Metabolism*** In vitro studies indicate that DM1, the small molecule component of KADCYLA, undergoes metabolism by CYP3A4/5. DM1 did not inhibit or induce major CYP450 enzymes *in vitro*. In human plasma, trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels.
Elimination (b) (4)	***Elimination*** Based on population pharmacokinetic analysis, the clearance of ADC was 0.68 L/day and the elimination half-life (t½) was approximately 4 days. No accumulation of KADCYLA was observed after repeated dosing of intravenous infusion every 3 weeks. Based on population pharmacokinetic analysis (n=671), body weight, sum of longest diameter of target lesions by RECIST, HER2 extracellular domain (ECD) concentrations, AST, albumin, and baseline trastuzumab concentrations were identified as statistically significant covariates for trastuzumab emtansine clearance. However, the magnitude of effect of these covariates on trastuzumab emtansine exposure suggests that, with the exception of body weight, these covariates are unlikely to have a clinically meaningful effect on KADCYLA exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates is considered appropriate.
Effects of Age and Race (b) (4)	***Effects of Age and Race*** Based on population pharmacokinetic analysis, age (< 65 (n=577); 65 - 75 (n=78); > 75 (n=16)) and race (Asian (n=73); non-Asian (n=598)) do not have a clinically meaningful effect of on the pharmacokinetics of trastuzumab emtansine.

(b) (4)	
Effect of Renal Impairment (b) (4)	***Effect of Renal Impairment*** Based on population pharmacokinetic analysis in 668 patients, including moderate (CLcr 30 - 59 mL/min, n=53) and mild (CLcr 60 - 89 mL/min, n=254) renal impairment, indicate that pharmacokinetics of the ADC is not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥ 90 mL/min, n=361). Data from only one patient with severe renal impairment (CLcr < 30 mL/min) is available [see Use in Specific Populations (8.7).
n/a	**12.6 Cardiac Electrophysiology** The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

PHARMACOMETRIC REVIEW	
BLA	125427
Submission Type	Original
Submission Date	7/30/2012
Generic Name	Trastuzumab emtansine
Sponsor	Genentech
Pharmacometric Reviewers	Jian Wang, Ph.D.; Pengfei Song, Ph.D.
Pharmacometrics Team Leader (Acting)	Nitin Mehrotra, Ph.D.
Clinical Division	Division of Oncology Products 1 (DOP1)

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

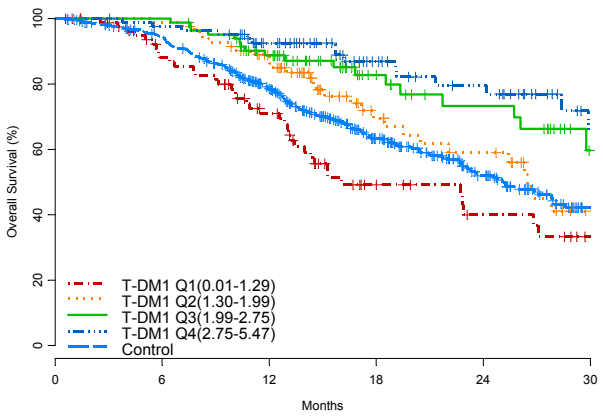
1.1.1 Do exposure-response analyses identify a subgroup of patient population that may benefit from dose optimization?

Yes, patients with lower exposures may benefit from increase in dose. This is because the exposure-response analyses, after accounting for baseline risk factors, demonstrated that increase in trastuzumab emtansine (T-DM1) exposure is related with better efficacy in terms of overall survival and progression free survival (co-primary endpoints), as well as the secondary endpoint objective response rate (TDM4370g/BO21977).

Overall survival (OS)

OS was the co-primary efficacy endpoint of the pivotal trial following 3.6 mg/kg of T-DM1 administered by intravenous infusion once every three weeks. Population PK predicted T-DM1 trough concentration on Day 21 in Cycle 1 ($C_{min,C1D21}$) was available for 68.2% patients (N=334) in T-DM1 arm (N=490). Kaplan-Meier survival analysis was performed with these patients stratified according to quartiles of $C_{min,C1D21}$ (≤1.29, 1.29–1.99, 1.99–2.75 and >2.75 µg/mL) or median value and the result is shown in Figure 1. The survival curve of patients without PK data lies between exposure groups dichotomized by median indicating that the population used for exposure-response analysis is representative of the overall patient population (Figure 1, Right).

A significant difference in survival was observed for patient groups divided according to quartiles of $C_{min,C1D21}$ (log rank test P<0.0001). The median [95% CI] survival time for patients within the lowest quartile of concentrations was 15.3 months [5.6–10.1 months], which is 8 months shorter than the median survival time for patients treated with lapatinib plus capecitabine. The median survival for patients with trough concentrations within other quartiles could not be estimated since these quartiles did not cross 50% survival cutoff. Since Kaplan Meier is a univariate analysis and the difference in survival in these exposure quartiles may be confounded by other covariates, cox-proportional hazard analysis was conducted.



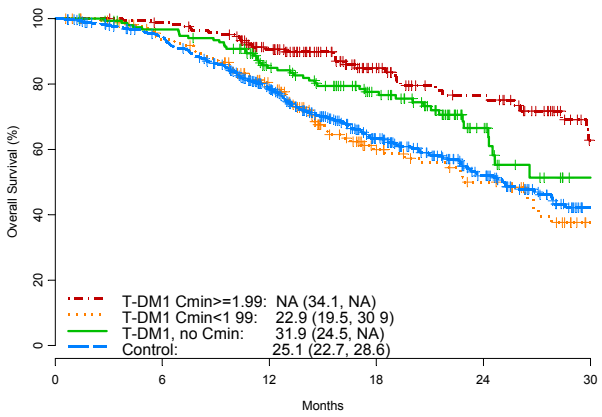


Figure 1. Kaplan-Meier curve of overall survival (OS) for the T-DM1 arm (N=490) by quartiles (left) or median (right) of $C_{min, C1D21}$ and for the active control arm (N=488) of the study TDM4370g/BO21977. The numbers in the right figure shows the median survival with 95% confidence interval.

Table 1 shows the comparison of distribution of these risk factors between each quartile group and the comparator group. Comparing the key covariates at baseline of quartiles, it appears that Quartile 1 and Quartile 2 are imbalanced with higher Her2 ECD shed antigen concentration, worse ECOG score, more measurable disease, more visceral disease, and higher tumor burden (**Table 1**), which may, along with low T-DM1 exposure, account for the less improved efficacy within the Q1 and Q2.

Table 1. Summary of covariates and exposure for patients per quartile of predicted T-DM1 trough concentration on Day 21 in Cycle 1 ($C_{min,C1D21}$). SOC is the lapatinib plus capecitabine

Parameter	SOC	TDM1	Q1	Q2	Q3	Q4
N	488	490	84	83	83	84
PK Patient (Yes/No)	0/488	307/183	76/8	74/9	77/6	79/5
Age (yr)	53 [11]	52 [11]	53 [10]	53 [13]	51 [10]	51 [11]
Weight (kg)	71 [19]	69 [14]	67 [15]	70 [16]	69 [12]	71 [13]
Race (White/Asian/Other)	367/85/36	355/92/43	58/18/8	48/24/11	62/16/5	65/10/9
ECD (ng/mL)	60 [121]	86 [248]	227 [517]	63 [90]	33 [50]	38 [56]
ECOG (0/1)	308/172	248/159	43/41	51/32	55/28	61/23
Prior Chemo (<=1/>1/NA)	18/404/66	15/409/66	4/71/9	3/74/6	2/70/11	1/66/17
Liver metastasis (Yes/No)	190/292	207/280	49/34	35/47	23/60	36/48
Measurable Disease (Yes/No)	386/102	392/98	75/9	72/1	52/31	64/20
Visceral Disease (Yes/No)	328/160	329/161	63/21	59/24	45/38	49/35
Tumor burden (cm)	14.77 [12.24]	14.54 [10.93]	19.75 [12.35]	14.57 [9.66]	15 [10]	10.47 [10.31]
Albumin(g/L)		41.3 [4.32]	39.79 [4.91]	41.12 [4.19]	41 [4]	42.13 [3.83]
Trastuzumab baseline (ug/mL)		10.79 [19.31]	4.8 [8.64]	8.04 [14.4]	8 [14]	19.29 [25.37]
AST (U/L)		28.76 [14.55]	36.17 [20.98]	28.94 [12.62]	25.1 [9.84]	24.73 [8.33]

Cox regression analysis identified four significant baseline risk factors for survival status: Baseline HER2 ECD (≥ median, < median), ECOG performance status (≥1 vs. 0), measurable disease (Yes vs. No) and tumor burden (≥ median, < median). Hazard ratio (HR) for each quartile of $C_{min,C1D21}$ referring the control arm was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: ECOG (0 vs. 1), number of disease sites (< 3 vs. ≥3), prior anthrocycline use (yes vs. no), prior transtuzumab treatment (yes vs. no), visceral disease (yes vs. no), measuable disease (yes vs. no), tumor burden, and HER2 shed antigen. HRs decreased with increasing T-DM1 exposure. However, it is noted that even the lowest quartile of $C_{min, C1D21}$ demonstrated a comparable OS with the active treatment arm (capecitabine + lapatinib).

Table 2.Hazard ratio (HR) for each of $C_{min,C1D21}$ quartiles vs. the active control arm (capecitabine + lapatinib) after adjusting baseline covariates including ECOG, number of disease sites, prior anthracycline use, prior transtuzumab treatment, visceral disease, measurable disease, and HER2 ECD and tumor burden.

Efficacy Endpoint		HR (95% CI)	P-value
PFS	TDM1 Q1 vs. Control	0.82 (0.57, 1.16)	0.25
	TDM1 Q2 vs. Control	0.73 (0.52, 1.02)	0.066
	TDM1 Q3 vs. Control	0.57 (0.39, 0.83)	0.0032
	TDM1 Q4 vs. Control	0.36 (0.24, 0.53)	< 0.0001
OS	TDM1 Q1 vs. Control	0.97 (0.65, 1.46)	0.89
	TDM1 Q2 vs. Control	0.68 (0.44, 1.05)	0.080
	TDM1 Q3 vs. Control	0.40 (0.22, 0.72)	0.0024
	TDM1 Q4 vs. Control	0.35 (0.20, 0.63)	0.0005

The statistical reviewer, Dr. Qiang (Casey) Xu, used P-splines within the additive Cox proportional hazards model based on patients in the T-DM1 arm to reflect the functional form of continuous $C_{min,C1D21}$ C_{min} level in relation to study outcome OS (Figure 2). The plot shows hazard ratios of OS across $C_{min,C1D21}C_{min}$ level with minimum of $C_{min,C1D21}C_{min}$ as the reference level, adjusted for liver metastasis status (Y vs. N), prior anthracycline use (Y vs. N), ECOG score, prior trastuzumab use for metastatic setting (Y vs. N), visceral disease status (Y vs. N), tumor burden, and log transformed ECD. The solid red line represents the point estimates with point wise 95% confidence intervals presented by two dash red lines. Three vertical reference lines separate plot space according to the $C_{min,C1D21}$ quartiles. The spline curve demonstrates a sharp change in hazard ratios in the first quartile of $C_{min,C1D21}$ level. The trend slows down in the later three quartiles. Caution should be exercised when trying to interpret the ends of the curve due to sparse samples. In addition, 23412 (4743%) out of 495 T-DM1 patients have missing data in at least one regression predictors or $C_{min,C1D21}$ level.

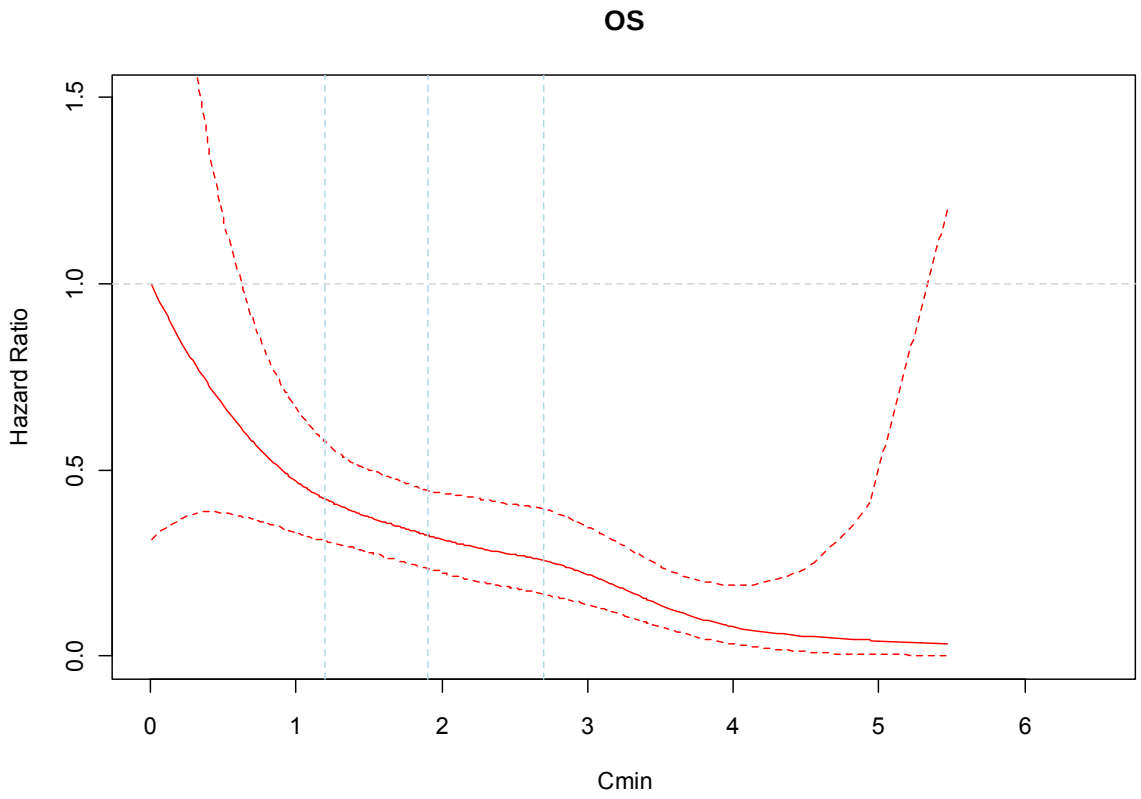


Figure 2. Ratios of overall survival (OS) hazard at different $C_{min,C1D21}$ levels compared with the hazard at $C_{min,C1D21}$ of 0. Solid line is the point estimates with 95%CI presented by dash lines. Three blue vertical lines separate space for quartiles of T-DM1 $C_{min,C1D21}$.

Progression free survival (PFS)

Kaplan-Meier survival analysis for PFS was performed with patients stratified according to quartile of trough TDM1 concentrations in cycle 1 (Q1: ≤ 1.29, Q2: >1.29 - ≤ 1.99, Q3: >1.99 - ≤ 2.75, Q4 >2.75 µg/mL) or median value. A significant difference in PFS was observed for patient groups divided according to quartiles of $C_{min,C1D21}$ (log rank test P<0.0001). The median [95% CI] PFS for patients within the lowest quartile of $C_{min,C1D21}$ was 6.7 months [5.6–10.1 months], which is 3.2 months shorter than the median PFS for patients with higher concentrations in other quartiles. The median [95% CI] PFS time for patients within less than median concentrations was 6.8 months [5.7–9.7 months], which is 5.6 months shorter than the median PFS for patients with concentrations within other quartiles. The PFS difference may not, however, attributed only to low concentrations but may also be due to confounding risk factors in this subgroup. A similar trend was observed using steady state trough concentrations as the stratification factors in the Kaplan-Meier analysis.

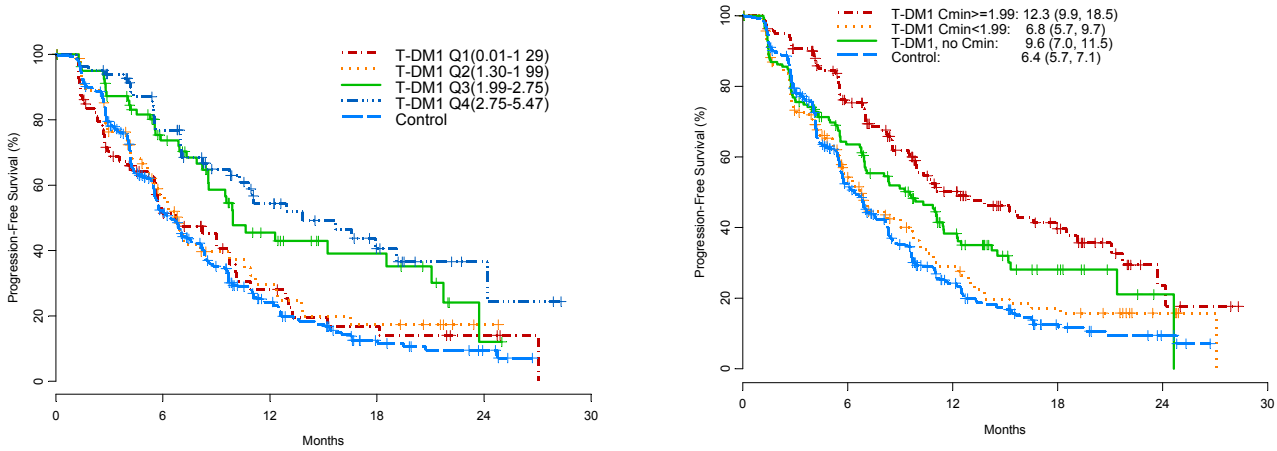


Figure 3. Kaplan-Meier curve of progression free survival (PFS) for the T-DM1 arm (N=490) by quartiles (left) or median (right) of $C_{min, C1D21}$ and for the active control arm (N=488) of the study TDM4370g/BO21977. The numbers in the right figure shows the median survival with 95% confidence interval.

A stepwise Cox regression model identified three significant baseline risk factors ($p<0.01$) for survival status: ECOG performance status (≥ 1 vs. 0), measurable disease (Yes vs. No) and tumor burden (≥ median, < median).

Hazard ratios (HR) were estimated for each of $C_{min,C1D21}$ quartiles refering to the control arm using a Cox proportional hazards model adjusted by the following baseline covariates: ECOG (0 vs. 1), number of disease sites (< 3 vs. ≥ 3), prior anthracycline use (yes vs. no), prior trastuzumab treatment (yes vs. no), visceral disease (yes vs. no), measurable disease (yes vs. no), tumor burden (Table 2). HRs of PFS decreased with increasing exposure. However, it is noted that even the lowest quartile of $C_{min, C1D21}$ demonstrated a comparable PFS with the active treatment arm (capecitabine + lapatinib).

The analysis for PFS using P-splines within the additive Cox proportional hazards model showed a similar pattern as compared to OS curve (Figure 4).

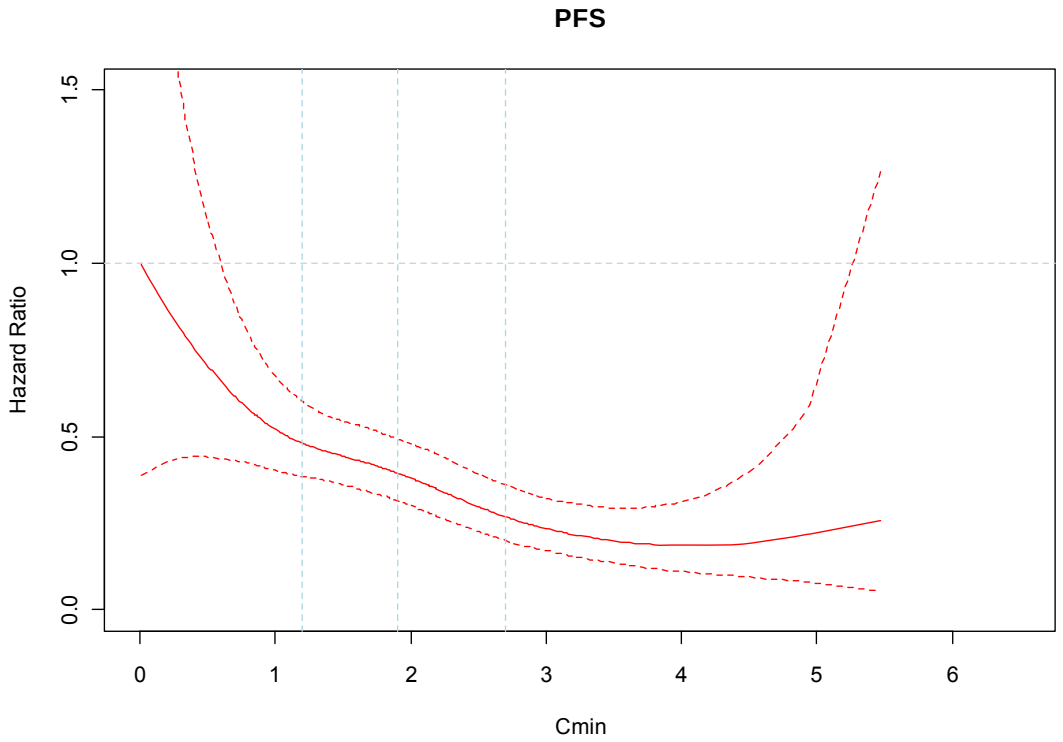


Figure 4. Ratios of progression free survival (PFS) hazard at different T-DM1 $C_{min,C1D21}$ levels compared with the hazard at T-DM1 $C_{min,C1D21}$ value of 0. Solid line is the point estimates with 95% CI presented by dash lines. Three blue vertical lines separate space for quartiles of T-DM1 $C_{min,C1D21}$.

Objective Response Rate (ORR)

ORR is the secondary efficacy endpoint in trial TDM4370g. T-DM1 exposure $C_{min,C1D21}$ is significantly related with objective response rate ($P < 0.01$), indicating higher T-DM1 exposures are related to better response rates (Figure 5).

A significant relationship was identified between $C_{min,C1D21}$ and objective response rates, the secondary efficacy endpoint in Trial 4370, with logistic regression using an E_{max} model. E_{max} logistic regression model were used, as it reasonably described the data (Figure 5). The objective response rate increases with T-DM1 exposure. Based on the model, the typical response rate for the median C_{min} of 1.98 ug/mL is 47% ((95% CI: 40% to 54%).). The EC50 is estimated as approximately 1.5 ug/mL. This analysis for ORR provides further supportive evidence for a significant E-R relationship.

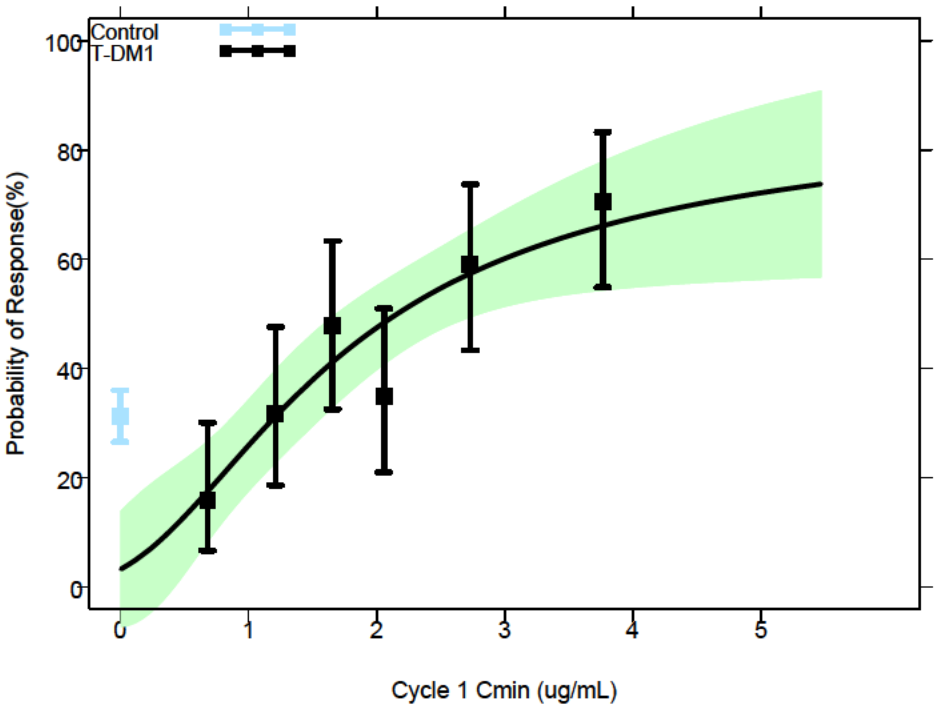


Figure 5. The logistic regression analysis between objective response rates (ORR) and T-DM1 $C_{min,C1D21}$ using an E_{max} model. Solid black squares represent the proportion of responders grouped by quantiles of T-DM1 $C_{min,C1D21}$ and plotted at the median for the groups. Solid blue square represents the response treated with active control (lapatinib plus capecitabine). Centered curves and shaded area represent predicted values and 95% of model predicted response probability, respectively.

Overall, the analysis indicated that the higher the T-DM1 exposure, the greater the OS or PFS improvement. Furthermore, T-DM1 exposure ($C_{min,C1D21}$) was significantly related to objective response rate (ORR, $P < 0.01$) (Figure 5), using a logistic regression analysis of an E_{max} model.

1.1.2 Are there exposure-response relationships for safety?

Using $C_{min, C1D21}$ available in 334 patients in the pivotal trial (TDM4370g/BO21977), an inverse trend was identified for Grade 3 or worse (Grade 3+) hepatotoxicity, but no significant exposure-response relationships were identified for thrombocytopenia and peripheral neuropathy. Using $C_{min, C1D21}$ available in 673 patients in all five trials submitted, the incidence of Grade 3 or worse adverse events (Grade 3+ AEs) in patients with low exposure (< median $C_{min, C1D21}$) is slightly higher than that in patients with high exposure (≥ median $C_{min, C1D21}$). Nontheless, the actual dose adjustments (including dose interruption, dose discontinuation, dose reduction) are similar across quartiles of $C_{min, C1D21}$. Compared to the control arm (capecitabine + lapatinib), T-DM1 treated patients has lower incidence of Grade 3+ AEs and lower rate of dose adjustments.

Individual toxicities

The most common adverse events leading to dose adjustments (including dose interruption, discontinuation, and reduction) were thrombocytopenia, hepatotocicity (AST/ALT increased), and peripheral neuropathy in either the pivotal study TDM4370g or all the five T-DM1 trials submitted in this BLA. Exposure-response analysis using a logistic regression model with $C_{min,C1D21}$ as the expsoure variable were conducted for these individual toxicities. Results suggested that an inverse trend was identified for hepatotoxicity (Figure 6, Left), but not for thrombocytopenia (Figure 7, Left) and peripheral neuropathy (Figure 8, Left). However, no trends were identified using the boxplots of TDM1 exposure for each grade of thrombocytopenia (Figure 7, Right), hepatotoxicity (Figure 6, Right), and peripheral neuropathy (Figure 8, Right).

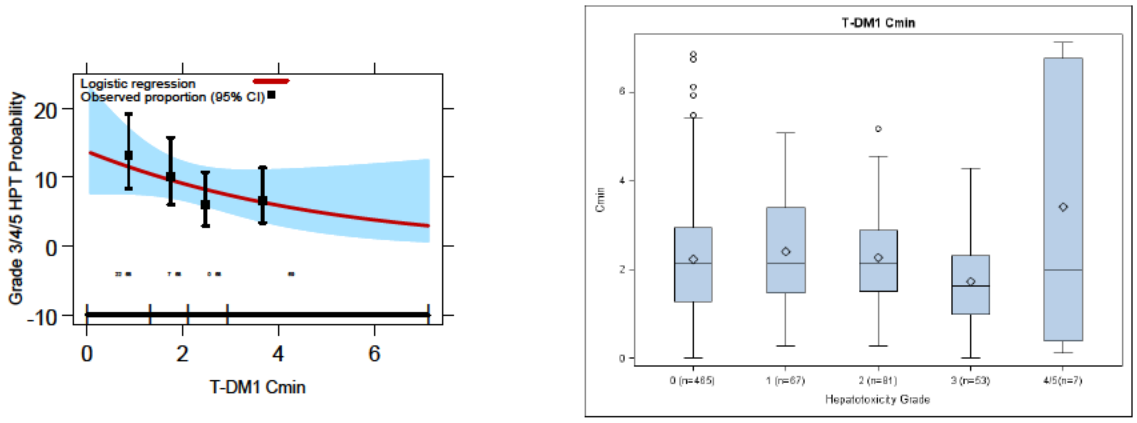


Figure 6. The relationship between $C_{min, C1D21}$ and the incidence of Grade 3 or worse hepatotoxicity using logistic regrssion model (left panel) and boxplot for grades of hepatotoxicity (right panel). In the left panel, solid black symbols represent the observed proportion of patients experiencing Grade 3 or worse hepatotoxicity in each quartile of $C_{min,C1\ D21}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of Grade 3 or worse hepatotoxicity. The exposure range in each quartile of $C_{min,C1D21}$ is denoted by the horizontal black line along with the number of patients with hepatotoxicity/total number of patients in each quartile.

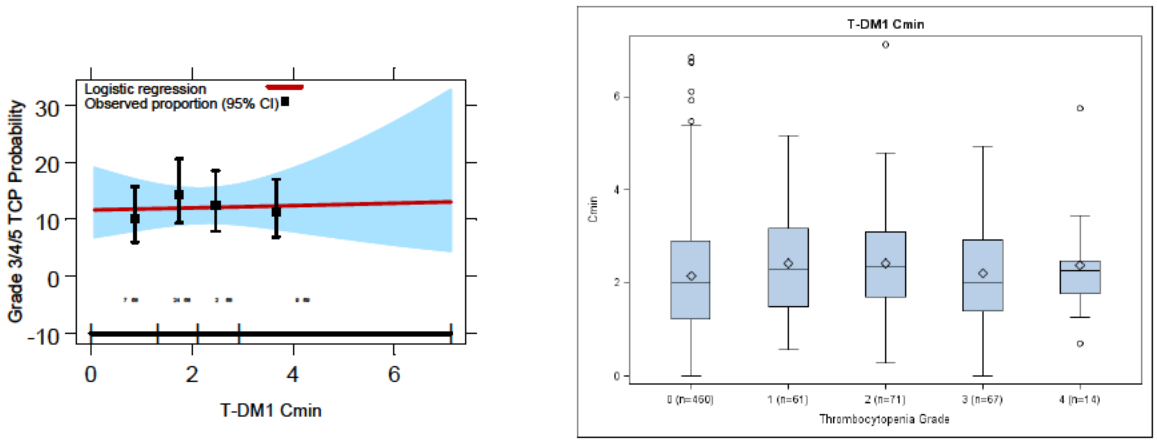


Figure 7. The relationship between $C_{min, C1D21}$ and the incidence of Grade 3 or wrose thrombocytopenia (TCP) using logistic regrssion model (left panel) and boxplot for grades of throbocytopenia (right panel). In the left panel, solid black symbols represent the observed proportion of patients experiencing Grade 3 or worse thrombocytopenia in each quartile of $C_{min,C1D21}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of Grade 3 or worse thrombocytopenia. The exposure range in each quartile of $C_{min,C1D21}$ is denoted by the horizontal black line along with the number of patients with thrombocytopenia/total number of patients in each quartile.

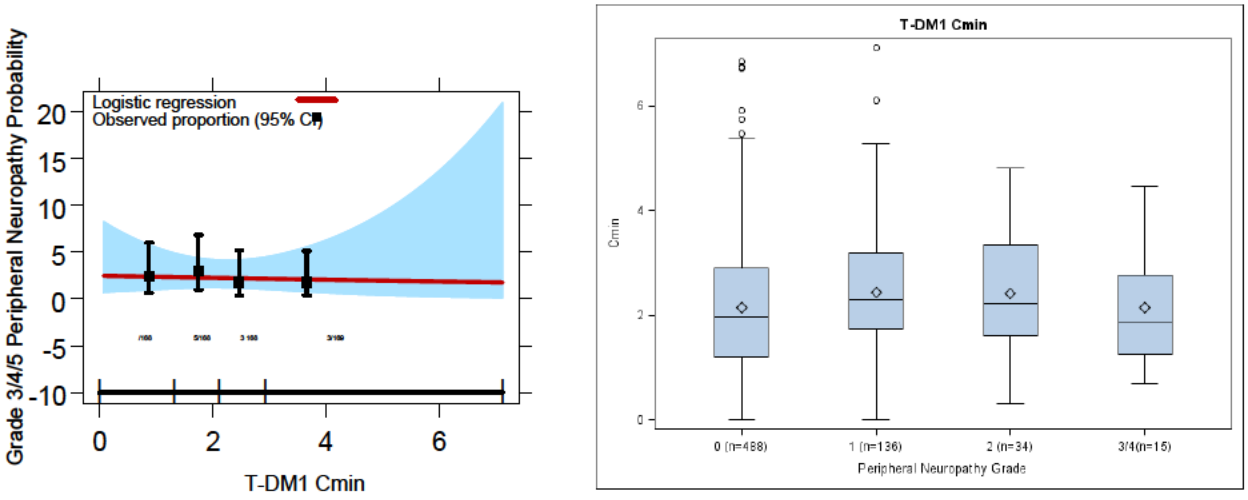


Figure 8. The relationship between $C_{min, C1D21}$ and the incidence of ≥ Grade 3 peripheral neuropathy using logistic regrssion model (left panel) and boxplot for grades of peripheral neuropathy (right panel). In the left panel, solid black symbols represent the observed proportion of patients experiencing Grade 3 or worse peripheral neuropathy in each quartile of $C_{min, C1D21}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area

represent the predicted mean and 95% confidence interval for the probability of Grade 3 or worse peripheral neuropathy. The exposure range in each quartile of $C_{min, C1D21}$ is denoted by the horizontal black line along with the number of patients with peripheral neuropathy/total number of patients in each quartile of $C_{min, C1D21}$.

Grade 3 or worse AEs

Exposure-response analyses using $C_{min, C1D21}$ as the expsoure variable were conducted for Grade 3 or worse AEs to evaluate whether the high exposure is related to the higher incidence of Grade 3 or worse AEs. A slightly higher incidence of Grade 3+ AEs was observed in patients with low exposure quartiles (Q1 and Q2) rather than in patients with high exposure (Q3 and Q4). A plausible explanation is that the poorer baseline prognostic factors in these patients lead to more AEs. The incidence of Grade 3 or worse AEs in the control arm (capecitabine and lapatinib) is higher than that in T-DM1 arm.

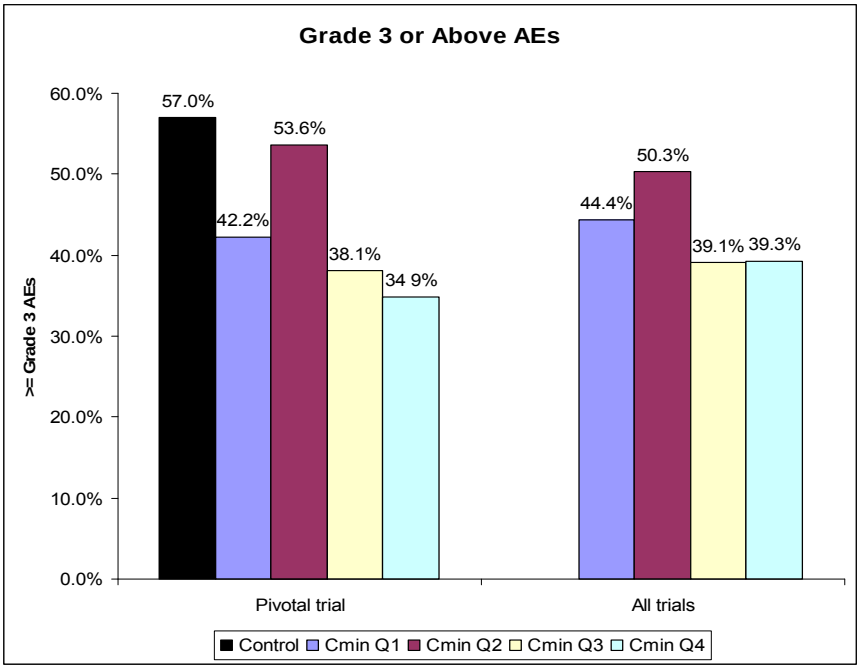


Figure 9. Bar graph represents the incidence of Grade 3 or worse AEs in 334 patients in the pivotal trial (TDM4370g/BO21977) or in 673 patients in a total of five clinical trials of T-DM1 including the the pivotal trial (TDM4370g/BO21977).

Dose adjustments

Actual dose adjustments in pivotal trial were stratified by the T-DM1 $C_{min, C1D21}$ to evaluate whether higher actual dose adjustments (dose interruption, early discontinuation, and dose reduction) are related with higher exposure. Results suggested that the actually dose adjustments are similar across the quartiles of T-DM1 exposure. The dose adjustments occurred more frequently in the active control arm with capecitabine and lapatinib than T-DM1 arm.

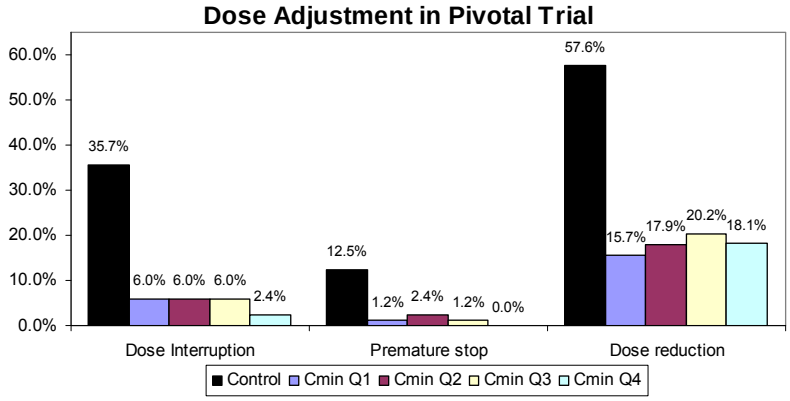


Figure 10. Bar graph for the dose adjustments including dose interruption, premature stop, or dose reduction in 334 patients in the pivotal trial whose $C_{min, C1D21}$ were available.

The actual dose adjustments were similar across exposures quartiles and were much lower than the standard of care, though the slightly higher Grade 3 or worse AEs in lower exposure quartiles may leave only limited room for higher dose.

1.1.3 Does renal function affect PK or safety of T-DM1?

The mild to moderate renal function does not appear to affect PK or safety of T-DM1 or DM1. Furthermore, mild to moderate renal function does not appear to affect incidence of Grade 3 or worse AEs, as well as the dose adjustments. Therefore, dose adjustment in patients with mild to moderate renal impairment may not be necessary. Information is limited in patients with severe renal impairment.

PK:

A total of 54% patients (N=361) had normal renal function in the population PK model development dataset. The impact of renal impairment on PK of trastuzumab emtansine was further assessed by categorizing patients with varying degrees of renal impairment into 4 categories based on their estimated CrCL: Normal (CLcr ≥ 90 mL/min, N=303), mild (60 mL/min ≤ creatinine clearance (CLcr) < 90 mL/min, N=223), moderate (30 mL/min ≤ CLcr < 60 mL/min, N=41), and severe (CLcr < 30 mL/min, N=1) renal impairment. There are no patients with end stage renal disease (ESRD) in this evaluation.

Based on the covariate assessment of the impact of serum creatinine clearance on inter-individual random effects of PK parameters (Figure 12) and the comparison of expected T-DM1 exposure simulated from post-hoc PK parameters of patients with different renal functions (Figure 11), mild or moderate impaired renal function appears to have no effect on T-DM1 exposure. However, no conclusions can be drawn for patients with severe renal impairment and ESRD, as the assessment was limited to only 1 patient with severe renal impairment.

T-DM1 exposure (Cmin for Cycle 1 Day 21 and Cycle 6 Day 21) was simulated using the Bayesian post-hoc PK parameters for trastuzumab emtansine at dose 3.6 mg/kg q3w. The impact of renal function on trastuzumab emtansine exposure are shown in Table 3 and Figure 11. The

differences for Cmin between the mild impairment and moderate impairment groups versus normal groups is < 10.5%. There is only 1 patient with severe renal impairment and the exposure parameters of this individual were similar to the mean values of the patients from the normal group.

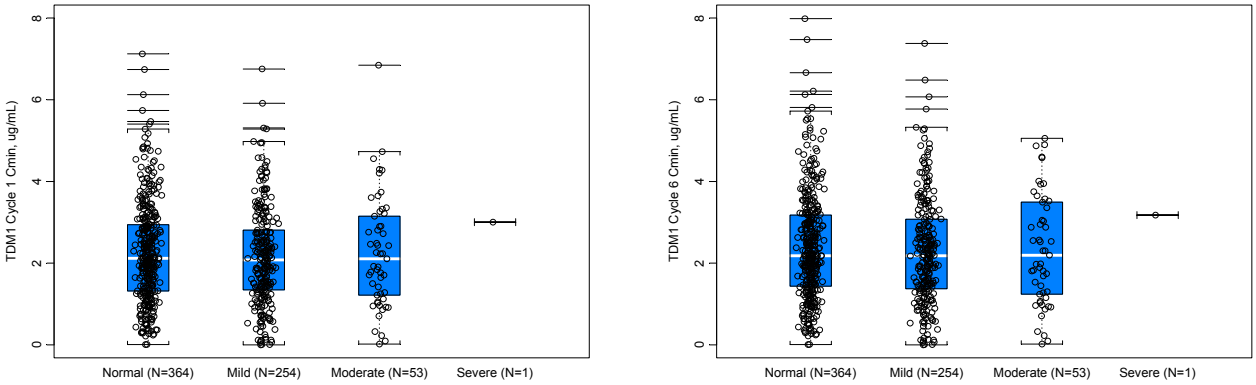


Figure 11: Plots of renal function vs 1st cycle and 6th cycle Cmin for TDM1.

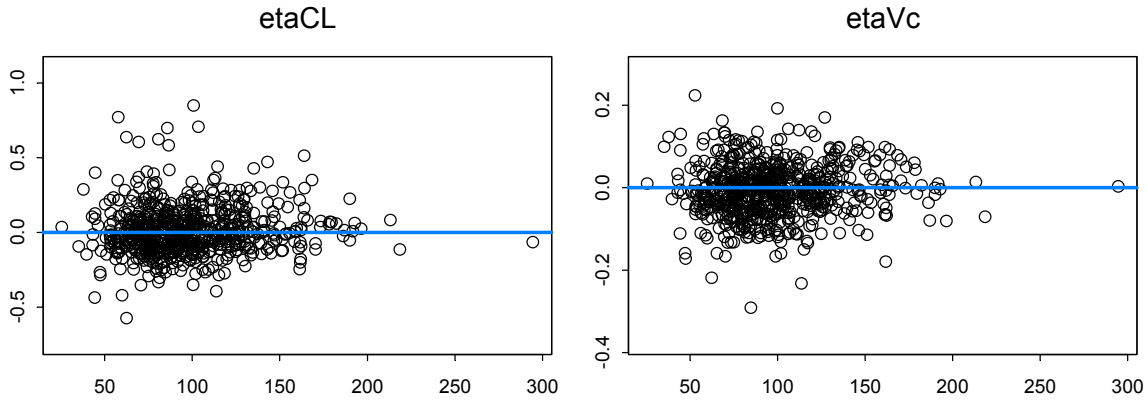


Figure 12: Plot of inter-individual random effects versus creatinine clearance for the final PK model

Table 3: Impact of renal function on steady state trastuzumab emtansine exposure after repeated dosing of 3.6 mg/kg by 0.5 hour IV infusion q3w

Characteristics	Renal Function			
	Normal	**Mild Impairment**	**Moderate Impairment**	**Severe Impairment**
No. of patients (%)	361 (53.96)	254 (37.97)	53 (7.922)	1 (0.149)
AUC (day*µg/mL)	391.6 (264.7, 524.8)	360.1 (218.0, 485.5)	350.2 (217.5, 493.3)	375.5
Cmin (µg/mL)	2.390 (0.507, 4.755)	2.295 (0.408, 4.607)	2.547 (0.285, 4.708)	3.161
Cmax (µg/mL)*	85.45 (71.33, 102.7)	79.60 (65.31, 94.99)	77.65 (62.09, 96.09)	78.08

As the renal function may affect the excretion of DM1 and subsequently affect the safety of T-DM1, exploratory analyses were conducted to explore the relationships between the renal function and DM1 C_{max}, between the renal function and the incidence of Grade 3+ AEs or dose adjustments. Results suggested that renal function does not affect DM1 C_{max} (Figure 13) and the incidence of Grade 3+ AEs, as well as the dose adjustments (Table 4). The results indicate that dose adjustment based on renal impairment appears unnecessary.

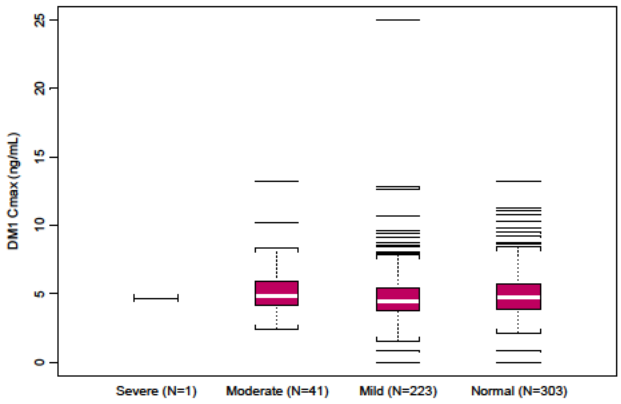


Figure 13. Box-plots for the DM1 C_{max} in patients with various degrees of renal function. Based on each patient's baseline creatinine clearance (CLcr), renal function groups are defined as normal renal function (CLcr ≥ 90 mL/min, N=303), mild (60 mL/min ≤ creatinine clearance (CLcr) < 90 mL/min, N=223), moderate (30 mL/min ≤ CLcr < 60 mL/min, N=41), and severe (CLcr < 30 mL/min, N=1) renal impairment.

Safety:

Renal function does not appear to affect the incidence of Grade 3 or worse AEs, as well as the dose adjustments (Table 4).

Table 4. The incidence of Grade 3 or worse adverse events (G3+ AEs) and dose adjustments (including dose interruption, discontinuation, or reduction) in patients with baseline creatinine clearance (CrCL).

Renal function	Pivtoal trial				All trial			
	G3+ AEs		Dose Adjustments		G3+ AEs		Dose Adjustments	
	N	%	N	%	N	%	N	%
Severe (CrCL < 30 mL/min)	1	100%	0	0%	3	66.7%	1	0%
Moderate (30 mL/min ≤ CrCL< 60 mL/min)	17	23.5%	17	0%	42	47.6%	34	17.7%
Mild (60 mL/min ≤ CrCL < 90 mL/min)	122	51.6%	122	23.0%	233	52.8%	202	27.7%
Normal (CrCL ≥ 90 mL/min)	169	37.9%	169	24.9%	324	40.1%	279	30.5%

Note: Dose adjustments include dose interruption, discontinuation or reduction.

1.1.4 Is the proposed body weight based dosing acceptable?

The reviewers concluded that the body weight based dose of 3.6 mg/kg every 3 week is acceptable:

1. Baseline body weight was identified as the significant covariate impacting trastuzumab emtansine steady state AUC and C_{max}. The figures below show the covariate assessment of the impact of body weight on inter-individual random effects of PK parameters (Figure 14) and the expected T-DM1 exposures simulated from post-hoc PK parameters of patients using body weight based dosing regimen (Figure 15)
2. Considering that the MTD of T-DM1 was established based on body weight-based dosing, and it has been used in clinical trials, the current body weight-based dosing of T-DM1 is acceptable.

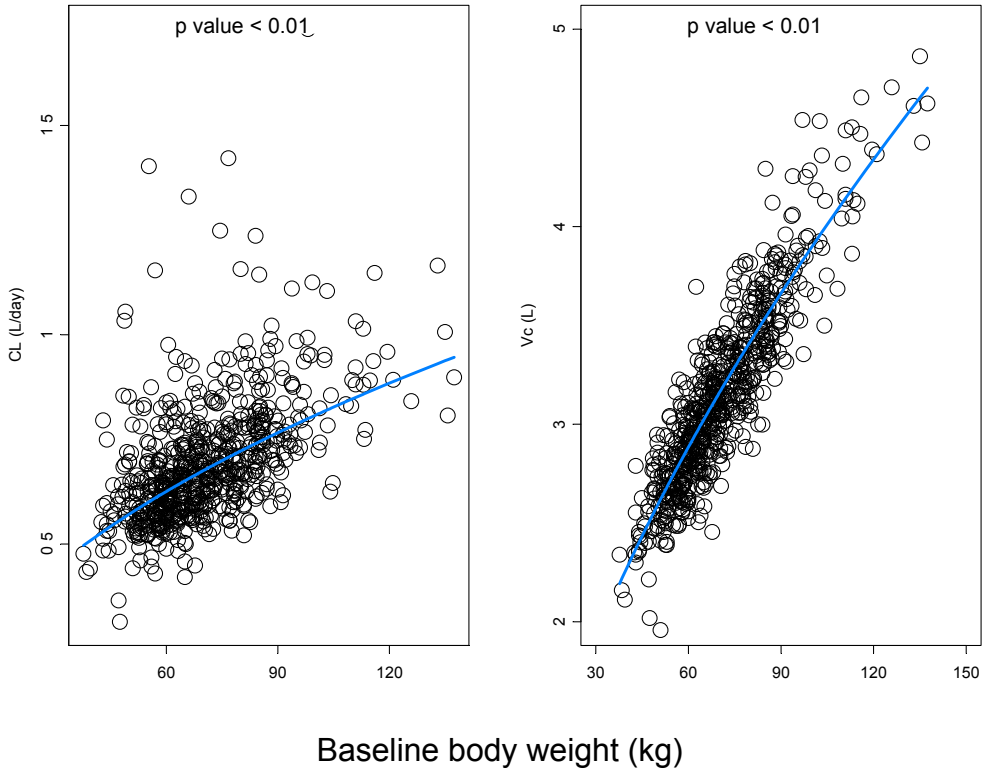


Figure 14: Plots of CL vs body weight (left) and central volume of distribution vs. body weight (right).

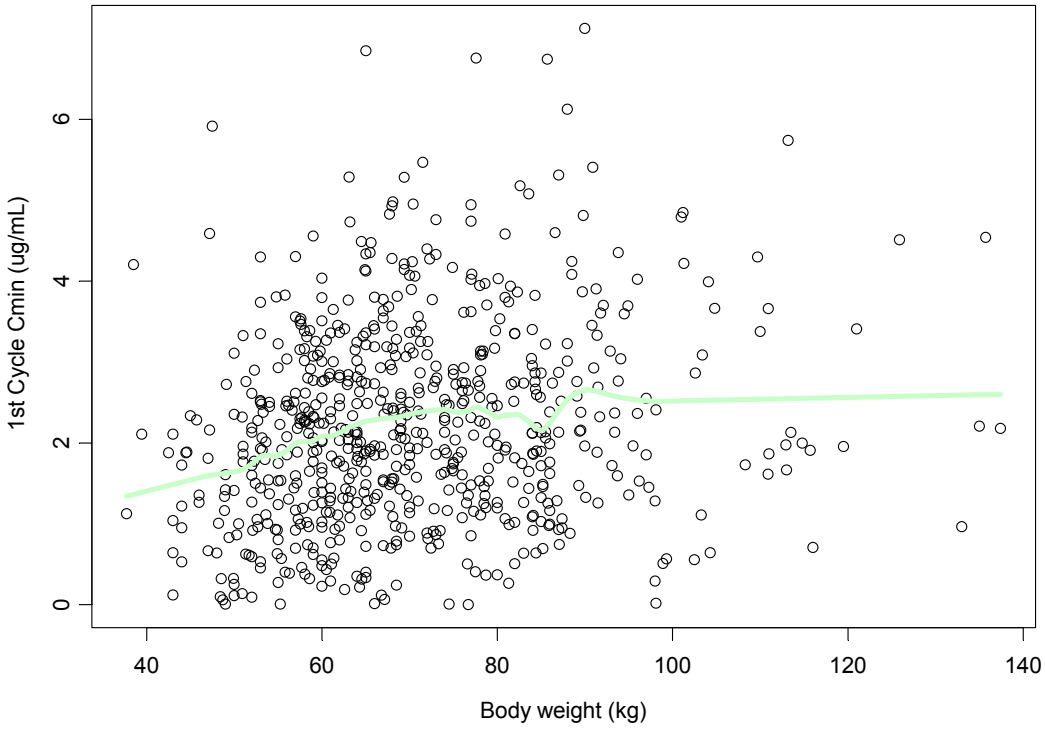


Figure 15: Plots of 1st cycle Cmin vs. body weight indicating that body weight based dosing is appropriate since we observe random scatter of exposures across body weight range.

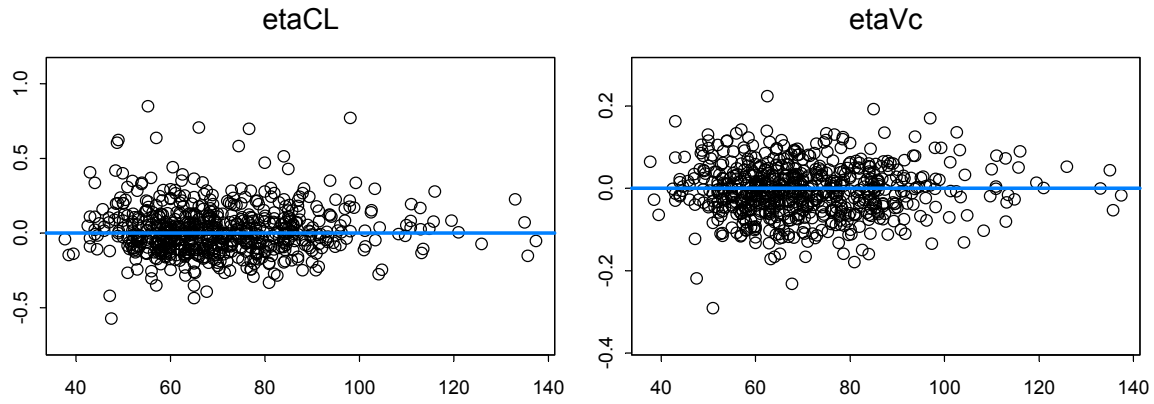


Figure 16: Plot of inter-individual random effects versus body weight for the final PK model

1.1.5 Based on PopPK analyses, what intrinsic factors other than body weight affect T-DM1 PK?

In addition to body weight, albumin, sum of longest diameter of target lesions by RECIST, HER2 ECD, baseline trastuzumab concentrations and AST were identified as statistically significant covariates for trastuzumab emtansine pharmacokinetic parameters. A summary of the covariate effects on clearance is shown in Table 5 and Figure 17. The magnitudes of effect of these covariates on clearance indicate that no dose adjustment is required based on these covariates. The impact of those significant covariates on inter-individual random effects of PK parameters are shown below. After including the significant covariates in the model, IIV for CL was decreased from 25.6% to 19.1%.

Although AST has been identified as a significant factor for T-DM1 clearance, the magnitude of its effect on T-DM1 Cmin is less than 20%. In addition, the study population does not include enough numbers of patients with hepatic impairment. The range of AST may not be enough to draw any meaningful conclusion. Therefore, the effect of hepatic impairment on T-DM1 pharmacokinetics could not be determined from this analysis.

Table 5: Covariate effects on clearance of TDM1 from the applicant's PopPK model.

		Covariate Value	CL (L/day)	CL change %	AUC (day*ug/mL)	AUC change %	Cmax (ug/mL)	Cmax change %
Typical CL			0.676		373		79.8	
body weight (kg)	5th percentile	49	0.566	-16.27	312	-16.35	68.7	-13.91
	95th percentile	98	0.799	18.20	441	18.23	91.9	15.16
Albumin (g/L)	5th percentile	33	0.738	9.17	342	-8.31	79.3	-0.63
	95th percentile	48	0.634	-6.21	398	6.70	80.3	0.63
ECD (ng/mL)	5th percentile	8.5	0.647	-4.29	390	4.56	80.1	0.38
	95th percentile	332	0.75	10.95	336	-9.92	79.2	-0.75
Tumor Burden (cm)	5th percentile	1.5	0.615	-9.02	410	9.92	80.5	0.88
	95th percentile	30.3	0.72	6.51	350	-6.17	79.4	-0.50
Baseline trastuzumab (ug/mL)	5th percentile	0	0.676	0.00	373	0.00	79.8	0.00
	95th percentile	54	0.613	-9.32	411	10.19	80.6	1.00
AST (U/L)	5th percentile	15.3	0.651	-3.70	387	3.75	80.1	0.38
	95th percentile	64	0.715	5.77	353	-5.36	79.5	-0.38

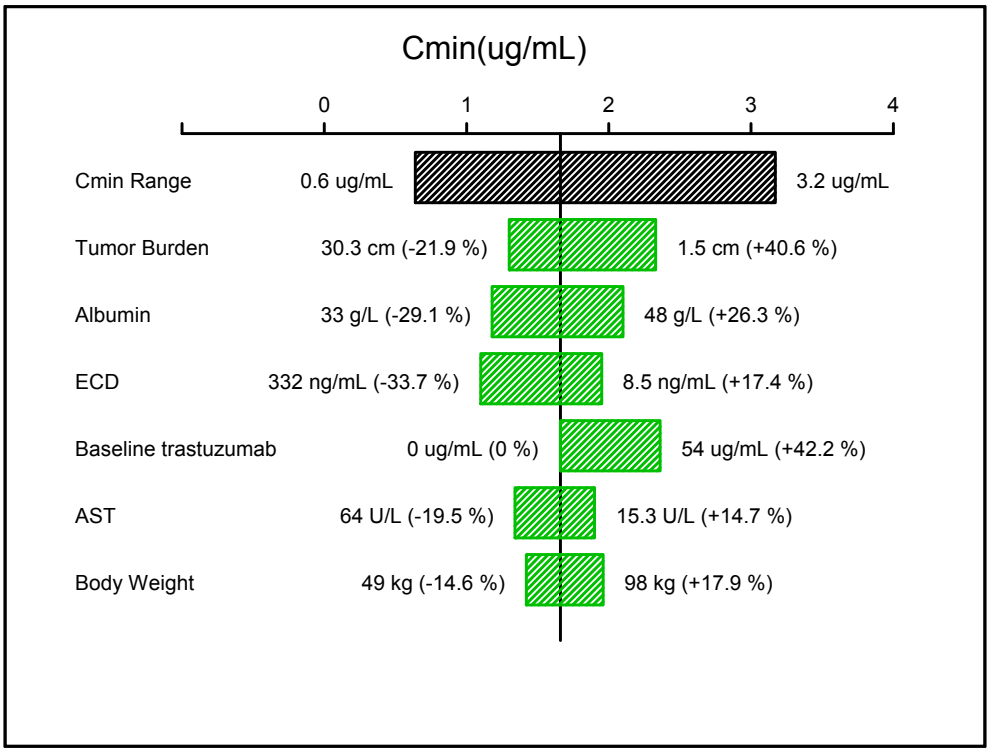
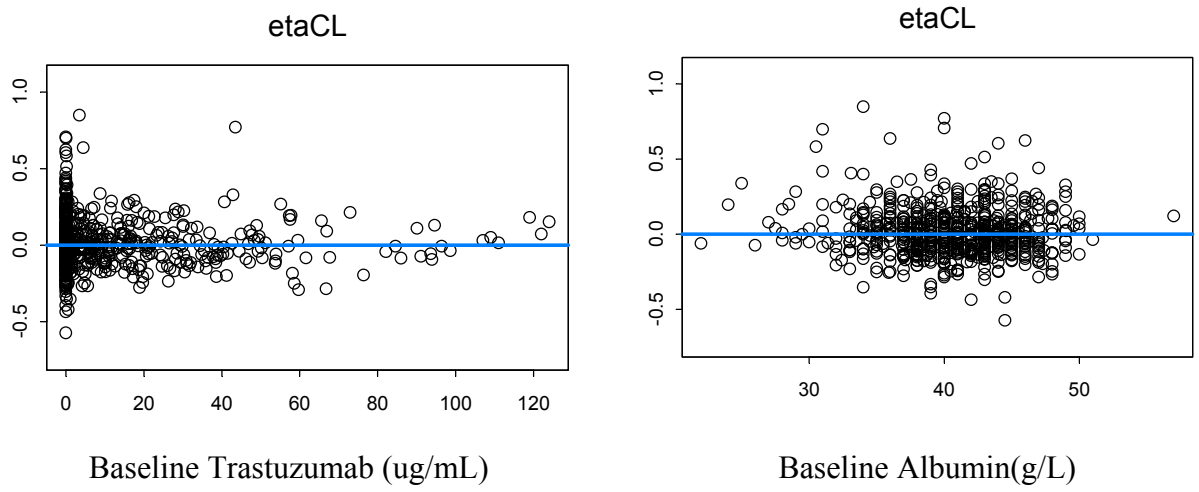


Figure 17: The effect of covariates on trastuzumab emtansine steady state exposure



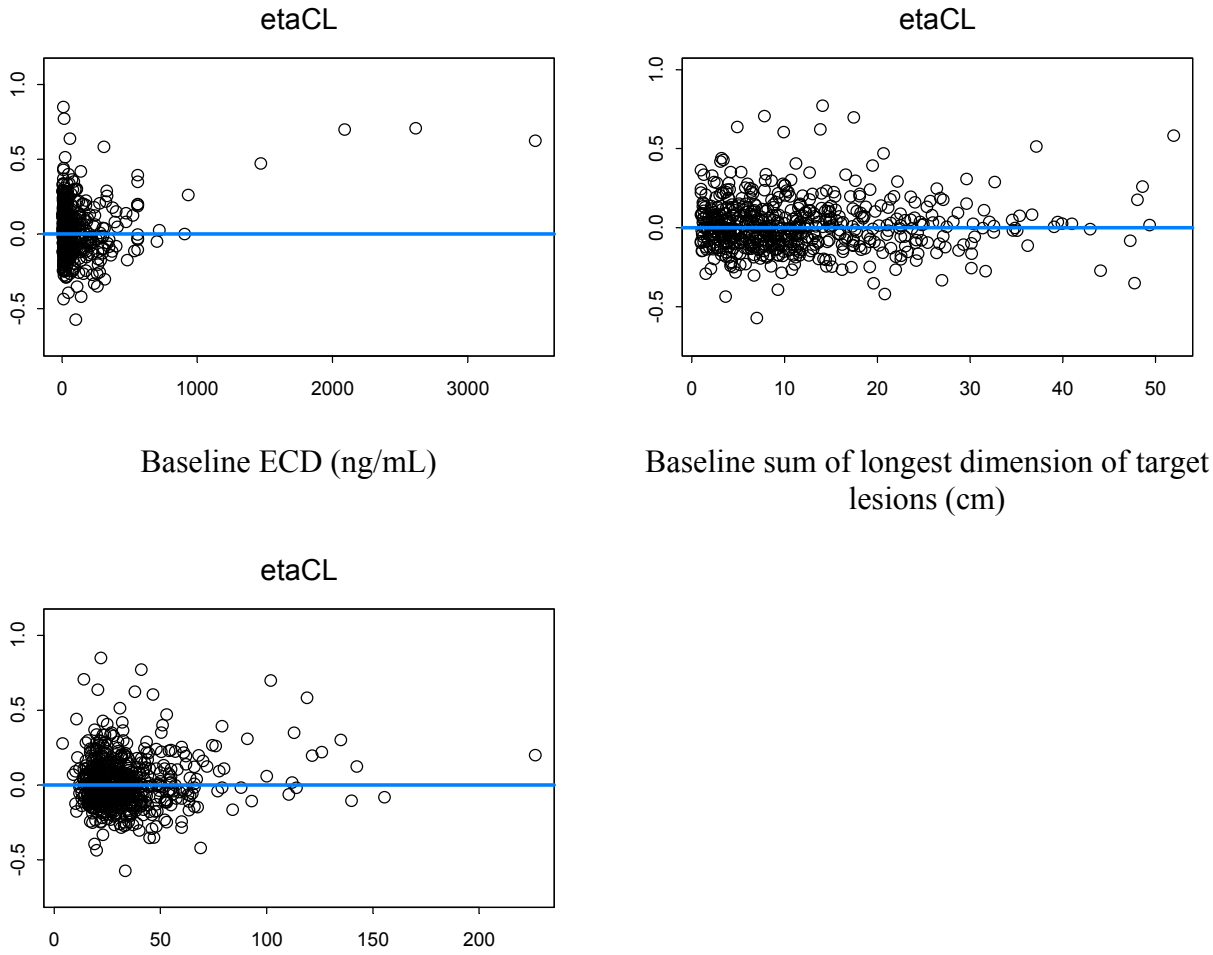


Figure 18: Plot of inter-individual random effects for CL (etaCL) versus baseline factors.

1.2 Recommendations

Division of Pharmacometrics finds that the BLA125427 is acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the Applicant and the Agency regarding the post marketing commitment and labeling language.

1.3 Post Marketing Commitments

To conduct xxx-trastuzumab emtansine conjugate exposure-response analyses for progression free survival, final overall survival, and safety endpoints utilizing data from trial BO25734/TDM4997 (TH3RESA). Evaluation of the results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will determine the need, or

otherwise, for a postmarketing trial to optimize the dose in metastatic breast cancer patients with lower xxx-trastuzumab emtansine conjugate exposure at the approved dose (3.6 mg/kg q3w)

1.4 Label Statements

Only relevant clinical pharmacology sections are included.

APPLICANT PROPOSED PACKAGE INSERT	FDA RECOMMENDED PACKAGE INSERT
6.2 Immunogenicity As with all therapeutic proteins, there is the potential for an immune response to KADCYLA. A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to KADCYLA. Following KADCYLA dosing, 5.3% (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. (b) (4) Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. (b) (4)	**6.2 Immunogenicity** As with all therapeutic proteins, there is the potential for an immune response to KADCYLA. A total of 836 patients from six clinical studies were tested at multiple time points for anti-therapeutic antibody (ATA) responses to KADCYLA. Following KADCYLA dosing, 5.3% (44/836) of patients tested positive for anti-KADCYLA antibodies at one or more post-dose time points. The presence of KADCYLA in patient serum at the time of ATA sampling can interfere with the ability of this assay to detect anti-KADCYLA antibodies. As a result, data may not accurately reflect the true incidence of anti-KADCYLA antibody development. In addition, neutralizing activity of anti-KADCYLA antibodies has not been assessed. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to KADCYLA with the incidence of antibodies to other products may be misleading. Clinical significance of anti-KADCYLA antibodies it not known.
7 Drug Interactions No formal drug-drug interaction studies with KADCYLA in humans have been conducted. (b) (4)	**7 Drug Interactions** No formal drug-drug interaction studies with KADCYLA have been conducted. *In vitro* studies indicate that DM1, the cytotoxic component of KADCYLA, is metabolized mainly by CYP3A4, and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with KADCYLA should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying KADCYLA treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors)

	when possible. If a strong CYP3A4 inhibitor is coadministered and KADCYLA treatment can not be delayed, patients should be closely monitored for adverse reactions.
8.5 Geriatric Use (b) (4)	**8.5 Geriatric Use** Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab emtansine [see Clinical Pharmacology (12.3)].
8.7 Renal Impairment (b) (4)	**8.7 Renal Impairment** No dedicated renal impairment trial for KADCYLA has been conducted. Based on the population pharmacokinetics, as well as analysis of Grade 3 or greater adverse drug reactions and dose modifications, dose adjustments of KADCYLA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited data available [see Clinical Pharmacology (12.3)].
8.8 Hepatic Impairment (b) (4)	**8.8 Hepatic Impairment** *In vitro* studies in human liver microsomes indicate that DM1 is metabolized by CYP3A4/5. The influence of hepatic impairment on the pharmacokinetics of trastuzumab emtansine conjugate (ADC) or DM1 has not been determined.
	n/a
12.3 Pharmacokinetics ***Distribution*** (b) (4)	**12.3 Pharmacokinetics** The pharmacokinetics of KADCYLA was evaluated in a phase 1 study and in a population pharmacokinetic analysis for the trastuzumab emtansine conjugate (ADC) using pooled data from 5 trials in patients with breast cancer. A linear two-compartment model with first-order elimination from the central compartment adequately describes the ADC concentration-time profile. In addition to ADC, the pharmacokinetics of total antibody (conjugated and unconjugated trastuzumab), DM1 were also determined. The pharmacokinetics of KADCYLA are summarized below.

(b) (4)	***Distribution*** Maximum concentrations (Cmax) of ADC and DM1 were observed close to the end of infusion. In Study 1, mean (SD) ADC and DM1 Cycle 1 Cmax following KADCYLA administration was 83.4 (16.5) µg/mL and 4.61 (1.61) ng/mL, respectively. *In vitro*, the mean binding of DM1 to human plasma proteins was 93%. In vitro, DM1 was a substrate of P-glycoprotien (P-gp). Based on population pharmacokinetic analysis, the central volume of distribution of ADC was 3.13 L.
Metabolism (b) (4)	***Metabolism*** In vitro studies indicate that DM1, the small molecule component of KADCYLA, undergoes metabolism by CYP3A4/5. DM1 did not inhibit or induce major CYP450 enzymes *in vitro*. In human plasma, trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1, and DM1 were detected at low levels.
Elimination (b) (4)	***Elimination*** Based on population pharmacokinetic analysis, the clearance of ADC was 0.68 L/day and the elimination half-life (t½) was approximately 4 days. No accumulation of KADCYLA was observed after repeated dosing of intravenous infusion every 3 weeks. Based on population pharmacokinetic analysis (n=671), body weight, sum of longest diameter of target lesions by RECIST, HER2 extracellular domain (ECD) concentrations, AST, albumin, and baseline trastuzumab concentrations were identified as statistically significant covariates for trastuzumab emtansine clearance. However, the magnitude of effect of these covariates on trastuzumab emtansine exposure suggests that, with the exception of body weight, these covariates are unlikely to have a clinically meaningful effect on KADCYLA exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates is considered appropriate.

Effects of Age and Race (b) (4)	***Effects of Age and Race*** Based on population pharmacokinetic analysis, age (< 65 (n=577); 65 - 75 (n=78); > 75 (n=16)) and race (Asian (n=73); non-Asian (n=598)) do not have a clinically meaningful effect of on the pharmacokinetics of trastuzumab emtansine.
Effect of Renal Impairment (b) (4)	***Effect of Renal Impairment*** Based on population pharmacokinetic analysis in 668 patients, including moderate (CLcr 30 - 59 mL/min, n=53) and mild (CLcr 60 - 89 mL/min, n=254) renal impairment, indicate that pharmacokinetics of the ADC is not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥ 90 mL/min, n=361). Data from only one patient with severe renal impairment (CLcr < 30 mL/min) is available [see Use in Specific Populations (8.7).
n/a	**12.6 Cardiac Electrophysiology** The effect of multiple doses of KADCYLA (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive metastatic breast cancer. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

2 APPLICANT'S ANALYSES

The applicant performed population PK analysis to identify significant factors affecting T-DM1 PK. Exposure-response analyses for efficacy was conducted using data from pivotal trial while data from all trials was utilized for exposure-safety analysis. The key findings from the Applicant's analyses are summarized below:

2.1 Population Pharmacokinetic Analysis

Sponsor performed population PK modeling utilizing data from one phase 1/ 2 (Study 251) and two phase 3 studies (Studies 351 and 352).

Primary objective of the population PK analysis was to characterize the population pharmacokinetics of INCB018424 and to quantify sources of variability in INCB018424 exposure.

2.1.1 Datasets

Detailed descriptions of all data stratified by studies are provided in Table 6.

2.1.2 Methods

PK data were then fitted using NONMEM Version 7.0 (Icon US, Hanover MD). Model building and covariate assessments were conducted using standard methods. The final model was evaluated for performance using several tests, including evaluation of an external validation database and visual predictive check (VPC) evaluation.

All exploratory data analyses and presentations of data were performed using S-Plus software and SAS software, Version 9.1. The PK analyses were done using NONMEM Version 7.0 and the Intel Fortran Compiler 11.0. NONMEM runs were executed using PDx-POP for NONMEM Version 4.0. Generalized additive model (GAM) analysis was performed using Xpose 3.10.S-Plus software was used for exploratory graphical analysis of covariates.

2.1.3 Results

Parameter estimates for fixed effect and random effects with standard errors are presented in Table 6 below. Basic goodness of fit plots from the sponsor's final model is presented in the Appendix.

Table 6 : Summary of clinical studies included in the PopPK analysis

Study	N	Population	Trastuzumab emtansine
TDM3569g Phase I	52	Patients with HER2+ mBC (previously treated by trastuzumab)	q3w (n=24): 0.3, 0.6, 1.2, 2.4, 3.6, and 4.8 mg/kg q1w (n=28): 1.2, 1.6, 2.0, 2.4, and 2.9 mg/kg
TDM4258g Phase II	111	Patients with HER2+ mBC (relapsed from HER2 direct therapy)	3.6 mg/kg q3w
TDM4374g Phase II	110	Patients with HER2+ mBC	3.6 mg/kg q3w
TDM4450g/BO21976 Phase II	67	Patients with HER2+ mBC (no prior chemotherapy for metastatic disease)	3.6 mg/kg q3w
TDM4370g/BO21977 (EMILIA) Phase III	341	Patients with HER2+ LABC or mBC (received prior trastuzumab and taxanes during adjuvant phase, LABC or mBC setting)	3.6 mg/kg q3w

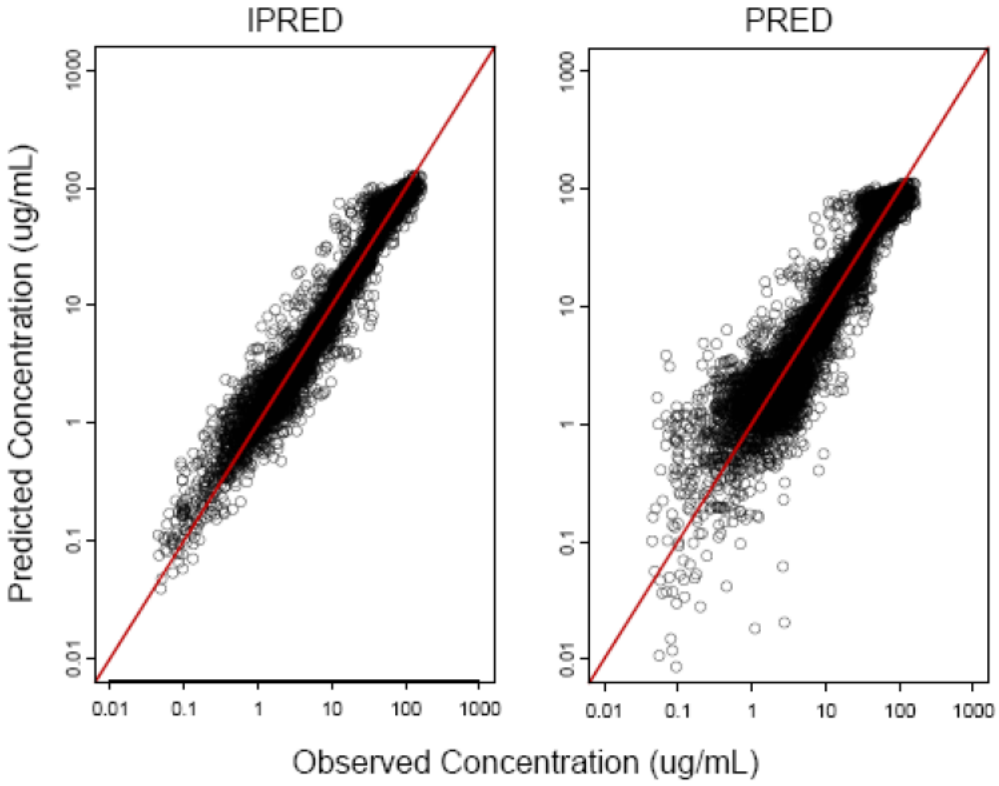


Figure 19: Predicted versus observed goodness-of-fit plots for the final PopPK model

Table 7: Parameter Estimates and Standard Errors from Final Population Pharmacokinetic Model

Parameter	Parameter Description	Final PopPK Model Point Estimates (95% CI)	Bootstrap Results of Final PopPK Model Median (2.5^{th}, 97.5^{th} Percentiles)
$\exp(\theta_1)*24$	Clearance, CL (L/day)	0.676 (0.661, 0.691)	0.673 (0.656, 0.691)
θ_6	Influence of weight on CL	0.49 (0.41, 0.57)	0.494 (0.402, 0.583)
θ_7	Influence of ECD on CL	0.035 (0.021, 0.05)	0.034 (0.013, 0.057)
θ_8	Influence of ALBU on CL	-0.423 (-0.553, -0.293)	-0.420 (-0.569, -0.264)
θ_9	Influence of TMBD on CL	0.052 (0.033, 0.071)	0.051 (0.031, 0.071)
θ_{10}	Influence of TBL on CL	-0.002 (-0.002, -0.001)	-0.002 (-0.002, -0.001)
θ_{11}	Influence of AST on CL	0.071 (0.036, 0.106)	0.072 (0.028, 0.111)
$\exp(\theta_2)$	Volume of distribution in central compartment, V_c (L)	3.127 (3.08, 3.174)	3.125 (3.077, 3.182)
θ_5	Influence of weight on V_c	0.596 (0.526, 0.666)	0.594 (0.518, 0.675)
$\exp(\theta_3)*24$	Distribution clearance, Q (L/day)	1.534 (1.286, 1.83)	1.420 (0.792, 1.761)
$\exp(\theta_4)$	Volume of distribution in peripheral compartment, V_p (L)	0.66 (0.58, 0.752)	0.642 (0.503, 0.754)
Inter-individual variability (%)	CL	19.11 (17.58, 20.52)	18.92 (17.05, 20.96)
	V_c	11.66 (10.18, 12.975)	11.78 (9.752, 13.71)
	Q	180.8 (165.8, 194.7)	180.6 (153.1, 203.4)
	V_p	74.50 (62.73, 84.65)	74.64 (56.96, 93.76)
$\omega^2_{CL,Vc}$	Covariance between CL and V_c	0.011 (0.008, 0.015)	0.012 (0.007, 0.016)
σ	Residual variability (%CV)	31.56 (31.07, 32.04)	31.46 (29.99, 32.94)

2.1.4 Conclusions

The applicant major conclusions are as follows:

Trastuzumab emtansine PK in the clinical dose range can be adequately described by a linear two-compartment model with first-order elimination from the central compartment. Typical CL was 0.676 L/day, typical V_c was 3.127 L, and typical elimination half-life was 3.94 days.

Given the low IIV of trastuzumab emtansine key PK parameters (CL and V_c), and the low to moderate effect of the statistically significant covariates on trastuzumab emtansine exposure, all tested covariates were not expected to have a clinically meaningful impact on trastuzumab emtansine exposure. The current body weight-based dose regimen of 3.6 mg/kg q3w is appropriate. Further dose adjustments based on other covariates are unlikely to have a clinically meaningful reduction in PK inter-individual variability of trastuzumab emtansine.

- The inter-individual variability in key trastuzumab emtansine PK parameters from the base model (before inclusion of any covariates) was low (25.6% for CL and 17.5% for V_c).
- Body weight, baseline HER2 shed extracellular domain concentration, albumin concentration, baseline sum of longest dimension of target lesions, baseline trastuzumab concentration, and serum aspartate aminotransferase were identified as statistically significant covariates of trastuzumab emtansine CL, and body weight was identified as a statistically significant covariate of trastuzumab emtansine V_c. These covariates explained 44.4% of CL variance and 55.8% of V_c variance. After inclusion of all statistically significant covariates in the final model, the inter-individual variability decreased to 19.1% for CL and 11.7% for V_c. The magnitude of effect of these covariates on trastuzumab emtansine CL and V_c was low (<20% on CL, <25% on V_c).
- Further comparison of expected trastuzumab emtansine exposure simulated from post-hoc PK parameters showed trastuzumab emtansine exposure is similar in elderly versus young patients, in Asian versus non-Asian patients, and in patients from Asia versus non-Asia regions.
- Based on the covariate assessment of the impact of serum creatinine clearance on trastuzumab emtansine PK parameters and the comparison of expected trastuzumab emtansine exposure simulated from post-hoc PK parameters of patients with different renal functions, mild or moderate impaired renal function appears to have no effect on trastuzumab emtansine exposure. However, no conclusions can be drawn for patients with severe renal impairment and end stage renal disease, as the assessment was limited to only 1 patient with severe renal impairment.
- Among the covariates related to disease severity and treatment history, it was found that increased baseline sum of longest dimension of target lesions, higher baseline HER2 ECD concentrations, higher serum aspartate aminotransferase concentrations, lower serum albumin levels or lower baseline trastuzumab concentrations only resulted in a small increase in trastuzumab emtansine clearance (<10%).

Reviewer's comments on Applicant's Population PK Analysis:

The applicant's population PK analysis is generally adequate and acceptable. There are three specific comments:

- *The continuous covariates were tested as exponential function. The reviewer re-analyzed the data and found they can be modeled as power function. The final parameter estimates are similar. Therefore, C_{min} concentrations used for the exposure-response analysis are based on the sponsor's model.*

- *The reviewer further analyzed the effects of covariates on the C_{min} at Cycle 1 Day 21. Refer to reviewer's analyses for details.*

- *The PopPK analysis using non-linear elimination was tested and the model does not improve the fit of observed data. Therefore, the applicant and the reviewer concluded that for the clinical dose of 3.6 mg/kg q3w, a non-linear model was not required.*

2.2 Exposure-Response Analyses

The goals of the exposure-response analysis were to:

- Explore whether there is an exposure-response (ER) relationship for efficacy and safety with trastuzumab emtansine in patients with HER2-positive metastatic breast cancer (mBC).
- Perform quantitative exposure-response analysis if a relationship is observed.
- Examine the extent of loss of efficacy in patients with lesser exposures, or the extent of increased safety risk in patients with greater exposures.

2.2.1 Methods

The primary exposure-efficacy analysis was conducted on the pivotal study (TDM4370g/ BO21977, EMILIA) patient population. Among 991 mBC patients enrolled in TDM4370g/ BO21977, 978 patients received 3.6 mg/kg q3w T-DM1 treatment or lapatinib plus capecitabine (control arm). Out of 490 patients treated with T-DM1, one or more NCA PK parameters were estimated for 307 patients. This analysis included 307 NCA evaluable patients from the T-DM1 arm. Additionally efficacy data from 183 patients in the T-DM1 arm without PK parameters were included in some of the analyses as well as efficacy data from 488 patients in the control arm. Efficacy endpoints were ORR, PFS, and OS.

The primary exposure-safety analysis included 618 T-DM1 patients with PK from TDM4258g, TDM4374g, TDM4450g/BO21976, TDM4688g, and TDM4370g//BO21977, all of whom received single agent 3.6 mg/kg q3w. Safety endpoints were thrombocytopenia (TCP) and hepatotoxicity (HPT) related adverse events. A secondary exposure-safety analysis included 307 T-DM1 patients with PK from TDM4370g/BO21977. Additional analyses focusing on longitudinal platelet counts and liver function tests (ALT, AST, TBIL) were conducted for the 618 T-DM1 patients from all five phase II/III studies and for the 307 TDM4370g/BO21977 PK patients. PK analytes of interest were serum T-DM1, serum total trastuzumab, and plasma DM1.

PK parameters, estimated per subject by non-compartmental analysis, were T-DM1 AUC and Cmax, total trastuzumab AUC, and DM1 Cmax.

Incidence variables were analyzed by linear logistic regression models (ORR, TCP, HPT). Time-to-event variables (PFS, OS, longitudinal platelet counts and liver function tests) were analyzed by Cox proportional-hazards models. Covariates were included in the models to reduce

variability attributed to known or plausible patient characteristics. Exposure parameters were always included in the model to evaluate the significance of the exposure-response relationship.

Efficacy covariates were baseline age, weight, Asian ethnicity (Yes/No), baseline HER2 ECD, ECOG score (0/>0), measurable disease (Yes/No), visceral disease (Yes/No), liver metastases (Yes/No), and number of prior chemotherapies (≤1/>1). Safety covariates were baseline age, weight, Asian ethnicity, baseline liver function tests and platelet counts, ECOG score, liver metastases, and number of prior chemotherapies. Covariates were tested at the two-sided 0.05 level of significance using a log-likelihood criteria. A twostep forward-selection, backward-elimination method was used for covariate selection.

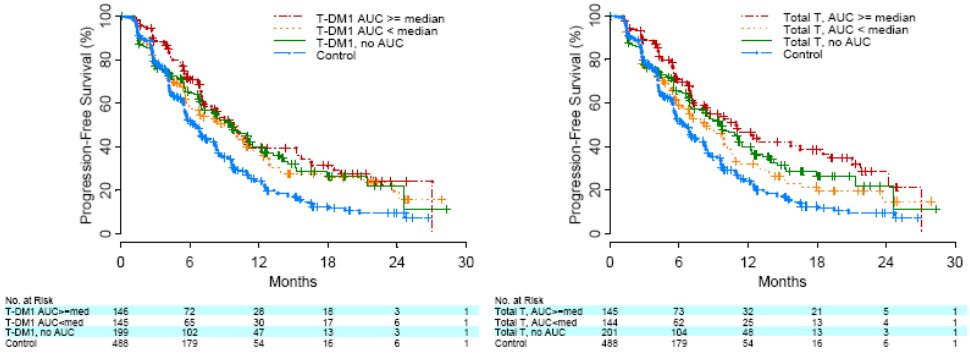
2.2.2 Results

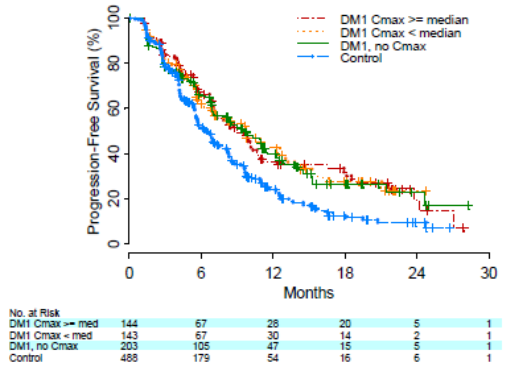
Exposure-efficacy analyses of the Phase 3 trial TDM4370g/BO21977 suggested that exposure variability of T-DM1, total trastuzumab, and DM1 did not affect the ORR, PFS, and OS outcome probabilities in mBC patients receiving T-DM1 at 3.6 mg/kg q3w (n=307). No significant exposure-efficacy relationship was detected after including covariates in the multivariate logistic regression for ORR, and the multivariate Cox proportional hazards analyses for PFS and OS.

Efficacy

1. PFS and OS

Figure C and Figure D show PFS curves and OS curves separated by T-DM1 AUC, total trastuzumab AUC, and DM1 Cmax, overlaid with patients who received T-DM1 but did not have the respective PK parameter, and patients in the control arm of study TDM4370g/BO21977. No significant ER relationship was observed.

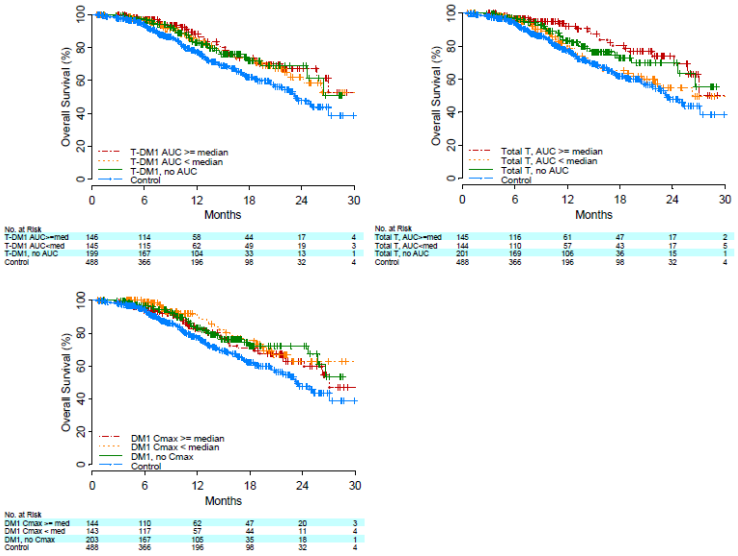




Note: Kaplan–Meier PFS curves for treated patients stratified by the median of T-DM1 AUC (top-left), total trastuzumab (top-right), or DM1 Cmax categories (bottom). The "T-DM1, no AUC" category includes both patients with no PK samples, and patients with PK samples but without evaluable T-DM1 AUC parameters in the NCA analysis. Similar for the "Total T, no AUC" and "DM1, no Cmax" categories.

Figure 20. Progression-free survival profiles stratified by exposure in TDM4370g/BO21977

Source: Figure C, on Page 14 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'



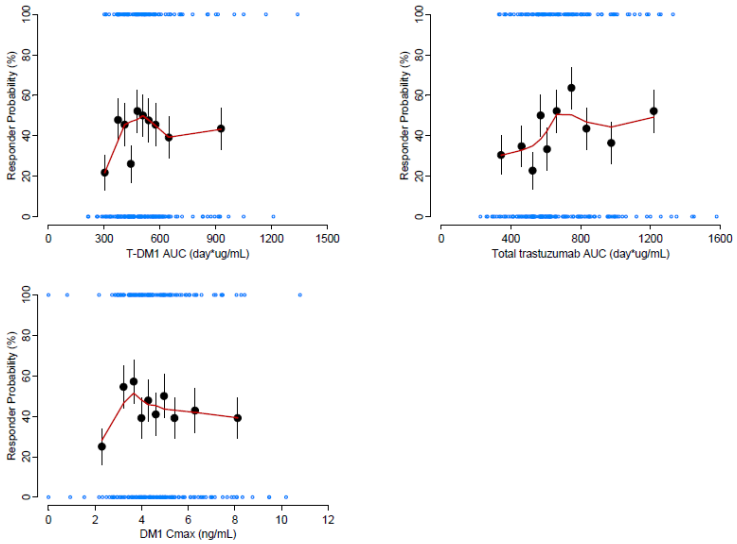
Note: Kaplan–Meier OS curves for treated patients stratified by the median of T-DM1 AUC (top-left), total trastuzumab (top-right), or DM1 Cmax categories (bottom). The "T-DM1, no AUC" category includes both patients with no PK samples, and patients with PK samples but without evaluable T-DM1 AUC parameters in the NCA analysis. Similar for the "Total T, no AUC" and "DM1, no Cmax" categories.

Figure 21. Overall survival profiles stratified by exposure in TDM4370g/BO21977

Source: Figure D, on Page 14 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'

2. ORR

Figure 22 shows the exposure-response (ER) relationship for OR, and Figure B shows the probability of achieving OR versus T-DM1 AUC, total trastuzumab AUC, or DM1 Cmax in TDM4370g/BO21977. No significant ER relationship was observed.



Note: The blue open circles represent OR data from individual patients (0% = non-responder, 100% = responder). The black solid circles are the observed probability of responder for deciles of serum concentration plotted at the mean value within each concentration decile. The vertical bars are ± one standard error [sqrt (P*(1-P)/N)]. The red line is a lowess spline to the black circles.

Figure 22. Probability of objective response versus exposure in TDM4370g/BO21977

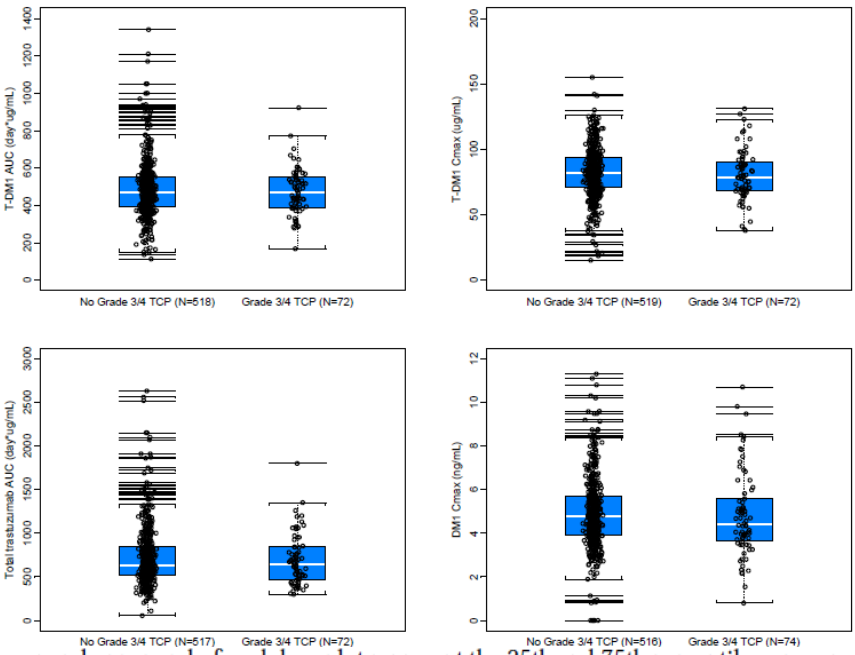
Source: Figure B, on Page 13 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'

Safety

Exposure-safety analyses of combined data from five Phase II/III studies in mBC patients receiving T-DM1 3.6 mg/kg q3w (n=618) suggested that exposure variability of T-DM1, total trastuzumab, and DM1 did not affect the probability of thrombocytopenia and hepatotoxicity events, or the risk of low platelet counts and elevated liver function tests.

No significant exposure-safety relationship was detected after including covariates in the multivariate logistic regression for TCP and HPT, and multivariate Cox proportional hazards analyses for platelet counts and liver function tests. Additional exposure-safety analyses of Phase III study TDM4370g/BO21977 (n=307) yielded similar results as the combined analysis. Overall, the exposure-safety analyses suggested that no increased safety risk is expected in mBC patients with greater exposures of T-DM1, total trastuzumab, or DM1 after receiving the 3.6 mg/kg q3w trastuzumab emtansine regimen. However, it should be noted that overall variability in exposure at this dose was limited; T-DM1 AUC, T-DM1 Cmax, total trastuzumab AUC, and DM1 Cmax coefficient of variation were 32%, 25%, 49%, and 40% respectively.

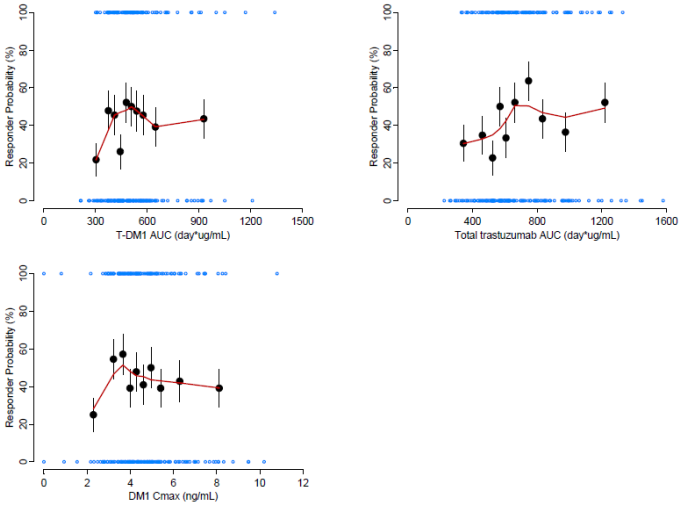
Figure E shows the ER relationship for Grade 3 or 4 thrombocytopenia, and Figure F shows the probability of Grade 3 or 4 thrombocytopenia versus T-DM1 AUC, T-DM1 Cmax, total trastuzumab AUC, or DM1 Cmax in patients from all five studies. Figure G and Figure H show the same plots for hepatotoxicity. No significant ER relationship was observed.



Note: The lower and upper end of each box plot represent the 25th and 75th percentile exposure value. The horizontal white line indicates the median per group. The brackets extending from the ends of the box represent 1.5 times the interquartile range. Points are individual PK data. Horizontal black lines represent points outside the brackets. Total N may vary slightly amongst plots according to the number of patients per estimatable PK parameter.

Figure 23. Exposure-response for Grade 3 or 4 thrombocytopenia in five studies

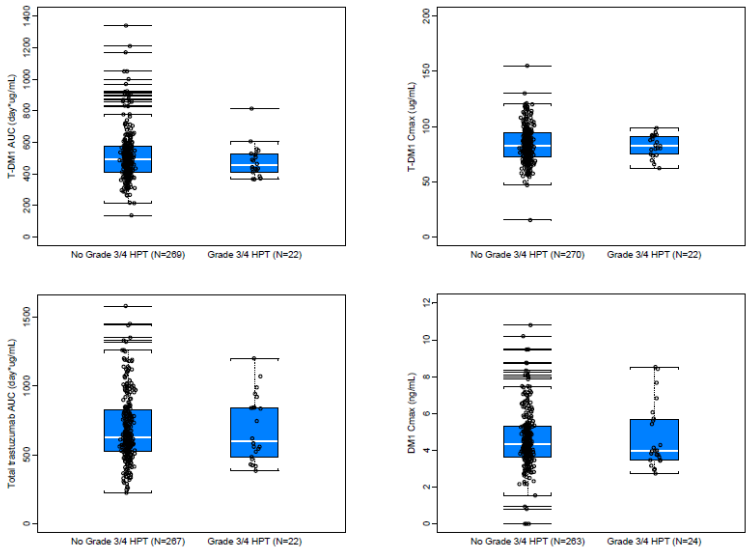
Source: Figure B, on Page 13 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'



Note: The blue open circles represent OR data from individual patients (0% = non-responder, 100% = responder). The black solid circles are the observed probability of responder for deciles of serum concentration plotted at the mean value within each concentration decile. The vertical bars are ± one standard error [sqrt (P*(1-P)/N)]. The red line is a lowess spline to the black circles.

Figure 24. Probability of Grade 3 or 4 thrombocytopenia versus exposure in five studies

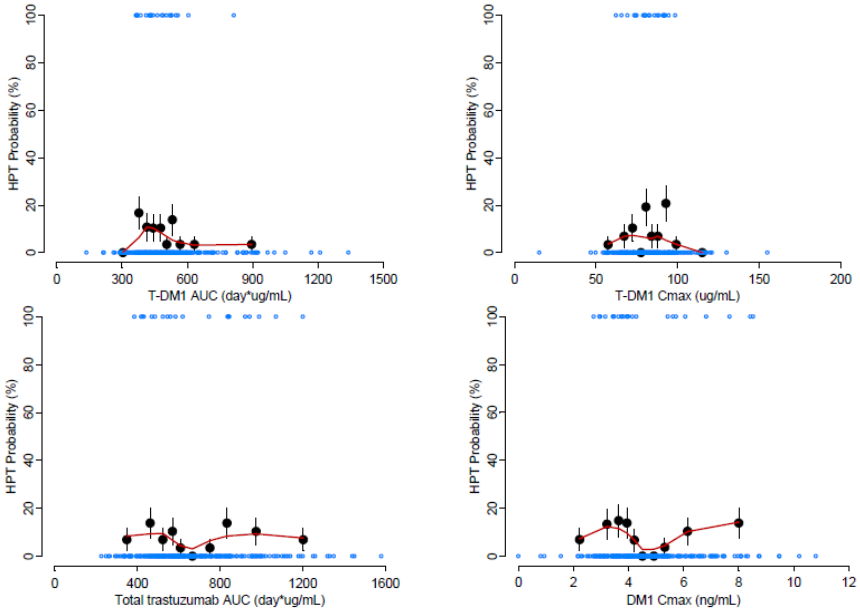
Source: Figure B, on Page 13 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'



Note: The lower and upper end of each box plot represent the 25th and 75th percentile exposure value. The horizontal white line indicates the median per group. The brackets extending from the ends of the box represent 1.5 times the interquartile range. Points are individual PK data. Horizontal black lines represent points outside the brackets. Total N may vary slightly amongst plots according to the number of patients per estimatable PK parameter.

Figure 25. Exposure-response for Grade 3 or 4 hepatotoxicity in five studies

Source: Figure B, on Page 13 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'



Note: The blue open circles represent HPT Grade 3 or 4 events from individual patients (0% = No, 100% = Yes). The black solid circles are the observed probability of an event for deciles of total plasma concentration plotted at the mean value within each concentration decile. The vertical bars are ± one standard error [sqrt (P*(1-P)/N)]. The red solid line is a lowess spline to the black circles.

Figure 26. Exposure-response for Grade 3 or 4 hepatotoxicity in five studies

Source: Figure B, on Page 13 of the study report entitled 'Exposure-Response Analysis of Trastuzumab Emtansine (T-DM1) in Patients with HER2-Positive Metastatic Breast Cancer'

2.2.3 Conclusions

The exposure-response analyses suggested that trastuzumab emtansine achieved substantial efficacy with good tolerability at the 3.6 mg/kg q3w regimen. No loss of efficacy is expected in

patients with lower exposures, and no increased safety risk for the events studied is expected in patients with greater exposures for the range of exposures achieved by the 3.6 mg/kg q3w regimen in mBC patients. However, it should be noted that overall variability in exposure at this dose was limited; T-DM1 AUC, T-DM1 Cmax, total trastuzumab AUC, and DM1 Cmax coefficient of variation were 32%, 25%, 49%, and 40% respectively. The following conclusions have been reached:

- No exposure-response relationship was observed for objective response, progression-free survival, and overall survival based on T-DM1, total trastuzumab, or DM1 exposure in Phase III Study TDM4370g/BO21977.
- Similar relationships observed in heavily pretreated patients and in patients not receiving prior mBC chemotherapy, suggest results are independent of the prior therapy that the patients received.
- No exposure-response relationship was observed for thrombocytopenia, hepatotoxicity, platelet counts, and liver function tests based on T-DM1, total trastuzumab, or DM1 exposure in combined data from five Phase II/III studies.
- Similar results observed in the Phase III study TDM4370g/BO21977, when analyzed separately.

Reviewer's Comments

1. *The applicant's PK analyses for serum T-DM1, serum total trastuzumab, and plasma DM1 were estimated per subject by non-compartmental analysis. There are 291 patients with TDM1 AUC data in the pivotal trial. The reviewer's E-R analysis included 334 patients with Cycle 1 and steady state Cmin data- there are 43 patients missing from the applicant's E-R analysis for TDM1 AUC and PFS relationship. In addition, in applicant's NCA analysis, the AUC values may not be reliable due to limited PK sampling in those patients. The applicants PopPK model provides more reliable estimates than NCA based on the GOF and validation analyses.*
2. *The applicant's exposure endpoint includes T-DM1 AUC and Cmax, total trastuzumab AUC, and DM1 Cmax. In addition to applicant's analysis, the reviewer analyzed the E-R relationship using PopPK model predicted AUC and Cmin for T-DM1 (See reviewer's analysis for detials).*

3 REVIEWER'S ANALYSES

Population PK Analysis

3.1.1 Objectives

The reviewer's analysis objectives are:

1. To quantify sources of inter-patient variability in T-DM1 exposure.

3.1.2 Methods

Data sets used in PopPK analysis are summarized below. Please refer to Section 2.1.2 for details.

Name	Link to EDR
poppkall.xpt	\\Cdsesub1\EVSPROD\125427\0004\m5\datasets\poppk\analysis

Software

NONMEM VI (Icon, Ellicott City, MD) was used to review the sponsor's population PK model. S-PLUS 8.0 (TIBCO Software Inc., Palo Alto, CA) was used to generate all plots and manage datasets. The statistical software R 2.10.1 (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots

3.1.3 Results

Reviewer's analysis showed that the OFV valued similar when covariates modeled with power function as compared to the applicant's model. The parameter estimates were comparable to the applicant's results. The goodness-of-fit plot shows similar pattern between the applicant's final model and the reviewer's model. By using power function, the reviewer identified the following significant parameter-covariate relationship:

CL=0.028*(WEIGHT/70)^0.51*(ECD/25)^0.04*(ALBU/41)^-0.49*(TMBD)^0.05*TBL*SGOT^0.07

Based on the final PopPK model, the typical clearance of trastuzumab emtansine was 0.68 L/day and the elimination half-life ($t_{1/2}$) was 3.95 days. The median half-life of the post-hoc estimates was 4.16 days. The central volume of distribution of trastuzumab emtansine was 3.13 L.

Age & Race:

Age and race does not have a clinically meaningful effect on the PK of TDM1. There is no significant trend between the inter-patient variability for PK parameter and age or race (Figure 27). Pharmacokinetics of TDM1 in Asian patients (n=73) were similar to non-Asian patients (n=598). A population pharmacokinetic analysis showed that age did not affect the pharmacokinetics of TDM1. The impact of age and race on inter-individual random effects of PK parameters are shown below.

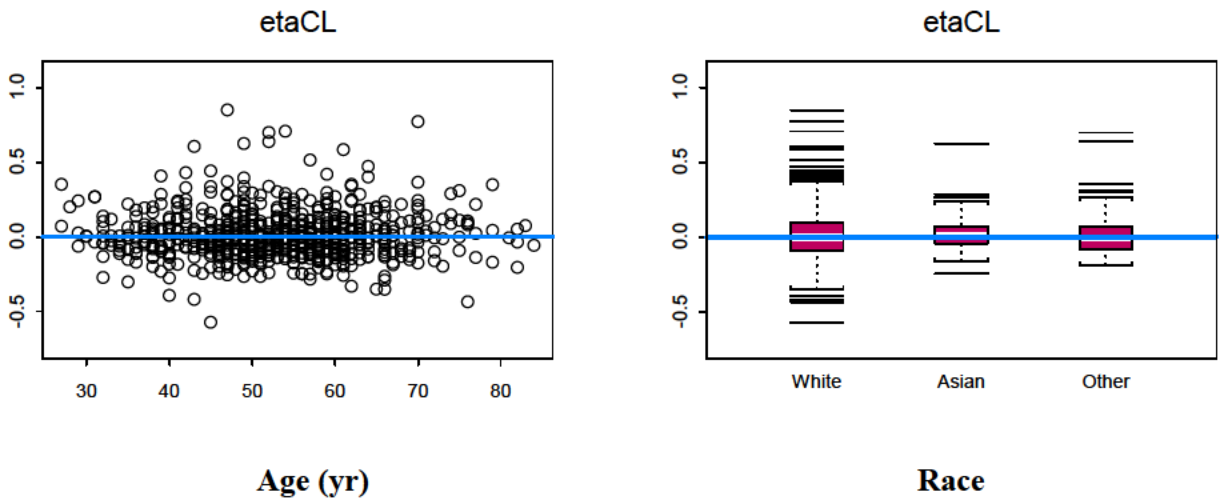


Figure 27: Plot of inter-individual random effects for CL versus age and race.

For other PopPK related questions, see Section 1.1.3-1.1.5 for details of the reviewer's analysis.

Based on the population pharmacokinetic analysis for the pooled data from 5 trials in patients with breast cancer, a linear two-compartment model with first-order elimination from the central compartment adequately describes the T-DM1 concentration-time profile at the clinical dose. The majority of the dose are in the range of 3.6 – 4.8 mg/kg. there are a few individuals at low doses of 0.3, 0.6 and 1.2 mg/kg q3w. and the Bayesian post-hoc clearance estimates of those individual indicated a faster clearance. However, the PopPK analysis using non-linear elimination was tested both by the applicant and the reviewer, and the model does not improve the fit of observed data. The reviewer concluded that in the clinical dose of 3.6 mg/kg q3w, a non-linear model was not required.

3.1.4 Conclusion

- Based on the final PopPK model, the typical clearance of trastuzumab emtansine was 0.68 L/day and the elimination half-life ($t_{1/2}$) was approximately 4 days. The central volume of distribution of trastuzumab emtansine was 3.13 L.
- Body weight, albumin, tumour burden (sum of longest diameter of target lesions) by RECIST, HER2 ECD, baseline trastuzumab concentrations and AST were identified as statistically significant covariates for trastuzumab emtansine pharmacokinetic parameters.
- PopPK analysis showed that creatinine clearance does not affect the pharmacokinetics of KADCYLA. Pharmacokinetics of KADCYLA in patients with mild renal impairment (creatinine clearance (CL_{cr}) of 60-89 mL/min (n=254)) or moderate renal impairment (CL_{cr} 30 to 59 mL/min; n=53) were similar to those patients with normal renal function ($CL_{cr} \geq 90$ mL/min, n=361).
- Age and race do not have clinically meaningful effects on the PK of trastuzumab emtansine.

3.2 Exposure-Response Analysis

3.2.1 Objectives

The objectives of the reviewer's analyses are:

- To explore the exposure-efficacy relationship using the co-primary endpoints, PFS and OS, as well as the secondary endpoint, ORR in the pivotal trial
- To explore exposure-safety relationships for thrombocytopenia, hepatotoxicity, and peripheral neuropathy in the safety population.

3.2.2 Methods

Individual predicted concentrations (predicted trough concentration $C_{min,\ Day\ 21\ Cycle\ 1}$ on Day 21 in Cycle 1) was computed for 334 out of 490 patients in the T-DM1 arm in pivotal trial using the applicant's population PK model. Kaplan Meier analysis was applied to establish a relationship between quartiles of $C_{min,\ C1D21}$ and PFS, and between $C_{min,\ C1D21}$ and OS. The relationship between $C_{min,C1D21}$ and ORR, the secondary efficacy endpoint in trial TDM4370g, was analyzed with logistic regression of an E_{max} model.

Logistic regression method was applied to analyze the relationships between $C_{min,\ C1D21}$ and thrombocytopenia, hepatotoxicity, or peripheral neuropathy in the safety population. In addition, boxplots was plot to evaluate the trend of TDM1 $C_{min,\ C1D21}$ for each grade of thrombocytopenia, hepatotoxicity, and peripheral neuropathy. The incidence of Grade 3 or worse adverse events (Grade 3+ AEs) in patients was compared across quartiles of T-DM1 $C_{min,\ C1D21}$. The dose adjustments (including dose interruption, dose discontinuation, dose reduction) were also compared across quartiles of $C_{min,\ C1D21}$.

3.2.3 Datasets

Data sets used in the analysis are summarized in Table 8.

Table 8.: Analysis datasets

Dataset description	Name	Link to EDR
Population PK analysis	poppkall.xpt	\\Cdsesub1\EVSPROD\125427\0004\m5\datasets\poppk\analysis
Efficacy and exposure data for pivotal study TDM4370g (Applicant's analysis)	expeff1.xpt	\\Cdsesub1\EVSPROD\125427\0004\m5\datasets\expresp\analysis
Safety and exposure data for all studies (Applicant's analysis)	exprsfae.xpt	\\Cdsesub1\EVSPROD\125427\0004\m5\datasets\expresp\analysis
Safety Data for all safety evaluable patients	patsaf.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0004\m5\datasets\iss\analysis
Adverse events data for pivotal study TDM4370g	ae.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0004\m5\datasets\tdm4370g\listings
Drug administration data for pivotal study TDM4370g	tx.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0004\m5\datasets\tdm4370g\listings
PFS data for pivotal study TDM4370g	patirf.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0004\m5\datasets\tdm4370g\analysis
First OS interim analysis data for pivotal study TDM4370g	pat.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0004\m5\datasets\tdm4370g\analysis
Second OS interim (final) analysis data for pivotal study TDM4370g	patos.xpt	\\Cbsap58\M\eCTD_Submissions\STN125427\0013\m5\datasets\tdm4370g\analysis

3.2.3.1 Softwares

SAS 9.2 and TIBCO Spotfire S-Plus 8.1 and NONMEM (Version 6.2) were used for the reviewer's analyses.

3.2.4 Results

3.2.4.1 Efficacy

Please refer to Question 1 for details. In addition, the reviewer analyzed the E-R relationship using PopPK predicted AUC. For both PFS and OS, the median survival time for patients within the lowest quartile of AUC was shorter than the median survival time for patients in the other quartiles (Figure 28, Figure 29).

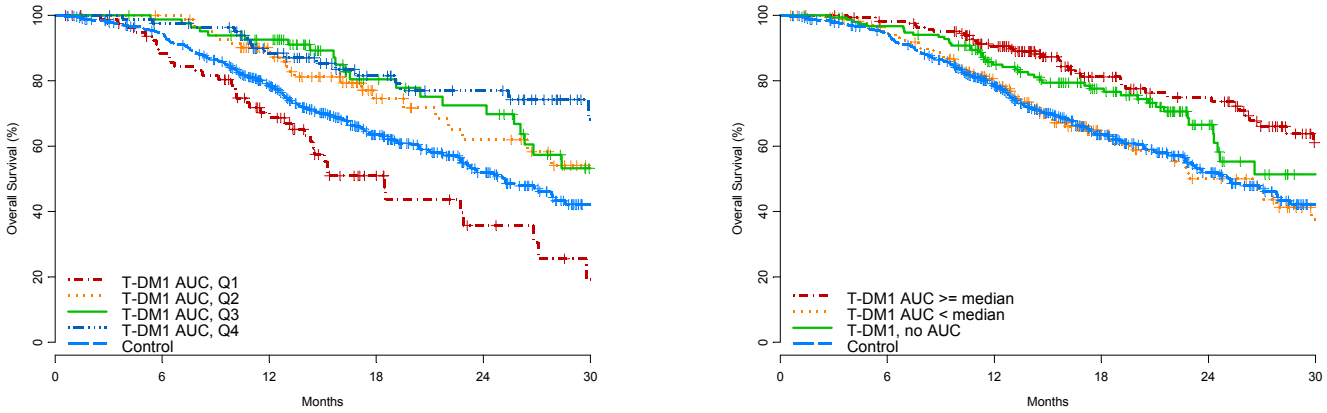


Figure 28. Kaplan-Meier curve of overall survival (OS) for the T-DM1 arm (N=490) by quartiles (left) or median (right) of AUC and for the active control arm (N=488) of the study TDM4370g/BO21977. The numbers in the right figure shows the median survival with 95% confidence interval.

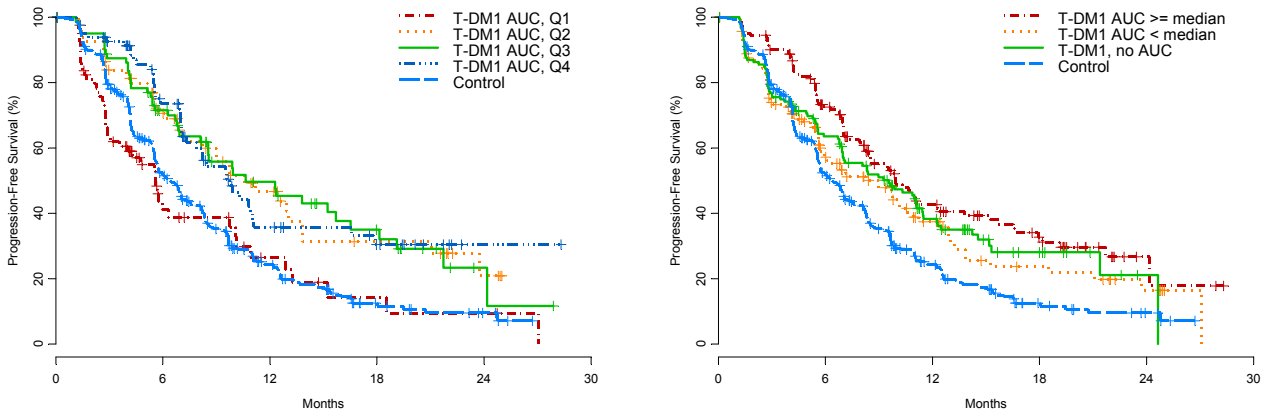
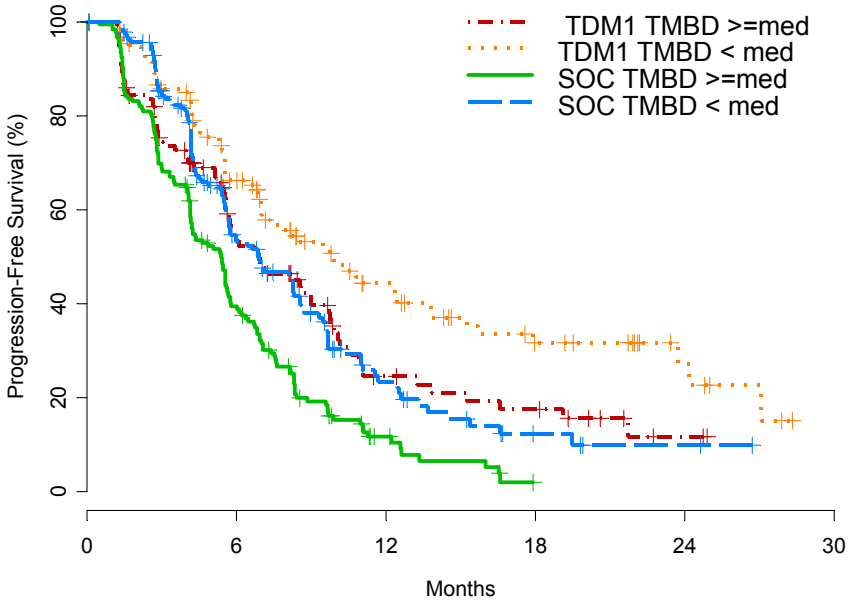


Figure 29. Kaplan-Meier curve of progression free survival (PFS) for the T-DM1 arm (N=490) by quartiles (left) or median (right) of AUC and for the active control arm (N=488) of the study TDM4370g/BO21977. The numbers in the right figure shows the median survival with 95% confidence interval.

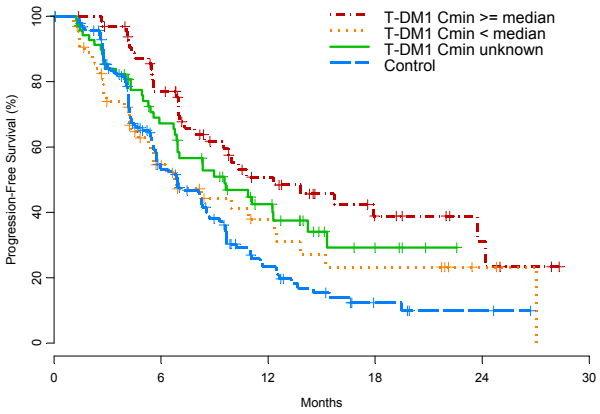
The reviewer further analyzed the data by dividing the patient based on median values of tumor burden. It shows that: 1) tumor burden is a risk factor for survival even in control (SOC) arm; 2) TDM1 improves the survival in both < med or > med group, as compared to the relevant SOC control. 3) Increasing dose in higher TMBD patients may improve survival because the analysis

for patient who have higher than median TMBD indicated that higher Cmin is correlated with improved survival.

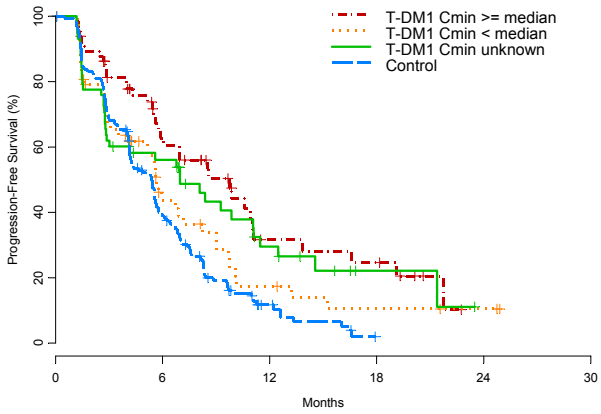


No. at Risk						
TDM1 TMBD >=med	132	47	16	11	3	1
TDM1 TMBD < med	131	71	33	17	7	1
SOC TMBD >=med	193	62	11	1	1	1
SOC TMBD < med	193	71	20	6	3	1

Figure 30:Progression free survival by Kaplan–Meier in patients divided by median tumor burden in patients for the T-DM1 arm (N=263) and the active control arm (N=386) of the study TDM4370g/BO21977.



Tumor Burden <11.6



Tumor Burden >=11.6

Figure 31:Progression free survival by Kaplan–Meier in patients for the T-DM1 arm by median $C_{min, C1D21}$ and median tumor burden and for the active control arm of the study TDM4370g/BO21977.

3.2.4.2 Safety

Please refer to Question 2 for details.

3.2.5 Conclusions

Overall, the analysis indicated that the higher the T-DM1 exposure, the greater the OS or PFS improvement. Furthermore, T-DM1 exposure ($C_{min,C1D21}$) was significantly related to objective response rate (ORR, $P < 0.01$) (Figure 5), using a logistic regression analysis of an E_{max} model.

The reviewers understand that the lowest quartile is comparable to current standard of care, lapatinib plus capecitabine. However, there is opportunity to optimize dose in the patients with lower exposures but we do realize that there may be patient specific factors which might restrict giving higher dose to this subpopulation. The statistical reviewer, Dr. Qiang Xu, also reached the same conclusions (b) (4)

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/s/

SARAH J SCHRIEBER
01/15/2013

JIAN WANG
01/15/2013

PENGFEI SONG
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01/15/2013

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01/15/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**BLA 125427 / 0**	**Brand Name**	**n/a**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Trastuzumab emtansine (T-DM1)**
Medical Division	**DDOP**	**Drug Class**	**Monoclonal antibody-drug conjugate**
OCP Reviewer	**Sarah J. Schrieber**	**Indication(s)**	**HER2-Positive Metastatic Breast Cancer**
OCP Team Leader	**Qi Liu**	**Dosage Form**	**160 mg Lyophilized single use vial (20 mg/ml after reconstitution)**
Pharmacometrics Reviewer	**Jian Wang**	**Dosing Regimen**	**3.6 mg/kg q3W**
Pharmacometrics Team Leader	**Nitin Mehrotra**	**Route of Administration**	**IV**
Date of Submission	**8/26/12**	**Sponsor**	**Genentech**
Estimated Due Date of OCP Review	**12/14/12**	**Priority Classification**	**Priority**
Medical Division Due Date	**12/17/12**		
PDUFA Due Date	**2/26/13**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**3**	**3**	
I. Clinical Pharmacology				
Mass balance:	**x**	**1**	**1**	**Preclinical 08-1136**
Isozyme characterization:	**n/a**			
Blood/plasma ratio:	**n/a**			
Plasma protein binding:	**x**	**1**	**1**	**Preclinical 05-1047-1459**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**n/a**			
multiple dose:	**n/a**			
Patients-				
single dose:	**n/a**			
multiple dose:	**x**	**6**	**6**	**TDM3569g, TDM4258g, TDM4374g, TDM4450g, TDM4688g (QTc), TDM4370g**
Dose proportionality -				
fasting / non-fasting single dose:	**n/a**			
fasting / non-fasting multiple dose:	**x**	**1**	**1**	**TDM3569g,**
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**n/a**			**PopPK**
In-vivo effects of primary drug:	**n/a**			
In-vitro:	**x**	**3**	**3**	**09-1344, 09-2382, 10-1207**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Subpopulation studies -				
ethnicity:	**n/a**			**PopPK (12-0489)**
gender:	**n/a**			**PopPK (12-0489)**
pediatrics:	**n/a**			**Requested waiver**
geriatrics:	**n/a**			**PopPK (12-0489)**
renal impairment:	**n/a**			**PopPK (12-0489)**
hepatic impairment:	**n/a**			**(dedicated study BO25499 ongoing)**
PD -				
Phase 2:	**n/a**			
Phase 3:	**n/a**			
PK/PD -				
Phase 1 and/or 2, proof of concept:	**n/a**	**2**	**2**	**TDM4688g (QTc), TDM3569g**
Phase 3 clinical trial:	**n/a**			
Population Analyses -				
Data rich:	**x**	**2**	**2**	**PopPK (12-0489), E-R (12-0490)**
Data sparse:	**n/a**			
II. Biopharmaceutics				
Absolute bioavailability	**n/a**			
Relative bioavailability -				
solution as reference:	**n/a**			
alternate formulation as reference:	**n/a**			
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**3**	**3**	**07-1474, 07-1475, 08-800 (nonclinical PK comparability for manufacturing scale-up)**
replicate design; single / multi dose:	**n/a**			
Food-drug interaction studies	**n/a**			
Bio-waiver request based on BCS	**n/a**			
BCS class	**n/a**			
Dissolution study to evaluate alcohol induced dose-dumping	**n/a**			
III. Other CPB Studies				
Genotype/phenotype studies	**n/a**			
Chronopharmacokinetics	**n/a**			
Pediatric development plan	**n/a**			**Requested waiver**
Literature References	**x**			
Total Number of Studies		**20**	**20**	

Other Comments	
	Comments
QBR (key issues to be considered)	1. Is there evidence of exposure-response for efficacy (OS, PFS, ORR)? 2. a) Is there evidence of exposure-response for safety (e.g., thrombocytopenia, hepatic toxicity, pulmonary toxicity, left ventricular dysfunction, neurotoxicity)? b) Are dose reductions for adverse events supported by exposure-response? 3. a) Based on popPK analyses, do intrinsic factors (age, gender, wt, race organ function, etc) impact T-DM1 PK? b) Is body weight based dosing the optimal dosing strategy? 4. Is there a need for dose adjustment based on organ impairment? 5. What is the immunogenicity incidence rate and does it impact the safety/efficacy/PK?
Other comments or information not included above	n/a

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Human BE data not provided.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR	x			

	requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the BLA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the BLA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an BLA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waiver submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waiver submitted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant: N/A

9/19/12

Sarah J. Schrieber, Pharm.D. Date
Reviewing Clinical Pharmacologist

9/19/12

Qi Liu, Ph.D. Date
Team Leader/Supervisor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH J SCHRIEBER
09/19/2012

QI LIU
09/19/2012