Official Title: A Two-Cohort, Open-Label, Multicenter, Study of Trastuzumab Emtansine (T-DM1) in HER2 Positive Locally Advanced or Metastatic Breast Cancer Patients Who Have Received Prior Anti-HER2 and Chemotherapy-Based Treatment

NCT Number: NCT01702571

Document Date: SAP Version 2: 02-February-2020

Statistical Analysis Plan

F. HOFFMANN-LA ROCHE LTD

Protocol: MO28231

Treatment: Trastuzumab emtansine (RO5304020)

A TWO-COHORT, OPEN-LABEL, MULTICENTER, STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) IN HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER PATIENTS WHO HAVE RECEIVED PRIOR ANTI-HER2 AND CHEMOTHERAPY-BASED TREATMENT

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Document Status: Version 2, Final

Version Dates: Version 2, Draft 1: 14Oct2019

Version 2, Final: 02Feb2020

Pages: 50

Contents

Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT (SGPT)	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST (SGOT)	Aspartate Aminotransferase
BC	Breast Cancer
BOR	Best Overall Response
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CHF	Congestive Heart Failure
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria For Adverse Events
DoR	Duration of Response
DRM	Data Review Meeting
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
G-GT	Gamma-Glutamyl Transpeptidase
HER2	Human Epidermal growth factor Receptor 2
ICU	Intensive Care Unit
iDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
ISR	Injection Site Reaction
ITT	Intent-To-Treat
KM	Kaplan Meier
kg	Kilogram
LABC	Locally Advanced Breast Cancer
LDH	Lactate Dehydrogenase
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
mBC	Metastatic Breast Cancer
mg	Milligram
Min	Minimum
MRI	Magnetic Resonance Imaging
MUGA	Multiple-Gated Acquisition
NCI	National Cancer Institute
NRH	Nodular Regenerative Hyperplasia
ORR	Overall Response Rate

OS	Overall Survival
PFS	Progression Free Survival
PR	Partial Response
PTT	Partial Thromboplastin Time
q3w	every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
T-DM1	Trastuzumab Emtansine
TTP	Time To Progression
TTR	Time To Response
ULN	Upper Limit of Normal
WBC	White Blood Cell Count

1 Introduction

This document presents the statistical analysis plan (SAP) for F. Hoffmann-La Roche Ltd, Protocol No. MO28231: A two-cohort, open-label, multicenter, study of trastuzumab emtansine (T-DM1) in HER2 positive locally advanced or metastatic breast cancer (BC) patients who have received prior anti-HER2 and chemotherapy-based treatment.

This analysis plan is based on the final protocol, dated 12 June 2012; incorporating Amendment 1, dated 22 June 2012; Amendment 2, dated 21 August 2012; Amendment 3, dated 11 February 2013; Amendment 4, dated 30 May 2013; and Amendment 5, dated 31 January 2014; and Amendment 6, dated 18th July 2019.

The final analysis of each cohort will be performed when all patients within the respective cohort have been followed up for safety and efficacy for a period of up to 2 years after the last patient has been enrolled into Cohort 2 of the trial. The analysis of Cohort 1 will be conducted and then combined for the pooled analysis of Cohorts 1 and 2. This pooled analysis will be conducted in parallel to the final analysis of Cohort 2.

In addition to the final analysis, there were seven interim safety analyses in the Cohort 1 for review by the independent Data Monitoring Committee (iDMC): after approximately 50 and 350 patients have completed Cycle 1, Day 1 and after approximately 1000, 1500 and 2000 patients have completed the first cycle of study medication (Cycle 1, Day 21), and two which were approximately every 6 months thereafter, as per the iDMC charter.

In addition to the final analysis, there will be one interim safety analysis in Cohort 2 for review by the iDMC after approximately 100 patients have completed Cycle 1 (Cycle 1, Day 21).

Also, there might be additional interim analyses for Health Authority purposes (e.g., to support the China Food and Drug Administration [CFDA] [China]) after 150 Chinese patients have been enrolled and completed Cycle 1 (Cycle 1, Day 21) or by January 2017, whichever occurs first.

This SAP provides the description of the analysis for the final analyses.

History of Changes		
Version 1, Final : 16Feb2017		Reason for Change
Page	Section	
17,21	3.5.3, 4.1	Update to the subgroups given in the protocol
17,21	3.5.3, 4.1	Addition of Unvalidated HER2 tables and figures
22	4.1	Addition of listings for 11 patients in China
42	5.3.2	Addition of Table 14.2.5.3 and Table 14.2.5.4 (Responders only)

2 Study Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

- The primary objective of this study is to evaluate the safety and tolerability of trastuzumab emtansine.

2.1.2 Secondary Objective

- The secondary objectives of the study include the evaluation of the following parameters:
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Overall response rate (ORR) = partial response (PR) + complete response (CR)
  - Clinical benefit rate (CBR)
  - Duration of response (DoR)
  - Time to Response (TTR)

2.1.3 Exploratory objective

- The exploratory objective of the study includes the evaluation of the following parameters:
  - Time to Progression (TTP)

2.1.4 Pharmacoeconomics outcome objective

- The pharmacoeconomics outcome objective for this study is of health resource utilization and will be as follows:
  - To evaluate the resource expenditures, while on study treatment, due to hospitalizations that are not study-defined evaluations. The number of hospital visits and type of visits (Intensive Care Unit [ICU] versus other) will be recorded, as detailed in Section 4.13.

2.2 Endpoints

2.2.1 Primary endpoint

The primary endpoint in this study is the incidence of AEs Grade 3 or higher specifically for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, also all other AEs Grade 3 or higher related to trastuzumab emtansine, and pneumonitis of all grades.

2.2.2 Secondary endpoints

2.2.2.1 Secondary safety endpoints

All AEs of primary interest that constitute the primary endpoint will be analyzed separately as secondary safety endpoints:

- AEs Grade 3 or higher for hepatic events,
- AEs Grade 3 or higher for allergic reactions,
- AEs Grade 3 or higher for thrombocytopenia,
- AEs Grade 3 or higher for hemorrhage events,
- AEs Grade 3 or higher related to trastuzumab emtansine,
- pneumonitis of all grades

Adverse events of special interest (AESIs) for this study include the following:

- Potential drug-induced liver injury
- Suspected transmission of an infectious agent by the study drug

In addition, AEs leading to treatment interruption and discontinuation, related and unrelated SAEs, cause of death, peripheral neuropathy, left ventricular dysfunction disorders, incidence of CHF, infusion-related reaction/hypersensitivity, premature discontinuation from study and treatment, laboratory test abnormalities, left ventricular ejection fraction (LVEF) decrease over the course of the study as measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) and exposure to study drug, will be analyzed as secondary safety endpoints.

All the AEs or safety parameters that are not mentioned above will be also analyzed to respond to the primary objective.

2.2.2.2 Secondary efficacy endpoints

The secondary efficacy endpoints of this study are as follows:

- Progression Free Survival (PFS)
- Overall Survival (OS)
- Overall Response Rate (ORR) = PR + CR
- Clinical Benefit Rate (CBR)
- Duration of Response (DoR)
- Time to Response (TTR)

2.2.2.3 Exploratory efficacy endpoints

The exploratory efficacy endpoint of this study is as follows:

- Time to Progression (TTP)

2.2.2.4 Pharmacoeconomic endpoints

The pharmacoeconomic endpoints of this study are as follows:

- Number of hospital visits
- Type of visits (ICU versus other)

3 Study Design

3.1 Discussion of Study Design

This study is a two-cohort, open-label, international, multicenter Phase IIIb study to evaluate the safety and tolerability of trastuzumab emtansine.

This study will enroll patients with HER2-positive, unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer (mBC) who have previously received prior anti-HER2 and chemotherapy treatment and have progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy.

Approximately 2220 patients will be enrolled into the study.

- Cohort 1 (approximately 2000 patients)
- Cohort 2 (will include approximately 220 patients only of Asian race)

Enrollment into Cohort 2 will begin around the end of enrollment into Cohort 1. Therefore, the entire length of the study (covering enrollment and follow-up period) is estimated to be 6 years. Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment.

All patients will be followed up for survival every 6 months (± 14 working days) until death, loss to follow-up or withdrawal of consent until study closure. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months until study closure.

The schedule of assessments is presented in Section 3.3, Table 1.

3.2 Study Treatment

Trastuzumab emtansine will be administered on Day 1 of a 3-week cycle; every 3 weeks (q3w) at a dose of 3.6 mg/kg IV unless dose reductions or dose delays are required. The total dose will be calculated based on the patient's weight up to 28 days before each cycle with no upper limit. If within these 28 days, the patient experiences a severe weight loss, the dose should be recalculated accordingly.

If the timing of trastuzumab emtansine coincides with a holiday that precludes the procedure, the procedure should be performed within 3 business days of the scheduled date and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.

The first infusion of trastuzumab emtansine will be administered over 90 minutes (±10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine may be administered over 30 minutes (±10 minutes), with a minimum 30 minutes observation period following infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after last patient first visit, whichever occurs first. Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment.

3.3 Study Schedule

Table 1: Schedule of Assessments

	Screening	**Treatment Period (all visits within ± 3 days of scheduled treatment day)**	**Post-treatment Follow-up**	
	Day -28 to Day 1	**Day 1 of each Treatment Cycle**	**Safety Follow-up Visit** (28–42 days after last dose)	**Follow-up until Study Closure[2]** (every 3–6 months)
Informed Consent	X[a]			
HER2 Status	X[b]			
Medical History and Demographics	X			
Complete Physical Examination	X			
Limited Physical Examination[c]		X	X	
Height and Weight[d]	X	X	X	
Vital Signs[e]	X	X	X	
ECOG Performance Status	X	X	X	
Concomitant Medication Reporting	X[f]	Ongoing		X[f]
Adverse Event Reporting	X[g]	Ongoing		X[h]
12-lead ECG	X			
ECHO/MUGA[i]	X[i]	X[i]	X[i]	
Tumor Assessments[j]	X	Every 12 weeks	X	X
Brain CT or MRI[k]	X	At the discretion of the investigator, if clinically indicated, until disease progression		

Table 1: Schedule of Assessments (Continued)

	Screening	Treatment Period (all visits within ± 3 days of scheduled treatment day)	Post-treatment Follow-up	
	Day -28 to Day 1	**Day 1 of each Treatment Cycle**	**Safety Follow-up Visit** (28–42 days after last dose)	**Follow-up until Study Closure[2]** (every 3–6 months)
Bone Scan/Imaging[l]	X	As clinically indicated or to confirm a response, until disease progression		
Hematology[m]	X[1]	X[n]	X	
Biochemistry[o]	X[1]	X[n]	X	
Urinalysis[p]	X[1]	As clinically indicated	X	
INR	X[1]	As clinically indicated, e.g. for patients receiving anti-coagulation therapy	X	
Pregnancy Test[q]	X	Every 3 cycles	X	X[q]
Assessment of Patient Hospitalizations and/or Hospital Visits		X	X	
Administration of Trastuzumab Emtansine		X[r]		

Table 1 Schedule of Assessments (Continued)

AE = Adverse Event; CT = Computed Tomography; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; D = Day; HER2 = human epidermal growth factor receptor 2; INR = International Normalized Ratio; MRI = Magnetic Resonance Imaging; MUGA = Multiple-Gated Acquisition; PD = Progressive Disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious Adverse Event.

– NOTE: Local laboratory (hematology, biochemistry, urinalysis, and INR assessments) at Screening: to be performed within **14 days** prior to first study treatment. Screening laboratory assessments may be done on the day of first study treatment (Cycle 1, Day 1).

– All patients will be followed up for survival every 6 months (± 14 working days; except for pregnancy test which is at 3 and 6 months after safety follow-up visit) until death, loss to follow-up, or withdrawal of consent until study closure and until disease progression and/or until a new anti-cancer treatment is initiated (whichever occurs first). Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months. If assessments cannot be done at survival visits, the study site is permitted to collect survival information by phone call. Patients will also be followed for subsequent anti-cancer therapies (not all concomitant medications).

a) Informed consent may be obtained at any time (including prior to the 28-day screening period) but must be obtained prior to the performance of any screening assessments. Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to first study treatment may be used rather than repeating required tests.

b) HER2 positivity is defined as IHC 3+ or gene amplification by ISH, it will be performed locally.

c) Defined as a directed physical rather than thorough examination of all body systems. For example if a patient presents with a symptom, there should be a more comprehensive assessment of the affected body system.

d) Height to be obtained at screening or at Cycle 1, Day 1 only.

e) Vital signs should be obtained and reviewed but are not required to be entered into the eCRF. Abnormal vital signs at any time during the course of study treatment should be recorded as AEs or SAEs.

f) Record all prior investigational, anti-cancer therapies and concomitant medications within 28 days prior to first study treatment. At follow-up, assessment of anti-cancer therapies only.

g) During screening, only SAEs considered related to protocol-mandated procedures will be collected.

Table 1 Schedule of Assessments (Continued)

h) Patients will be followed for new or worsening AEs for 28 days following the last infusion of study drug, until treatment-related AEs resolve or stabilize, or until the initiation of another anti-cancer therapy, whichever occurs first, and until disease progresses for tumor assessments. After 28 days following last study treatment administration, the investigator should continue to follow all unresolved study-related AEs and SAEs until their resolution or stabilization, the patient is lost to follow-up or until it is determined that the study treatment or participation is not the cause of the AE/SAE. Additionally, patients will be contacted regarding the occurrence of any new SAE considered to be treatment-related at 60 and 90 days following the last study treatment administration or until initiation of another anti-cancer therapy, whichever occurs first.

i) Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, and on Day 21 (or -7 days) of the cycle for Cycle 1, Cycle 3 and every third cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed ≥ 28 days after last study treatment administration or if no post-treatment evaluation was performed. The same imaging technique should be used per patient throughout the study. Results must be reviewed and documented prior to administration of study treatment. If treatment is delayed for any reason, LVEF assessments can be postponed to allow them to be performed within 7 days prior to the next treatment administration.

j) From Cycle 1, Day 1 onwards, tumor assessments, including a CT or MRI with contrast of the chest, abdomen, and pelvis should be performed according to the indicated schedule (± 5 working days), regardless of any delays in treatment or other assessments. Tumor assessments obtained within 28 days prior to first study treatment may be used for screening purposes. Tumor response must be assessed through physical examination and imaged-based evaluation using RECIST version 1.1. Assessments should include an evaluation of all sites of disease. In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled assessment should be performed. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study for the same patient, e.g. the same contrast protocol for CT scans. For patients who discontinue study treatment for reasons other than PD, continued tumor assessments according to the protocol every 3-6 months. After disease progression, assessments are no longer required to evaluate new lesions, non-target lesions, and target lesions.

k) Patients with isolated brain metastases may continue study treatment if they demonstrate clinical benefit (CR or PR of any duration or SD ≥ 4 months) as detailed in Section 4.4.1.4 of the protocol. A brain MRI or CT should be performed along with regularly scheduled tumor assessments in these instances.

l) An isotope bone scan and/or other radiographic modalities (as a consequence of the anticipated Tc-99 shortage), will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions. If an isotope-based scan was performed >28 days but ≤ 60 days prior to first study treatment, non-isotopic radiographic modalities should be utilized to document the extent of bony metastatic disease. Refer to Appendix 3 for additional details.

Table 1 Schedule of Assessments (Continued)

m) Hematologic assessments include Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cells (WBC) with differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils).

n) Scheduled for Day 1 of Cycle 1 and beyond: to be performed within 72 hours preceding administration of study treatment; results must be reviewed and documented prior to administration of study treatment.

o) Biochemistry assessments include: sodium, potassium, chloride, calcium, magnesium, glucose, BUN, creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin (and direct bilirubin where total bilirubin > ULN).

p) Includes specific gravity, pH, protein, glucose, blood, ketones and bilirubin.

q) Serum β-HCG test must be performed during screening. Urine β-HCG test must be performed at subsequent time points for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal (refer to Section 5.2.4). Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication (Cycle 1, Day1). For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. Urine pregnancy test in women of childbearing potential must be performed every 3 cycles and at 3- and 6- months after the safety follow-up visit. All positive urine pregnancy tests must be confirmed by a serum β-HCG test. Contraception should be used for 7 months after the last dose of study medication.

r) The initial dose of trastuzumab emtansine will be administered over 90 minutes if well tolerated subsequent infusions may be administered over 30 (±10) min.

3.4 Concomitant Medication

Concomitant therapy and premedication are defined as non-investigational medicinal products.

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient between the 28 days preceding first treatment and the safety follow-up visit (28 – 42 days after last dose). Afterwards, only anti-cancer therapies will be recorded on the Concomitant Medications electronic Case Report Form (eCRF), as part of the survival follow-up period. Premedication is allowed according to standard practice guidelines. No premedication for the first infusion of trastuzumab emtansine is required; however, premedication is allowed at the investigator's discretion. Concomitant use of erythropoiesis-stimulating agents is allowed if clinically indicated in accordance with local prescribing guidelines.

Palliative radiotherapy may be permitted to treat pre-existing painful bone metastases or to treat brain metastases (for patients who have disease control outside of the brain). Radiotherapy should be finished at least 7 days before resuming administration of trastuzumab emtansine and all toxicities need to have resolved. If not, the cycle may be delayed for up to 42 days.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. Use of bisphosphonates or denosumab is permitted for the control of bone pain, prevention and/or treatment of bony metastases, and treatment of osteoporosis. If bisphosphonates are required for the treatment of symptomatic malignancy-associated hypercalcemia, tumor assessments should be performed to assess for potential disease progression. Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, antihistamines such as diphenhydramine, or corticosteroids) may also be given at the investigator's discretion.

Any Chinese traditional medicines that could potentially negatively impacting the liver functions are not permitted. However, any Chinese traditional medicines having a liver protective action would be considered acceptable, at the investigator's discretion. It will be the investigator's responsibility to verify whether a specific Chinese medication could potentially affect liver function.

Prohibited Therapy

The medications and or therapies described below are prohibited during the study prior to discontinuation of study treatment.

Any therapies intended for the treatment of cancer, other than trastuzumab emtansine, whether they are approved by national health authorities or experimental, including cytotoxic chemotherapy, immunotherapy, hormonal therapy (other than megestrol acetate), and biologic or targeted agents (other than granulocyte colony-stimulating factor and erythropoiesis stimulating agents), are prohibited. The use of Chinese traditional medicines in case when they have no anti-cancer activity are allowed at the investigator's discretion.

Radiotherapy for unequivocal disease progression is not permitted while on study treatment, with the exception of new brain metastases or isolated progression of previously treated brain lesions. Patients who have disease control outside of the brain, defined as continued PR or CR of any duration, or SD for ≥3 months, but who have developed brain metastases that are treatable with radiation will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain that

cannot be treated with additional radiation. Radiotherapy should be finished at least 7 days before resuming administration of trastuzumab emtansine and all toxicities need to have resolved. Patients with thrombocytopenia and on anti-coagulant treatment must be monitored closely during treatment with trastuzumab emtansine. Platelet counts will be monitored prior to each trastuzumab emtansine dose.

3.5 Study Analysis Populations

There will be 2 analysis populations (Safety and Intent-to-Treat (ITT)) defined for the study analyses. The Safety and ITT populations are described below.

This is a safety study with the safety populations being the main analysis populations. Per-protocol (PP) population will not be defined; however major protocol violations will be summarized and defined.

3.5.1 Safety Population

The safety population includes all patients who have received at least one dose of study medication. Two safety populations will be defined: Safety Population 1 will include all patients enrolled in Cohort 1, while Safety Population 2 will include all patients in Cohort 2.

Safety Population 1 and Safety Population 2 will be used to summarize safety variables for Cohort 1 and Cohort 2, respectively.

Pooled analysis for safety will be performed on the Safety Population that includes all patients in Safety Population 1 and Safety Population 2.

3.5.2 ITT Population

The ITT population includes all patients enrolled to the study (with informed consent signed and enrolled for the study). Two ITT populations will be defined: ITT Population 1 will include all patients enrolled in Cohort 1, while ITT Population 2 will include all patients in Cohort 2.

ITT Population 1 and ITT Population 2 will be used to summarize efficacy variables for Cohort 1 and Cohort 2, respectively.

Pooled analysis for efficacy will be performed on the ITT Population that includes all patients in ITT Population 1 and ITT Population 2.

3.5.3 Subgroups

The following subgroup analyses will be performed for both cohorts and pooled across cohorts for safety analyses:

- AST or ALT increases that are > 3 × ULN and total bilirubin > 2 × ULN except in patients with documented Gilbert's syndrome
- Country; see below for more details.
- Race (Asian, non-Asian, NA or Unknown)
- Age (≤65, 66-74, ≥75)
- ECOG 0–1 versus ECOG ≥ 2

Country has been replaced by pooled countries for safety reporting. Singular countries will still be used for patient disposition. The regrouped countries are given as follows:

Asia: Hong Kong, Korea, Taiwan, China and United Arab Emirates (UAE)

North America: Canada

South America: Argentina, Brazil, Dominican Republic, Ecuador, Guatemala, Mexico, Panama, Peru and Venezuela

Europe : Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Turkey and UK

Australia: Australia

Analyses on the subgroups of patients for whom non-validated tests were used, will be performed for demography, HER2 status, baseline characteristics and AEs (including most common AEs, SAEs and AEs leading to discontinuation). In addition, Kaplan-Meier estimates will be calculated for PFS and OS, as well as the BOR, in this subgroup.

The subgroup comprised patients who had either:

- a non-validated IHC test result and no ISH test performed
- or a non-validated ISH test result and no IHC test performed
- or a non-validated IHC test result and a non-validated ISH test result

3.6 Withdrawn Subjects

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Noncompliance
- Disease progression

In addition, patients must permanently discontinue study drug if they experience any of the following:

- Clinical signs and symptoms suggesting CHF.
- Dyspnea or clinically significant hypotension (defined per investigator discretion).
- Symptomatic left ventricular dysfunction (NCI-CTCAE version 4.0 Grade 3 or 4) with a drop in LVEF consistent with cardiac failure.
- Pregnancy.
- Patients who experience Grade ≥ 3 neurotoxicity in the form of peripheral neuropathy that does not resolve to Grade ≤ 2 within 42 days after last dose received.

- Patients who experience Grade > 3 elevation of liver function which does not recover within 42 days
- Trastuzumab emtansine treatment in patients with serum transaminases > 3 × ULN and concomitant total bilirubin > 2 × ULN
- Patients who are diagnosed with NRH (Nodular Regenerative Hyperplasia)
- Patients who are diagnosed with ILD or pneumonitis
- Patients who experience a Grade ≥ 3 allergic reaction or acute respiratory distress syndrome

Patients who discontinue study drug prematurely will be asked to return to the clinic for a safety follow-up visit, and may undergo follow-up assessments.

The primary reason for discontinuation of study drug and/or withdrawal from the study will be recorded on the appropriate eCRF pages.

The following reasons will be collected:

- Adverse event/Unacceptable toxicity
- Death
- Lost to follow-up
- Lack of compliance
- Withdrew consent
- Investigator's decision
- Trial terminated by Sponsor
- Completed treatment per protocol
- Disease Progression
- Other

Patients who discontinue study drug prematurely will not be replaced.

3.7 Randomization

N/A

3.8 Blinding

N/A

3.9 Sample Size

A sample size of approximately 2000 patients is planned for Cohort 1. For the purpose of the estimation of sample size, the incidence of AEs of Grade 3 or higher related to trastuzumab emtansine was chosen as a safety endpoint of primary interest. If the observed incidence of AEs Grade ≥ 3 related to trastuzumab emtansine e.g., hepatic events, pneumonitis, thrombocytopenia or allergic reactions is between 5% and 10% (Study TDM4450g/BO21976), the precision for the estimation of the incidence of AE is presented in Table 2 by 95% Clopper-Pearson Confidence Intervals (CIs).

Table 2 Cohort 1: Clopper-Pearson 95% Confidence Intervals for the Incidence of AEs Grade ≥ 3 Based on 2000 Patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
20 (1%)	0.6% - 1.5%
40 (2%)	1.4% - 2.7%
60 (3%)	2.3% - 3.8%
80 (4%)	3.2% - 5%
100 (5%)	4.1% - 6%
120 (6%)	5% - 7.1%
140 (7%)	5.9% - 8.2%
160 (8%)	6.8% - 9.3%
180 (9%)	7.8% - 10.3%
200 (10%)	8.7% - 11.4%

For the purpose of the sample size estimate of Cohort 2, the incidence of Grade ≥ 3 thrombocytopenia in Asian patients was chosen as a safety endpoint of primary interest.

This is based on the pooled analysis of trials: TDM4370g/BO21977, TDM4450g/BO21976, TDM4373g/BO22495, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430, and the results of a subset of 99 Asian patients (see the trastuzumab emtansine Investigator's Brochure).

If the observed incidence of Grade ≥ 3 thrombocytopenia in Asian patients is between 30% and 55%, the precision for the estimation of the incidence of AEs is presented in Table 3 by 95% Clopper-Pearson CIs.

Table 3 Cohort 2: Clopper-Pearson 95% Confidence Intervals for the Incidence of Grade ≥ 3 Thrombocytopenia Based on 220 Asian Patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CIs
2 (1%)	0.1% - 3.6%
10 (5%)	2.4% - 9%
20 (10%)	6.2% - 15%
60 (30%)	23.7% - 36.9%
70 (35%)	28.4% - 42%
80 (40%)	33.2% - 47.1%
90 (45%)	38% - 52.2%
100 (50%)	42.9% - 57.1%
110 (55%)	47.8% - 62%

The sample size of approximately 2220 patients is planned for the pooled analysis of Cohorts 1 and 2. Table 4 shows the precision for the estimation of the incidence of AEs.

Table 4 Clopper-Pearson 95% Confidence Intervals for the Incidence of Grade ≥ 3 AEs based on 2220 patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
22 (1%)	0.6% - 1.5%
44 (2%)	1.5% - 2.7%
66 (3%)	2.3% - 3.8%
88 (4%)	3.2% - 4.9%
110 (5%)	4.1% - 6%
132 (6%)	5% - 7.1%
154 (7%)	6% - 8.1%
176 (8%)	6.9% - 9.2%
198 (9%)	7.8% - 10.3%
220 (10%)	8.8% - 11.3%

4 Statistical Methodology

4.1 Planned Analyses

This study includes only one treatment arm; hence treatment comparability is not applicable.

All safety and efficacy summaries will be presented for each cohort separately, and for the pooled analysis of Cohorts 1 and 2. The analysis of Cohort 1 will be conducted and then the pooled analysis of Cohorts 1 and 2 will be conducted in parallel to the final analysis of Cohort 2.

Safety Population 1 and Safety Population 2 will be used to summarize safety variables for Cohort 1 and Cohort 2, respectively.

Pooled analysis for safety will be performed on the safety population that includes all patients in Safety Population 1 and Safety Population 2.

The following subgroup analyses will be performed on Safety Population 1, Safety Population 2 and the overall safety population (pooled analysis) for all safety analyses:

- AST or ALT increases that are > 3 × ULN and total bilirubin > 2 × ULN except in patients with documented Gilbert's syndrome
- Country
- Race (Asian, non-Asian, NA or Unknown)
- Age (≤65, 66-74, ≥75)
- ECOG 0–1 versus ECOG ≥ 2

Country has been replaced by pooled countries for safety reporting. The regrouped countries are given as follows:

- Asia: Hong Kong, Korea, Taiwan, China and UAE

- North America: Canada
- South America: Argentina, Brazil, Dominican Republic, Ecuador, Guatemala, Mexico, Panama, Peru and Venezuela
- Europe: Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Turkey and UK
- Australia: Australia

ITT Population 1 and ITT Population 2 will be used to summarize efficacy variables for Cohort 1 and Cohort 2, respectively.

Pooled analysis for efficacy will be performed on the ITT population that includes all patients in ITT Population 1 and ITT Population 2.

Demography and baseline characteristic summaries will be presented for both the safety and ITT populations (Populations 1, 2 and pooled). Summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Baseline and disease characteristics that are continuous variables will also present the first and third quartiles. Percentages will be calculated using the total subjects.

There are no formal statistical hypothesis tests to be performed. There are no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Notes:

- Baseline is defined as the last value recorded prior to first dose of study drug (except for the laboratory data, where a value recorded the date of first dose of study drug and corresponding to screening visit will be also considered as baseline).
- Where a change from baseline is presented, results for baseline are those recorded immediately prior to treatment. Where this value is missing or unavailable, then the next available preceding result will be used.
- All data will be listed.
- Listings will be provided for 11 patients in China who continued study treatment after clinical data cutoff pending delayed entry into a rollover study (per Protocol Amendment 5). These listings will contain additional data from these patients' visits after 10th July 2019 (protocol LPLV) until their actual last visit.

4.2 Interim Analysis Plan

In addition to the final analysis, for Cohort 1 there will be seven safety interim analyses for review by the iDMC: after approximately 50 and 350 patients have completed Cycle 1, Day 1 and after approximately 1,000, 1,500, and 2,000 patients have completed the first cycle of study medication (Cycle 1, Day 21), and two which were approximately at 6 and 12 months thereafter, as per the iDMC charter. For Cohort 2, there will be one interim safety analysis for review by the iDMC after approximately 100 patients have completed Cycle 1 (Cycle 1, Day 21).

As discussed and agreed with the iDMC members, the following has approach will be implemented.

1) The 100th patient enrolled and dosed should occur at the same time as the DBL
2) To allow for programing and data cleaning activities, the iDMC review was moved by 4 months.

In addition to the above interim analyses, there may be additional interim analyses for Health Authority purposes (e.g., to support CFDA [China]) after 150 Chinese patients have been enrolled and completed Cycle 1 (Cycle 1, Day 21) or by January 2017, whichever occurs first.

The description of the analyses required for the iDMC is presented in the iDMC charter.

The final analysis of each cohort will be performed when all patients within the respective cohort have been followed up for safety and efficacy for a period of up to 2 years after the last patient has been enrolled in Cohort 2 of the trial.

4.3 Disposition of Subjects

The number of screened patients (enrolled, inform consent form signed) and eligible patients will be presented.

The number of patients eligible for the study, number and percentage, in each analysis population will be presented. It should be noted that for this study the patients eligible for the study correspond to the ITT population.

The number of patients who completed treatment (Yes/No), in follow-up (Yes/No), completed study (Yes/No) and the reasons for discontinuation of treatment and discontinuation from study will be presented for each analysis population.

The number of patients by country and pooled country will also be presented.

The summary of patients receiving the study drug at each cycle will be presented graphically.

4.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarized for the safety population, and repeated for ITT population. Included will be age, age in classes([<65 and ≥ 65], [<75 and ≥75], [≤65, 66-74, ≥ 75] , [18-64, 65-74, ≥ 75] and [18-64, 65-84, ≥ 85] years old), gender, race, self-reported ethnicity, country of the site in which the patient was screened, female reproductive status, height, weight, ECOG status, smoking history, alcohol and drug abuse, human epidermal growth factor receptor 2 (HER2) test results, ongoing and all medical history, cancer history, tumor assessments at baseline, previous cancer therapy and surgery, neoadjuvant treatment, adjuvant treatment, locally advanced /metastatic treatment, visceral disease at screening and location of metastasis at diagnosis.

Notes:

- Age will be as reported on the eCRF at screening and will not be derived.
- Medical history will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). At the time of the pooled analyses the MedDRA version will be different from the MedDRA version used at the Cohort 1 analyses. For the pooled analyses the latest version of MedDRA will be used for all patients.
- Ongoing medical history is defined as histories marked as ongoing at time of screening.

- All medical histories are all medical histories recorded in the eCRF

4.5 Exposure

Summaries of study treatment exposure will be presented for the safety population, and repeated for ITT population.

The total number of cycles received will be summarized both by descriptive statistics and by presenting the number and percentage of patients in each cohort.

Study drug administration details will be summarized by descriptive statistics and will include the duration of exposure, the number and percentage of patients with missed doses, doses reduced and doses interrupted, and the cumulative doses received.

Missed Dose is identified from the following question in the CRF –'Was the study medication administered at this visit?'

Number of Doses Reduced is derived from planned and received dose. If received dose is less than planned dose then this is considered as dose reduced.

Dose Interruption is when the infusion is interrupted, taken from the 'Was infusion interrupted?' in the CRF

The duration of exposure and duration of follow-up will be displayed.

Duration of exposure (months) will be derived as follows:

((Date of last administration – Date of first administration) + 1)/ 30.4375

Duration of follow-up (months) is the duration the patient is in the study and will be derived as follows:

((Date of end of study – Date of inclusion) + 1)/ 30.4375

Cumulative doses received (mg/kg) will be calculated over all received infusions, according to received dose (in mg) divided by patient's body weight at each dose.

4.6 Concomitant Medication

Summaries of prior and concomitant medications will be presented for the safety population. Prior medications are those that stopped before exposure to study drug; concomitant medications are all those taken during the study, including those started before (28 days) but ongoing at first dose of study drug.

Incidence of prior medications and concomitant medications will be presented in a listing separately by indication (pre-existing condition, prophylaxis, and adverse event) therapeutic area and preferred drug name.

Where a medication end date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Medications are coded using the latest version of the World Health Organization (WHO) Drug dictionary, by ATC Class and Preferred Drug Name.

Previous anti-cancer therapy refers to previous systemic therapies; chemotherapy, targeted therapy, anti-estrogen therapy and radiotherapy.

The number of patients with anti-tumor therapy will be summarized, as well as the number of patients having received each type of anti-cancer therapy, and the number of lines of metastatic treatment received.

A table per type of anti-cancer therapy will also be provided, describing the number of patients who received the anti-cancer treatment in each setting (neo-adjuvant, adjuvant setting etc), the reason for discontinuation of previous treatment, and the product received.

4.7 Efficacy Analysis

The efficacy variables will be summarized for ITT Population 1 and ITT Population 2, for Cohort 1 and Cohort 2, respectively.

Pooled analysis for efficacy will be performed on the ITT population that includes all patients from ITT Population 1 and ITT Population 2.

No formal hypothesis testing is planned.

4.7.1 Progression free survival

PFS is defined as the time from the date of first dose until the first documented progression of disease or death from any cause (event), whichever occurs first. Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of first dosing plus one day. The progression of disease as assessed by investigators will be taken for the analysis.

Time to event will be calculated in months as follows:

PFS (months) = ((date of event – date of first dosing) + 1)/ 30.4375

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% CI will be presented along with the estimates for the 1st and 3rd quartiles and the associated ranges (minimum, maximum). The estimate of the survivor function (probability of event) will be displayed graphically using a KM curve and listed along with the associated 95% CI; the log-log transformation is applied to the survivor function to obtain the CIs. PFS will be assessed for patients with either measurable or non-measurable disease at baseline.

Progression free survival rates at Week 12, and at 12-week intervals thereafter will be estimated and presented along with the corresponding two-sided 95% CI. The final analysis will take place 2 years after the last patient has been enrolled in the trial.

PFS outputs (i.e. table and KM figure) will be presented stratified by Previous Lines of Treatment and prior treatment with pertuzumab.

4.7.2 Overall survival

OS is defined as the time from the date of first dosing until the date of death, regardless of the cause of death. Patients who were alive at the time of the final analysis will be censored at the date of the last follow-up assessment.

Time to event will be calculated in months as follows:

OS (months) = ((date of event – date of first dosing) + 1) /30.4375

Overall survival will be assessed for patients with either measurable or non-measurable disease at baseline and analyzed and presented as described for PFS.

OS outputs will be presented stratified by Previous Lines of Treatment and prior treatment with Pertuzumab.

4.7.3 Best overall response and overall response rate

Overall response will be estimated via best (confirmed) overall response (BOR) as assessed by investigators. The BOR is defined as the best response recorded from the start of first dosing (date of first dosing) until disease progression/recurrence or death from any cause. To be assigned a status of PR or CR, i.e.to be a responder, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR. This status will be assessed only for patients with measurable disease at baseline. Patients with non-measurable disease at baseline will be assessed for the time-to-event endpoints (e.g., PFS, OS, etc).

Response as assessed by investigators will follow the RECIST version 1.1 criteria described in Table 5 and Table 6 below:

Table 5 Time point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 6 Time point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.
[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

The best confirmed overall response (BOR) will be computed in Table 7 (RECIST V1.1):

Table 7 Best Overall Response When Confirmation Is Required

Overall Response at First Time point	Overall Response at Subsequent Time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration[MD] for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration[MD] for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration[MD] for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[MD] Minimum duration = 6 weeks (42 days)

The analysis of overall response rate (ORR) is based on the best (confirmed) overall response (BOR). In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval equal to 6 weeks.

The BOR will be assessed by the number and proportion of responders and non-responders together with two-sided 95% Clopper-Pearson CIs. Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumor assessment will be considered to be non-responders. To assess the influence of baseline covariates, e.g. age groups (≤ 65 vs. >65) (≤65, 66-74, ≥75), ECOG 0-1 versus ECOG ≥ 2, a logistic regression analysis will be conducted for BOR as a univariate analysis, followed by a multiple regression analysis. The list of covariates to be included in this analysis was set before database lock for Cohort 1, during the pre-database lock dry-run review of outputs (on mature data): pooled countries, age groups (≤65 vs. >65, and ≤65, 66-74, ≥75), organs involved in target lesions (≤3 vs. >3 organs involved), hormone positivity, drug interruption

vs no drug interruption, dose reduction vs. no dose reduction, missing dose vs. no missing dose, histology grade at diagnosis Grade 3 vs. Grades 1,2, unknown, missing, aggressiveness of the disease using TNM [Tx-T0-T1-T2 vs T3-T4 (best case scenario) , T0-T1-T2 vs Tx-T3-T4 (worst case scenario), N0, NX versus N1, N2, N3 (best case) and N0 vs. N1, N2, N3, NX (worst case), N1, N2, N3 vs. N0 (Nx excluded), M0, MX vs. M1 (best case) and M0 vs M1, MX (worst case), M0 vs. M1 (Mx excluded) ; the selection of the variables in case of significance in the univariate model will be based on the Akaike criteria in the multivariate model], visceral vs. non-visceral, currently in 2nd line of treatment vs. currently in 3rd or later line of treatment, prior treatment with pertuzumab vs. no prior exposure to pertuzumab. In addition to these predictor factors, for the pooled analysis of Cohort 1 and 2, a further factor will be added: region (Asian versus non-Asian regions).
A univariate analysis will be performed for each covariate. The number of patients included in the analysis, the odds ratio of each covariate, the corresponding two-sided 95% Wald CI and the p-values (Wald test) for the covariate will be presented in a summary table. In this univariate model, the null hypothesis of the Wald test will be: “the covariate has no influence on the BOR”.

Further exploratory analysis will be performed. All covariates which are significant at the 0.20 level in the univariate analysis will be included in a multiple regression model (interaction will not be included), then backwards selection at the 5% level will be performed to obtain a final model. The number of patients included in the analysis and the odds ratio for each of the covariates included in the final model will be estimated and presented in a summary table, including the corresponding two-sided 95% Wald CI and the p-value (Wald test). In the multivariate model, the null hypothesis of the Wald test will be: “the covariate has no influence on the BOR when adjusting for other covariates in the model”.

4.7.4 Duration of response

DoR is defined as the period from the date of initial confirmed PR or CR (whichever occurs first) until the date of PD or death from any cause. DoR will be calculated in days as follows:

DoR (months) = ((Date of PD or death – Date of first confirmed PR or CR) + 1) /30.4375

Patients with no documented progression or death after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS. Only patients with BOR of CR or PR (i.e., responders) will be included in the analysis of DoR. The analysis and presentation of DoR will be as described for PFS.

4.7.5 Time to response

Time to (confirmed) response (TTR) is defined as the time from first dose to first documentation of confirmed PR or CR (whichever occurs first). TTR will be calculated in days as follows:

TTR (months) = ((Date of first response assessment of confirmed PR or CR - Date of first dosing) + 1) /30.4375

Patients who do not have a confirmed response will be censored at the date of the last tumor assessment.

To be assigned a status of PR or CR, i.e., to be a responder, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after

the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR. This status will be assessed only for patients with measurable disease at baseline.

The analysis and presentation of TTR will be as described for PFS.

4.7.6 Clinical benefit rate

CBR includes patients whose best (confirmed) response was PR, CR or SD that lasted at least 6 months. The number and proportions of responders and non-responders together with two-sided, 95% Clopper-Pearson CIs will be presented. This status will be assessed only for patients with measurable disease at baseline.

CBR will be summarized in a similar way to the ORR as assessed by BOR.

4.7.7 Lesions count

4.7.7.1 Target lesions

Target lesions will be identified at the Screening visit. A maximum of 5 target lesions may be identified, with no more than 2 target lesions per organ. The size of each target lesion and the sum of diameters of all target lesions will be recorded.

The sum of diameters of the target lesions (in mm) will be summarized by visit including change from baseline (Screening visit) and change from lowest measurement of their size.

4.7.7.2 New lesions and Non target lesions

The number of new lesions will be recorded for each organ site. The number and percentage of patients with new lesions will be presented at each visit.

Non target lesions will be identified at baseline (Screening visit). The number of non-target lesions (multiple or single) will be recorded for each organ site. At the post baseline visits the non-target lesions will be recorded for each organ site.

4.7.8 Time to progression

Time to progression (TTP) is defined as the time from first dose to the first documented progression of disease

TTP (months) = ((Date of progression of disease - Date of first dosing) + 1) /30.4375

4.8 Safety Analysis

4.8.1 General consideration

The safety variables will be summarized for Safety Population 1 and Safety Population 2, for Cohort 1 and Cohort 2, respectively.

Pooled analysis for safety will be performed on the safety population that includes all patients in Safety Population 1 and Safety Population 2.

The following subgroup analyses will be performed on Safety Population 1, Safety Population 2 and the overall safety population (pooled analysis) for all safety analyses:

- AST or ALT increases that are > 3 × ULN and total bilirubin > 2 × ULN except in patients with documented Gilbert's syndrome
- Country
- Race (Asian, non-Asian, NA or Unknown)
- Age (≤65, 66-74, ≥75)
- ECOG 0–1 versus ECOG ≥ 2

Country has been replaced by pooled countries for safety reporting, see section 3.5.3

All AEs and laboratory variables will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0 or later version grading system.

Prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be reported (e.g., SAEs related to invasive procedures such as biopsies, discontinuation of medicines etc.). After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period, investigator is not required to actively monitor patients for AEs; however, the Sponsor should be notified if the investigator becomes aware of any post study SAEs or non-serious AESIs.

Only treatment emergent AEs (starting on the day of or after the first administration of trastuzumab) will be included in the summary tables. Non-treatment emergent events (starting prior to first administration of trastuzumab) will be listed only. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed to be treatment emergent. Time to onset of AE will be calculated as follows:

(start date of AE – date of first study treatment) + 1.

If start date of AE was before study treatment administration, then time to onset of AE will be calculated as:
Date of assessment/event – Date of first study treatment

Imputation of Adverse Event Onset Date

For AEs, a missing or incomplete onset date will be imputed according to the following conventions:

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study treatment.

If only the month and year is known for onset date, the surrogate onset date will be set to the first day of that month and then the following rules applied:

1. If the month and year of the onset date is prior to the month and year of the first dose of study treatment, then the surrogate onset date will be the imputed onset date.
2. If the month and year of the onset date is on or after the month and year of the first dose of study treatment, then the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study treatment

- Surrogate onset date

If the imputed onset date of an adverse event is after the complete end date, the imputed onset date will be the same as the complete adverse event end date.

For the adverse events statistical analysis "related" refers to those events for which there is a reasonable suspected causal relationship to the study drug, or with an unknown relationship.

Adverse events will be coded using MedDRA dictionary. It is likely that at the time of the pooled analyses the MedDRA version will be different from the MedDRA version used at the Cohort 1 analyses. For the pooled analyses the latest version of MedDRA will be used.

4.8.2 Primary endpoint

The primary endpoint in this study is AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, also all other AEs Grade 3 or higher related to trastuzumab emtansine, and pneumonitis of all grades.

The primary endpoint will be computed for each patient, as the experience of at least:

- an AE Grade 3 or higher for hepatic events,
- an AE Grade 3 or higher for allergic reactions,
- an AE Grade 3 or higher for thrombocytopenia,
- an AE Grade 3 or higher for hemorrhage events,
- an AE Grade 3 or higher related to trastuzumab emtansine,
- or pneumonitis events of all grades

The incidence of the primary endpoint during the study will be provided in terms of number of patients and percentage with 95% Clopper-Pearson CI.

4.8.3 Secondary endpoints

4.8.3.1 Adverse events of special interest

Adverse events of special interest (AESIs) for this study include the following:

- Potential drug-induced liver injury
- Suspected transmission of an infectious agent by the study drug

Potential drug-induced liver injury:
Any potential case of drug-induced liver injury as assessed by laboratory criteria for Hy's law (according to laboratory results, not from the AE form), will be considered as a protocol-defined event of special interest and needs to be reported to the Sponsor expeditiously. The following laboratory abnormalities define potential Hy's law cases:

- AST and/or ALT elevations that are > 3 × ULN
  and

- Concurrent elevation of total bilirubin > 2 × ULN (or clinical jaundice if total bilirubin measures are not available), except in patients with documented Gilbert's syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin > 2 × ULN should be used instead.

Potential cases of drug-induced liver injury reported by the investigators were recorded as adverse events and were considered to be related to the study drug. These cases will be summarized.
In addition, potential drug-induced liver injury will be computed from the laboratory data and adverse events (clinical jaundice events) collected for the study, and summarized.

Suspected transmission of an infectious agent by the study drug will be analyzed:
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term ONLY applies when a contamination of the study drug is suspected, NOT for infections supported by the mode of action, e.g., immunosuppression.
Information on suspected transmission of an infectious agent by the study drug is taken from the AE form.

The incidence of each AESI for patients experiencing at least one AESI, will be provided in term of number and percentage, with 95% Clopper-Pearson confidence interval.

AESIs will be displayed as, potential drug-induced liver injury reported by the investigators, calculated potential drug-induced liver injury and suspected transmission of an infectious agent by the study drug (reported by the investigator).

4.8.3.2 Other adverse events of interest

Other adverse events of interest (included in the safety plan, but not mentioned as adverse events of primary interest or adverse events of special interest) include the following:

- Hepatic events all grades
- Allergic reactions all grades
- Thrombocytopenia all grades
- Hemorrhage events all grades
- Pneumonitis Grade 3 and above
- Peripheral neuropathy (neurotoxicity)
- Cardiac dysfunction (cardiotoxicity)

Incidence of each Other AE of Interest will be provided in term of number and percentage, with 95% Clopper-Pearson CI, of patients experiencing the AE at least once.

4.8.3.3 Summary of all adverse events

AEs and SAEs, related and unrelated, will be summarized separately by presenting the number and percentage of patients having any events, events leading to discontinuation of study drug, events leading to interruption of study drug, events by CTC grade, and relationship.

Summary tables by system organ class (SOC) and preferred term (PT) of the number and percentage of patients having events including number of events will be presented for:

- All AEs
- Related AEs
- All SAEs
- Related SAEs
- AEs leading to study drug discontinuation
- AEs leading to study drug interruption
- AEs of all NCI-CTCAE Grades
- AEs NCI-CTCAE Grade 3 and above
- AE of NCI-CTCAE Grades 1, 2, 3 and 4 – Hepatoxicity / Hematoxicity
- AEs by maximum CTC grade
- SAEs by maximum CTC grade
- AEs of primary interest (i.e. primary endpoint; AEs Grade 3 and above for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, AEs Grade 3 or higher related to trastuzumab emtansine, and pneumonitis all grades). Pneumonitis will be given overall and by grade
- AEs of special interest all grades, overall and by grade
- AEs of special interest Grade 3 and above
- Hepatic events all grades, overall and by grade
- Allergic reactions all grades, overall and by grade
- Thrombocytopenia all grades, overall and by grade
- Hemorrhage events all grades, overall and by grade
- Pneumonitis Grade 3 and above
- Peripheral neuropathy all grades, overall and by grade
- Peripheral neuropathy Grade 3 and above
- Cardiac dysfunction disorders all grades, overall and by grade
- Cardiac dysfunction disorders Grade 3 and above

If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal

relationship to study drug will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed, but will be classed as unknown.

In addition, analysis of incidence and time to onset will be provided for the following AEs: AEs leading to treatment interruption and discontinuation, SAEs, hepatic events, allergic reactions, thrombocytopenia, hemorrhage events all grades, pneumonitis Grade 3 and above, AESIs Grade 3 and above, peripheral neuropathy all grades and Grade 3 and above, left ventricular dysfunction disorders all grades and Grade 3 and above, CHF all grades and Grade 3 and above, and Infusion-Related Reaction/Hypersensitivity all grades and Grade 3 and above.

The incidence AEs for patients experiencing at least one AE, will be provided in term of number and percentage, with 95% Clopper-Pearson confidence interval.

A summary of deaths will be presented, tabulating the number and percentage of patients by primary cause of death, and underlying cause of death.

4.8.3.3.1 Subsets

The most frequent MedDRA preferred terms (≥ 5% patients in the total column) and system organ class will be presented. All other information collected (e.g. action taken) will be listed as appropriate.

4.8.4 Laboratory findings

Samples for hematology and biochemistry are scheduled at Screening, and on Day 1 (within 72 hours preceding administration of study treatment) of each treatment cycle and at the safety follow-up visit 28-42 days after last study treatment. Samples for urinalysis are scheduled at screening and safety follow-up visit and as clinically indicated during the treatment period.

Results from the following laboratory parameters will be converted to standard international units and summarized:

Hematology:

Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cells (WBC) with differential (including neutrophils, leukocytes, lymphocytes, monocytes, eosinophils and basophils).

Shift table for the any incidence of Hemorrhage adverse events and any incidence of Thrombocytopenia (lab results - platelet grade 3 or 4) by maximum grade will be presented.

Biochemistry:

Sodium, potassium, chloride, calcium, magnesium, glucose, blood urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), gamma glutamyl transferase, lactate dehydrogenase, total bilirubin (and direct bilirubin where total bilirubin > ULN).

Urinalysis:

Specific gravity, pH, protein, glucose, blood, ketones and bilirubin.

Hematology, biochemistry and continuous urinalysis laboratory values and changes from Baseline to each visit (where they are planned to be evaluated) will be summarized. Categorical urinalysis values will be presented by the number and percentage of patients within each category.

The graphical presentation of the mean value and 95% CI of selected laboratory parameters: AST, ALT, alkaline phosphatase, total bilirubin will be displayed.

Shift tables for the hematology and biochemistry laboratory parameters comparing NCI-CTC grade at baseline versus worst grade during the trastuzumab treatment period will be presented.

High and/or low grade values will be presented as applicable. Hematology and biochemistry laboratory parameters will also be presented by toxicity grade.

Notes:

- All results outside predefined normal ranges will be flagged in the data listings.
- Repeat laboratory results within a visit will replace the original value. Unscheduled results will be listed only.

Any other laboratory results will be listed only.

4.8.5 LVEF

LVEF observations are recorded at Screening and on Day 21 (or -7 days) of Cycle 1, Cycle 3 and every third cycle thereafter and at the Safety follow-up visit.

LVEF will be summarized over time using descriptive statistics. LVEF will also be summarized by number and percentage of patients for LVEF values ≥50% and <50%. LVEF will also be summarized by number and percentage of patients within the following categories by cycle and by worst (lowest) on treatment value.

- LVEF ≥ 50% and a 10% drop from baseline
- LVEF 45% – 49% and a 10% drop from baseline
- LVEF 40% – 44% and a 10% drop from baseline
- LVEF ≤ 39% and a 20% drop from baseline

Mean LVEF values with associated 95% CIs will be presented graphically with line graphs over time.

LVEF will be summarized over time using descriptive statistics.

4.8.6 ECG

ECG findings (normal, abnormal) and heart rate (bpm) are recorded and a 12-lead ECG examination performed at Screening. ECG findings and heart rate will be summarized as part of the baseline characteristics.

4.8.7 Weight

Weight (kg) is measured for all patients at Screening, at each treatment cycle and at the safety follow-up visit. Weight will be summarized over time using descriptive statistics.

4.8.8 ECOG

ECOG performance status will be recorded at Screening, at each treatment cycle and at the safety follow-up visit. ECOG performance status will be summarized by cycle presenting the number and percentage of patients in each grade.

ECOG performance status (Grade 0 - Grade 5) will be summarized by over time by presenting the number and percentage of patients in each grade.

4.8.9 Physical Examinations

A complete physical examination will be performed at Screening. A limited physical examination will also be performed at each treatment cycle and the safety follow-up visit recording any changes from the general physical exam performed at screening.

Physical examination results will be listed only.

4.8.10 Assessments of hospitalizations

The number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be recorded.

4.9 Adjustment for Covariates

4.9.1 Centre effects

This is a multi-center, international trial. Patients from all centers will be pooled.

4.10 Protocol Violations

No per-protocol population is defined but protocol violations will be identified.

Major protocol violations will be summarized in the Clinical Study Report (CSR).

The data will be provided by Roche Data Management from the Procedural Document Management System (PDMS).

A list of patients with important violations will be agreed upon and will be documented in the "Analysis Set Specifications" document.

4.10.1 Violation criteria

Where possible the PDMS will be used to identify violations from the protocol, otherwise protocol violations are to be identified programmatically. In general, the violations will be considered according to the following general categories:

- Non-compliance with inclusion criteria (Section 4.1.1 of the protocol)
- Non-compliance with exclusion criteria (Section 4.1.2 of the protocol)
- Unauthorized concomitant therapy

- Non-compliance with study treatment
- Subjects who did not take at least 6 doses of study medication over the 12 week study period (evaluable subject)
- Other, e.g. consent not signed

Note: Other reasons for violations may be added to this list.

4.11 Missing Values – Missing Visits

Unless otherwise specified, missing values will not be replaced.

4.12 Deviations from SAP

The SAP will be finalized before the database lock and changes from the final SAP will be described in the clinical study report with rationale provided by the Statistician.

4.13 Changes in Conduct or Planned Analyses from the Protocol

A change in the conduct or planned analyses (Section 2.3 of the protocol; 'the pharmacoeconomics outcome objective') is as follows:

- To evaluate the resource expenditures, while on study treatment, due to hospitalizations that are not study-defined evaluations. The number of hospital visits, number of days admitted and type of visits (emergency department versus inpatient care) will be recorded

Has been changed in the SAP to:

- To evaluate the resource expenditures, while on study treatment, due to hospitalizations that are not study-defined evaluations. The number of hospital visits and type of visits (ICU versus other) will be recorded.

A change in the Section 6.3 Safety Analyses of the protocol:

- Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of each AE is described in Section 5 will also be summarized via KM estimates.

Has been removed from the SAP. Indeed, KM outputs for 'Time to onset of AE' events will not be produced since during the pre-database lock dry-run review of outputs (on mature data) it was observed that there were insufficient events to determine estimates for the KM median (and CIs).

A change in the safety analyses (Section 6.3 of the protocol, exploratory analyses):

- Subgroup analyses Age (>65, ≤65)
- Subgroup analyses Age (>75, ≤75)
- Region (Asian versus non-Asian regions)

Subgroup analyses age (>65, ≤65) and age (>75, ≤75) have been removed from the SAP and replaced by the subgroup Age (≤65, 66-74, ≥75).

An analyses on the subgroups of patients for whom non-validated tests were used has been added in this SAP that was not mentioned in the protocol (Section 6.3 of the protocol, exploratory analyses).

An exploratory efficacy endpoint has been added in this SAP that was not mentioned in the protocol (Section 6.2 of the protocol, Summaries of treatment group comparability): a section 2.2.3 Exploratory efficacy endpoints has been added in this SAP, with the time to progression (TTP) as an exploratory endpoint.

4.14 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=DSET NOPRINT;
    VAR VAR1 VAR2 VAR3 … VARN;
    BY BYVAR; (optional)
    OUTPUT OUT=OUTNAME
    N=N MEAN=MEAN MIN=MIN MAX=MAX MEDIAN=MEDIAN  STD=STD;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=DSET NOPRINT;
    BY BYVAR; (optional)
    TABLES VAR1*VAR2;
    OUTPUT OUT=OUTNAME;
RUN;
```

- **Tables that need exact or asymptotic 95% CIs between groups for proportions:**

```
PROC FREQ DATA=DSET;
    BY BYVAR; (optional)
    TABLES VAR1 * VAR2 / measures riskdiff alpha=0.05;
    EXACT MEASURES;
RUN;
```

Notes: 1 Estimates are computed for 2x2 tables only
2 This code also gives exact 95% CIs within group for binomial proportions

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=DSET;
    BY BYVAR; (optional)
    TABLES VAR1;
    EXACT BINOMIAL;
RUN;
```

- **Tables that need life table with estimates of survival, with CIs and log rank test:**

```
PROC LIFETEST DATA=DSET
                    OUTSURV=LIFE
                    METHOD=KM
                   CONFTYPE=LOGLOG
                   PLOTS=(s,ls,lls);
     TIME duration*censor (0 or 1);
    ID patient;
RUN;
```

- **Tables that require logistic regression, including 95% CIs:**
  PROC LOGISTIC DATA= dset descending;
  CLASS variables/param=ref ref=FIRST;
  MODEL 'Responses' = variables ;
  WHERE wherever; (optional)
  BY byvar; (optional)
  RUN;

Notes: (Treatment order: 1= responder, 2= non-responder)

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.1.3 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-

value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, subject and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

5.3 Tables

In the following table titles list, the population or set of patients indicated in brackets applies for:
- Enrolled Patients Cohort 1, Cohort 2 and pooled cohorts
– Safety/ITT Population 1, 2 and overall (pooled)

For safety subgroup analysis, Tables and Figures to be performed for each subgroup are flagged with an asterisk (*)

(Patients with potential drug-induced liver injury (calculated) – Safety population/ Safety Population 1, 2)
(Pooled countries - Safety population/ Safety population 1, 2)
(Race with Asian / non-Asian/ NA or Unknown - Safety population/ Safety population 1, 2)
(Patients with age ≤65, 66-74, ≥75 - Safety population/ Safety population 1, 2)
(Patients with ECOG 0–1, ≥ 2 - Safety population/ Safety population 1, 2)

For safety subgroup analysis, Tables to be performed only on patients with potential drug-induced liver injury (calculated) are flagged with #.

For safety subgroup analysis, Tables not to be performed on patients with ECOG group are flagged with +.

For safety subgroup analysis, Tables not to be performed on patients with age ≤65, 66-74, ≥75 group are flagged with ~.

5.3.1 Section 14.1: Demographic and Baseline

Table 14.1.1.1*	Patient Disposition (Enrolled Patients)
Table 14.1.1.2	Patient Disposition by Country and Pooled Country (Safety Populations)
Table 14.1.2.1	Major Protocol Violations (Safety Populations)
Table 14.1.3.1*	Demographics (Safety Populations)
Table 14.1.3.2	Demographics (ITT Populations)
Table 14.1.3.3	Demographics - Unvalidated HER2 (Safety Populations)
Table 14.1.4.1*	Baseline Characteristics (Safety Populations)
Table 14.1.4.2	Baseline Characteristics (ITT Populations)
Table 14.1.4.3	Baseline Characteristics - Unvalidated HER2 (Safety Populations)
Table 14.1.5.1*	HER2 Status (Safety Populations)
Table 14.1.5.2	HER2 Status - Unvalidated HER2 (Safety Populations)

Table 14.1.6*	Previous Breast Cancer History (Safety Populations)
Table 14.1.7.1	Ongoing Medical History (Safety Populations)
Table 14.1.7.2	All Medical History (Safety Populations)
Table 14.1.8.1*	Previous Anti-Cancer Therapy (Safety Populations)
Table 14.1.8.2*	Previous Anti-Cancer Therapy: Chemotherapy (Safety Populations)
Table 14.1.8.3*	Previous Anti-Cancer Therapy: Targeted Therapy (Safety Populations)
Table 14.1.8.4*	Previous Anti-Cancer Therapy: Anti-Estrogen (Safety Populations)
Table 14.1.8.5*	Previous Anti-Cancer Therapy: Radiotherapy (Safety Populations)
Table 14.1.8.6*	Previous Cancer Surgery (Safety Populations)
Table 14.1.9.1	Prior Medications (Safety Populations)
Table 14.1.9.2	Concomitant Medications (Safety Populations)
Table 14.1.10.1*	Study Drug Exposure – Number of Cycles (Safety Populations)
Table 14.1.10.2*	Study Drug Exposure – Duration, Missed Doses, Doses Reduced and Interruptions, and the Cumulative Doses Received (Safety Populations)
Table 14.1.11	HER2 testing (Safety Populations)

5.3.2 Section 14.2: Efficacy

Table 14.2.1.1.1*	Progression Free Survival (ITT Populations)
Table 14.2.1.1.2*	Progression Free Survival by Previous Lines of Treatment (ITT Populations)
Table 14.2.1.1.3	Progression Free Survival by Prior Pertuzumab (ITT Populations)
Table 14.2.1.1.4	Progression Free Survival - Unvalidated HER2 (ITT Populations)
Table 14.2.1.2.1	Progression Free Survival Rates (ITT Populations)
Table 14.2.1.2.2	Progression Free Survival Rates - Unvalidated HER2 (ITT Populations)
Table 14.2.1.3	Time to Progression (ITT Populations)
Table 14.2.2.1.1*	Overall Survival – Time to Death (ITT Populations)
Table 14.2.2.1.2*	Overall Survival – Time to Death by Previous Lines of Treatment (ITT Populations)
Table 14.2.2.1.3	Overall Survival – Time to Death by Prior Pertuzumab (ITT Populations)
Table 14.2.2.1.4	Overall Survival – Time to Death - Unvalidated HER2 (ITT Populations)
Table 14.2.2.2.1	Overall Survival Rates (ITT Populations)
Table 14.2.2.2.2	Overall Survival Rates - Unvalidated HER2 (ITT Populations)
Table 14.2.3.1.1*	Best Overall Response (ITT Populations)
Table 14.2.3.1.2	Best Overall Response - Unvalidated HER2 (ITT Populations)
Table 14.2.3.2.1	Best Overall Response: Logistic Regression univariate analysis results (ITT Populations)
Table 14.2.3.2.2	Best Overall Response: Logistic Regression multivariate analysis results (ITT Populations)
Table 14.2.3.3	Overall Response by Cycle (ITT Populations)
Table 14.2.4.1	Duration of Response (ITT Populations - Patients with Measurable Disease)

Table 14.2.4.2	Duration of Response Rates (ITT Populations - Patients with Measurable Disease)
Table 14.2.5.1	Time to Response (ITT Populations - Patients with Measurable Disease)
Table 14.2.5.2	Time to Response Rates (ITT Populations - Patients with Measurable Disease)
Table 14.2.5.3	Time to Response - Responders (ITT Populations - Patients with Measurable Disease)
Table 14.2.5.4	Time to Response Rates - Responders (ITT Populations - Patients with Measurable Disease)
Table 14.2.6	Clinical Benefit Rate (ITT Populations)
Table 14.2.7.1	Sum of diameters: Target Lesions (ITT Populations)
Table 14.2.7.2	Lesion Counts: New Target Lesions (ITT Populations)

5.3.3 Section 14.3: Safety

5.3.3.1 Primary endpoint

Table 14.3.1.1*	Primary Endpoint – Incidence and 95% Clopper-Pearson CI (Safety Populations)

5.3.3.2 Secondary endpoints

5.3.3.2.1 Adverse Events of primary interest

Table 14.3.1.2.1#	Adverse events of primary interest – Hepatic events Grade 3 or higher – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.2.2#	Adverse events of primary interest – Hepatic events Grade 3 or higher By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.3#	Adverse events of primary interest – Hepatic events Grade 3 or higher By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.2.4	Adverse events of primary interest – Allergic reactions Grade 3 or higher – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.2.5	Adverse events of primary interest – Allergic reactions Grade 3 or higher By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.6	Adverse events of primary interest – Allergic reactions Grade 3 or higher By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.2.7	Adverse events of primary interest – Thrombocytopenia Grade 3 or higher – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.2.8	Adverse events of primary interest – Thrombocytopenia Grade 3 or higher By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.9	Adverse events of primary interest – Thrombocytopenia Grade 3 or higher By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.2.10#	Adverse events of primary interest – Hemorrhage events Grade 3 or higher – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.2.11#	Adverse events of primary interest – Hemorrhage events Grade 3 or higher By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.12#	Adverse events of primary interest – Hemorrhage events Grade 3 or higher By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.2.13#	Adverse events of primary interest – Related to trastuzumab emtansine Grade 3 or higher – Incidence and 95% Clopper-Pearson CI (Safety

	Populations)
Table 14.3.1.2.14#	Adverse events of primary interest – Related to trastuzumab emtansine Grade 3 or higher By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.15#	Adverse events of primary interest – Related to trastuzumab emtansine Grade 3 or higher By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.2.16	Adverse events of primary interest – Pneumonitis of all grades – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.2.17	Adverse events of primary interest – Pneumonitis of all grades By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.2.18	Adverse events of primary interest – Pneumonitis of all grades By System Organ Class, Preferred Term and Grade (Safety Populations)

5.3.3.2.2 Adverse Events of special interest

Table 14.3.1.3.1#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.3.2#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.3.3#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.3.4#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) grade 3 and above – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.3.5#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) grade 3 and above By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.3.6#	Adverse events of special interest – Potential drug-induced liver injury (investigator reported) grade 3 and above By System Organ, Preferred Term and Grade (Safety Populations)
Table 14.3.1.3.7#	Adverse events of special interest – Concurrent elevation of ALT/AST and bilirubin meeting Hy's Law laboratory criteria – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.3.8#	Adverse events of special interest – Concurrent elevation of ALT/AST and bilirubin meeting Hy's Law laboratory criteria By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.3.9#	Adverse events of special interest – Concurrent elevation of ALT/AST and bilirubin meeting Hy's Law laboratory criteria By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.3.10	Adverse events of special interest – Suspected transmission of an infectious agent by the study drug – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.3.11	Adverse events of special interest – Suspected transmission of an infectious agent by the study drug By System Organ Class and Preferred Term (Safety Populations)

Table 14.3.1.3.12	Adverse events of primary interest – Suspected transmission of an infectious agent by the study drug By System Organ, Preferred Term and Grade (Safety Populations)
Table 14.3.1.3.13	Adverse events of special interest – Suspected transmission of an infectious agent by the study drug grade 3 and above – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.3.14	Adverse events of special interest – Suspected transmission of an infectious agent by the study drug grade 3 and above By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.3.15	Adverse events of special interest – Suspected transmission of an infectious agent by the study drug grade 3 and above By System Organ Class, Preferred Term and Grade (Safety Populations)

5.3.3.2.3 Other Adverse Events of interest

Table 14.3.1.4.1#	Other Adverse events of interest – Hepatic events all grades – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.2#	Other Adverse events of interest – Hepatic events all grades By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.3#	Other Adverse events of interest – Hepatic events all grades By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.4	Other Adverse events of interest – Allergic reactions all grades – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.5	Other Adverse events of interest – Allergic reactions all grades By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.6	Other Adverse events of interest – Allergic reactions all grades By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.7	Other Adverse events of interest – Thrombocytopenia all grades – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.8	Other Adverse events of interest – Thrombocytopenia all grades By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.9	Other Adverse events of interest – Thrombocytopenia all grades By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.10#	Other Adverse events of interest – Hemorrhage events all grades – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.11#	Other Adverse events of interest – Hemorrhage events all grades By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.12#	Other Adverse events of interest – Hemorrhage events all grades By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.13	Other Adverse events of interest – Pneumonitis grade 3 and above – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.14	Other Adverse events of interest – Pneumonitis grade 3 and above By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.15	Other Adverse events of interest – Pneumonitis grade 3 and above By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.16	Other Adverse events of interest – Peripheral neuropathy (Neurotoxicity) – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.17	Other Adverse events of interest – Peripheral neuropathy (Neurotoxicity) By System Organ Class and Preferred Term (Safety Populations)

Table 14.3.1.4.18	Other Adverse events of interest – Peripheral neuropathy (Neurotoxicity) By System Organ Class, Preferred Term and Grade (Safety Populations)
Table 14.3.1.4.19	Other Adverse events of interest – Cardic dysfunction (Cardiotoxicity) – Incidence and 95% Clopper-Pearson CI (Safety Populations)
Table 14.3.1.4.20	Other Adverse events of interest – Cardic dysfunction (Cardiotoxicity) By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.4.21	Other Adverse events of interest – Cardic dysfunction (Cardiotoxicity) By System Organ Class, Preferred Term and Grade (Safety Populations)

5.3.3.2.4 Summary of all Adverse Events

Table 14.3.1.5.1*	Cause of Death (Safety Populations)
Table 14.3.1.5.2.1*	Summary of Adverse Events (Safety Populations)
Table 14.3.1.5.2.2	Summary of Adverse Events - Unvalidated HER2 (Safety Populations)
Table 14.3.1.5.3.1*	Summary of Serious Adverse Events (Safety Populations)
Table 14.3.1.5.3.2	Summary of Serious Adverse Events - Unvalidated HER2 (Safety Populations)
Table 14.3.1.5.4.1*	Most Frequent Adverse Events By Preferred Term (≥ 5% Patients) (Safety Populations)
Table 14.3.1.5.4.2	Most Frequent Adverse Events By Preferred Term - Unvalidated HER2 (≥ 5% Patients) (Safety Populations)
Table 14.3.1.5.4.3*	Most Frequent Non-Serious Adverse Events By Preferred Term (≥ 5% Patients) (Safety Populations)
Table 14.3.1.5.5*+	Adverse Events By System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.5.6*+	Adverse Events By System Organ Class, Preferred Term and ECOG Status (Safety Populations)
Table 14.3.1.5.7*	Serious Adverse Events by System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.5.8*	Related Adverse Events by System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.5.9*	Adverse Events of Special Interest for Analysis by System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.5.10.1*	Adverse Events Leading to Study Drug Discontinuation By System Organ Class And Preferred Term (Safety Populations)
Table 14.3.1.5.10.2	Adverse Events Leading to Study Drug Discontinuation By System Organ Class And Preferred Term - Unvalidated HER2 (Safety Populations)
Table 14.3.1.5.11*	Adverse Events Leading to Study Drug Interruption by System Organ Class And Preferred Term (Safety Populations)
Table 14.3.1.5.12.1*~	Adverse Events of all NCI-CTCAE Grades by System Organ Class and Preferred Term (Safety Populations)
Table 14.3.1.5.12.2	Adverse Events of all NCI-CTCAE Grades by System Organ Class and Preferred Term - Unvalidated HER2 (Safety Populations)
Table 14.3.1.5.13.1	Adverse Events of all NCI-CTCAE Grades by System Organ Class, Preferred Term and Age Group <65 years (Safety Populations)
Table 14.3.1.5.13.2	Adverse Events of all NCI-CTCAE Grades by System Organ Class, Preferred Term and Age Group ≥65 years (Safety Populations)
Table 14.3.1.5.13.3	Adverse Events of all NCI-CTCAE Grades by System Organ Class,

	Preferred Term and Age Group 65 - 74 years (Safety Populations)
Table 14.3.1.5.13.4	Adverse Events of all NCI-CTCAE Grades by System Organ Class, Preferred Term and Age Group ≥75 years (Safety Populations)
Table 14.3.1.5.14*	Adverse Events of all NCI-CTCAE Grades by System Organ Class, Preferred Term and Relationship (Safety Populations)
Table 14.3.1.5.15*	Adverse Events of NCI-CTCAE Grades 1, 2, 3 and 4 – Hepatoxicity/Hematoxicity (Safety Populations)
Table 14.3.1.5.16*	Adverse Events by System Organ Class, Preferred Term and Maximum CTC Grade (Safety Populations)
Table 14.3.1.5.17.1*	Serious Adverse Events by System Organ Class, Preferred Term and Maximum CTC Grade (Safety Populations)
Table 14.3.1.5.17.2	Serious Adverse Events by System Organ Class, Preferred Term and Maximum CTC Grade - Unvalidated HER2 (Safety Populations)

5.3.3.3 Laboratory results

Table 14.3.5.1	Laboratory Parameter Results – Hematology Observed Values and Change from Baseline (Safety Populations)
Table 14.3.5.2	Shift Table of Laboratory Parameter NCI CTC Toxicity Grades – Hematology (Safety Populations)
Table 14.3.5.3	Laboratory Parameter Results – Biochemistry Observed Values and Change from Baseline (Safety Populations)
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Table 14.3.5.6	Laboratory results – Urinalysis (categorical) (Safety Populations)
Table 14.3.5.7	Any Incidence of Haemorrhage Adverse Events and Any Incidence of Thrombocytopenia (Lab Results - Platelet Grade 3 or 4)

5.3.3.4 ECG

Table 14.3.6.1	Summary of 12-Lead ECG at Baseline (Safety Populations)

5.3.3.5 ECOG

Table 14.3.6.2	Summary of ECOG (Safety Populations)

5.3.3.6 LVEF

Table 14.3.6.3.1	Summary of Left Ventricular Ejection Fraction (%) by Visit (Safety Populations)
Table 14.3.6.3.2	Summary of Left Ventricular Ejection Fraction (%) Worst on Treatment Value (Safety Populations)

5.3.3.7 Hospitalizations

Table 14.3.6.4	Assessment of Hospitalizations (Safety Populations)

5.3.3.8 Weight

Table 14.3.6.5	Weight over time (Safety Populations)

5.4 Listings

Listings indicated with an # will be repeated for 11 patients in China who are still on study treatment and are waiting for rollover study. These listings will contain additional data from these patients visits after 10th July 2019 (LPLV) until their last visit.

Listing 16.2.1.1#	Patient Disposition (End of Treatment)
Listing 16.2.1.2#	Patient Disposition (End of Study)
Listing 16.2.2.1	Inclusion Criteria Questions
Listing 16.2.2.2	Inclusion Criteria – Patient Responses
Listing 16.2.2.3	Exclusion Criteria Questions
Listing 16.2.2.4	Exclusion Criteria – Patient Responses
Listing 16.2.2.5	Patient Eligibility
Listing 16.2.3.1	Analysis Sets and Protocol Violations
Listing 16.2.4.1	Patient Demography and Informed Consent
Listing 16.2.4.2	HER-2 Status
Listing 16.2.4.3	Medical History
Listing 16.2.4.4.1	Cancer History
Listing 16.2.4.4.2	Cancer History Current Status
Listing 16.2.4.5.1	Previous Cancer Treatment: Neo-Adjuvant Treatment
Listing 16.2.4.5.2	Previous Cancer Treatment: Chemotherapy in a Neo-Adjuvant Setting
Listing 16.2.4.5.3	Previous Cancer Treatment: Targeted Therapy in a Neo-Adjuvant Setting
Listing 16.2.4.5.4	Previous Cancer Treatment: Anti-Estrogen Therapy in a Neo-Adjuvant Setting
Listing 16.2.4.5.5	Previous Cancer Treatment: Radiotherapy in a Neo-Adjuvant Setting
Listing 16.2.4.6	Previous Cancer Surgery
Listing 16.2.4.7.1	Previous Cancer Treatment: Adjuvant Treatment
Listing 16.2.4.7.2	Previous Cancer Treatment: Chemotherapy in an Adjuvant Setting
Listing 16.2.4.7.3	Previous Cancer Treatment: Targeted Therapy in an Adjuvant Setting
Listing 16.2.4.7.4	Previous Cancer Treatment: Anti-Estrogen in an Adjuvant Setting
Listing 16.2.4.7.5	Previous Cancer Treatment: Radiotherapy in an Adjuvant Setting
Listing 16.2.4.8.1	Previous Cancer Treatment: Locally Advanced/Metastatic Treatment
Listing 16.2.4.8.2	Previous Cancer Treatment: Chemotherapy in a Metastatic Setting
Listing 16.2.4.8.3	Previous Cancer Treatment: Targeted Therapy in a Metastatic Setting
Listing 16.2.4.8.4	Previous Cancer Treatment: Anti-Estrogen Therapy in a Metastatic Setting
Listing 16.2.4.8.5	Previous Cancer Treatment: Radiotherapy in a Metastatic Setting
Listing 16.2.4.9	Prior Medications
Listing 16.2.4.10#	Concomitant Medications
Listing 16.2.5.1.1#	Study Drug Administration
Listing 16.2.5.1.2#	Study Drug Administration – Missed Doses, Modifications and Interruptions
Listing 16.2.5.1.3#	Study Drug Administration and Exposure – Derived Data
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Listing 16.2.6.4	Overall Survival
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Listing 16.2.6.6	Disease Progression – Safety Follow up

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Listing 16.2.7.2	Serious Adverse Events
Listing 16.2.7.3	Related Adverse Events
Listing 16.2.7.4	Adverse Events Leading to Treatment Discontinuation of Study Drug
Listing 16.2.7.5	Adverse Events Leading to Study Drug Interruption
Listing 16.2.7.6	Adverse Events NCI-CTC Grade 3 or Higher
Listing 16.2.7.7	Adverse Events – Primary endpoint
Listing 16.2.7.8	Adverse Events – Adverse events of special interest
Listing 16.2.7.9	Adverse Events of Special Interest – Hy's Law
Listing 16.2.7.10	Adverse Events – Other Adverse events of interest
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Figure 14.2.5.3	Kaplan Meier Curve of Overall Survival by Prior Pertuzumab, ITT populations

Figure 14.2.5.4*	Kaplan Meier Curve of Overall Survival - Unvalidated HER2, ITT populations
Figure 14.2.6	Kaplan Meier Curve of Duration of Response, ITT populations
Figure 14.2.7	Kaplan Meier Curve of Time to Response, ITT populations

5.6 Appendices

Appendix 1	Raw SAS Statistical Output for primary criterion and for modelling (variable selection for BOR analysis) only.

5.7 References

- ICH E3, Structure and Content of Clinical Study Reports, November 1995;
- ICH E9, Statistical Principles for Clinical Trials, February 1998
- Investigator's Brochure, Trastuzumab Emtansine, December 2012