Official Title:	**Phase I Study of the Combination of Trastuzumab Emtansine (T-DM1) and Capecitabine in HER2-Positive Metastatic Breast Cancer and HER2-Positive Locally Advanced/Metastatic Gastric Cancer Patients, Followed by a Randomized, Open-Label Phase II Study of Trastuzumab Emtansine and Capecitabine Versus Trastuzumab Emtansine Alone in HER2-Positive Metastatic Breast Cancer**
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Statistical Analysis Plan

F. HOFFMANN-LA ROCHE LTD

Protocol: MO28230

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Treatment: Trastuzumab emtansine (RO5304020)
Capecitabine (RO091978)

PHASE I STUDY OF THE COMBINATION OF TRASTUZUMAB EMTANSINE (T-DM1) AND CAPECITABINE IN HER2-POSITIVE METASTATIC BREAST CANCER AND HER2-POSITIVE LOCALLY ADVANCED/METASTATIC GASTRIC CANCER PATIENTS, FOLLOWED BY A RANDOMIZED, OPEN-LABEL PHASE II STUDY OF TRASTUZUMAB EMTANSINE AND CAPECITABINE VERSUS TRASTUZUMAB EMTANSINE ALONE IN HER2-POSITIVE METASTATIC BREAST CANCER

Author: [redacted]

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Abbreviations

5-FU	5-Fluorouracil
AE	Adverse Event
AEGT	Adverse Event Grouped Terms
AESI	Adverse Events of Special Interest
ALT (SGPT)	Alanine Transaminase/Serum Glutamic Pyruvic Transaminase
aPTT	Activated Partial Thromboplastin Time
AST (SGOT)	Aspartate Transaminase/Serum Glutamic Oxaloacetic Transaminase
AUC	Area Under the Curve
bid	Twice daily
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Concentration
CR	Complete Response
CSR	Clinical Study Report
CT	Computer Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EOS	End of Study
G-GT	Gamma-Glutamyl Transferase
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
INR	International Normalized Ratio
ISH	*In Situ* Hybridization
ITT	Intent-to-Treat
IV	Intravenous(ly)
LA	Locally Advanced
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
mBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mGC	Metastatic Gastric Cancer
MTD	Maximum Tolerated Dose

NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
q3w	Every 3 weeks
qw	Weekly
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Stable Disease
SI	International Standard
SOC	System Organ Class
SP	Safety Population
$T_{1/2}$	Terminal Half-life
T-DM1	Trastuzumab Emtansine
TTF	Time to Treatment Failure
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
V_d	Volume of Distribution
WBC	White Blood Cell
β-HCG	Beta-Human Chorionic Gonadotrophin

1 Introduction

This document presents the statistical analysis plan (SAP) for F. Hoffmann-La Roche Ltd, Protocol No. MO28230: Phase I Study of the Combination of Trastuzumab Emtansine (T-DM1) and Capecitabine in HER2-Positive Metastatic Breast Cancer and HER2-Positive Locally Advanced/Metastatic Gastric Cancer Patients, Followed by a Randomized, Open-Label Phase II Study of Trastuzumab Emtansine and Capecitabine versus Trastuzumab Emtansine Alone in HER2-Positive Metastatic Breast Cancer.

This analysis plan is based on the final protocol version dated 23rd March 2016 and electronic case report form (eCRF) draft version 8.01, dated 18th June 2015.

The SAP provides the description of the analysis for the final analyses for all 3 cohorts [Phase I, Cohort 1: Patients with metastatic breast cancer (mBC), Randomized Phase II: Patients with mBC and Phase I, Cohort 2: Patients with locally advanced (LA)/metastatic gastric cancer (mGC)].

2 Study Objectives

2.1 Phase I, Cohort 1: Patients with mBC

2.1.1 Primary Objective

- To determine the maximum tolerated dose (MTD) of the combination of trastuzumab emtansine and capecitabine in patients with human epidermal growth factor receptor 2 (HER2)-positive mBC.

2.1.2 Secondary Objectives

To assess the:

- Pharmacokinetics (PK) of trastuzumab emtansine, capecitabine, and their metabolites;
- Safety of the combination of trastuzumab emtansine and capecitabine
- Overall response rate (ORR).

2.1.3 Primary Endpoint

The number and the proportion of patients with dose limiting toxicities (DLTs) will be used as the primary measure for the MTD determination and will be summarized for each dose level.

2.1.4 Secondary Endpoint

The main efficacy endpoint of this phase is:

- ORR, based on best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, per investigator local assessment.

2.1.5 Safety Endpoints

Safety endpoints will be summarized for each dose level:

- Incidence, nature, and severity of adverse events (AEs,) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.0
- Incidence, nature, and severity of serious adverse events (SAEs), according to NCI CTCAE v. 4.0
- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AEs of special interest (AESIs), according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Laboratory parameters
- Left Ventricular Ejection Fraction (LVEF)
- Exposure to study medication
- Physical examination

- Eastern Cooperative Oncology Group (ECOG) performance status
- Premature withdrawal from study medication and/or study.

2.1.6 Pharmacokinetic Endpoints

The PK endpoints to be assessed in patients receiving trastuzumab emtansine and capecitabine will include:

- Serum concentrations of trastuzumab emtansine (conjugated drug) and total trastuzumab (free and conjugated to DM1)
- Plasma concentration of DM1
- Plasma concentration of capecitabine and its active metabolite 5-Fluoroucil (5-FU)
- Total exposure [e.g., area under the curve (AUC)]
- Maximum concentration (C_{max})
- Clearance (CL)
- Volume of distribution (V_d)
- Terminal half-life ($T_{1/2}$).

2.2 Randomized Phase II: Patients with mBC

2.2.1 Primary Objective

- To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in patients with HER2-positive mBC, as measured by ORR by RECIST v.1.1 per investigator local assessment.

2.2.2 Secondary Objectives

- To assess the safety profile of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone;
- To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in mBC patients, as measured by:
    - Time to response (TTR)
    - Duration of response (DoR)
    - Time to progression (TTP)
    - Time to treatment failure (TTF)
    - Progression-free survival (PFS)
    - Clinical benefit rate (CBR)
    - Overall survival (OS).

The primary and secondary efficacy endpoints will be presented for each treatment group.

2.2.3 Primary Endpoint

The primary endpoint is ORR by investigator assessment, based on BOR (defined as the best response recorded from randomization into the Phase II part of the study and until progressive disease (PD), death, withdrawal of consent, start of new anticancer treatment, or end of study (EOS), whichever occurs first) according to RECIST v.1.1 (See Appendix 3 of the protocol).

2.2.4 Secondary Endpoints

Secondary efficacy outcomes include:

- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS.

2.2.5 Safety Endpoints

The summary of safety endpoints will be presented for each treatment group:

- Incidence, nature, and severity of AEs, according to NCI CTCAE v. 4.0
- Incidence, nature, and severity of SAEs, according to NCI CTCAE v. 4.0
- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AESIs, according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Events to monitor [based on adverse event grouped terms (AEGT) specifications]
- Laboratory parameters
- LVEF
- Exposure to study medication
- Physical examination
- ECOG performance status
- Premature withdrawal from study medication and/or study.

2.2.6 Pharmacokinetic Endpoints

Not applicable for Phase II.

2.3 Phase I, Cohort 2: Patients with LA/mGC

2.3.1 Primary Objective

- To determine the MTD of the combination of trastuzumab emtansine and capecitabine in patients with LA/mGC.

2.3.2 Secondary Objectives

To assess the:

- PK of trastuzumab emtansine, capecitabine, and their metabolites
- Safety of the combination of trastuzumab emtansine and capecitabine
- ORR.

2.3.3 Primary Endpoint

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination and will be summarized for each dose level.

2.3.4 Secondary Endpoint

The secondary efficacy outcome of this phase is ORR, based on BOR according to RECIST v.1.1 according to investigator assessment.

2.3.5 Safety Endpoints

Safety endpoints will be summarized for each dose level:

- Incidence, nature, and severity of AEs, according to NCI CTCAE v. 4.0
- Incidence, nature, and severity of SAEs, according to NCI CTCAE v. 4.0
- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AESIs, according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Events to monitor (based on AEGT specifications)
- Laboratory parameters
- LVEF
- Exposure to study medication
- Physical examination
- ECOG performance status
- Premature withdrawal from study medication and/or study.

2.3.6 Pharmacokinetic Endpoints

The PK endpoints to be assessed in patients receiving trastuzumab emtansine and capecitabine will include:

- Serum concentrations of trastuzumab emtansine (conjugated drug) and total trastuzumab (free and conjugated to DM1)
- Plasma concentration of DM1
- Plasma concentration of capecitabine and its active metabolite 5-FU
- Total exposure (e.g., AUC)
- C_{max}
- CL
- V_d
- $T_{1/2}$.

3 Study Design

3.1 Discussion of Study Design

This is an international, multicenter Phase I/II dose-finding study of two dosing schedules of trastuzumab emtansine and capecitabine combination therapy in HER2-positive mBC and LA/mGC.

The study is designed to determine the MTD of capecitabine in combination with trastuzumab emtansine in patients with HER2-positive mBC or LA/mGC using a Phase I design, followed by a randomized, open-label Phase II part of the study to explore the efficacy and safety of the combination in patients with HER2-positive mBC. There will be no follow-on randomized exploration of efficacy in mGC. Results from the Phase I study in LA/mGC will be used as supporting information for future studies in the indication.

Cohort 1 for patients with mBC will open first and the MTD will be established. Once the MTD is defined, both the randomized Phase II trial for patients with HER2-positive mBC and the Phase I Cohort 2 for patients with LA/mGC will open.

All patients will be treated until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. In case of toxicities requiring the discontinuation of capecitabine, single agent trastuzumab emtansine may be continued. In case of toxicities requiring the discontinuation of trastuzumab emtansine, the patient will be followed up until EOS (treatment with capecitabine alone is not allowed).

If at the time of study closure there are patients whose disease has not progressed and who are still receiving study treatment, they will be offered the possibility to continue treatment by enrolling in an extension study at the discretion of the investigator.

All patients will be followed up until withdrawal of consent, death, or for up to a maximum of 2 years after the last patient was randomized in the Randomized Phase II part of the study, whichever occurs first.

The duration of the study is estimated to be approximately 4 years. Recruitment is estimated to last 2 years in total (1 year for the MTD-Finding study in mBC and 1 year for the Phase II Exploration of Efficacy and Safety in mBC).

Specifically in Phase I, cohort 2, if dose level -2 is too toxic in LA/mGC, recruitment into the LA/mGC cohort will be closed.

The trial will first investigate the feasibility of the combination of capecitabine and trastuzumab emtansine every three weeks (q3w) in one cohort of up to 18 patients, by de-escalating the dose of capecitabine from 750 mg/m^2 twice daily (bid) to 650 mg/m^2 bid on Days 1 to 14 q3w with a 3 plus 3 classical Phase I design. Cohort 1 will open first and enroll patients with HER2-positive mBC.

According to the 3 plus 3 classical study design, Cohort 1 will start with the enrollment of 3 patients at Dose Level 1. Patients will be evaluated for DLTs as specified in the DLT definition (see Section 5.1.4 of the protocol). The dose of trastuzumab emtansine is fixed at 3.6 mg/kg q3w. Three dose levels of capecitabine administered bid on Days 1 to 14 q3w will be tested.

The following doses will be explored in Cohort 1:

Dose Level 1: 750 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

Dose Level -1: 700 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

Dose Level -2: 650 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

The following MTD determining rules will be applied during the MTD-Finding treatment phase:

- Step 1: Three patients will be enrolled at Dose Level 1
- Step 2: The toxicity of Dose Level 1 will be monitored and the following actions taken:
  a) If none of these 3 patients (0/3) experiences a DLT, the MTD will be established as the current dose level and will need to be confirmed in 3 more patients (to achieve DLTs in ≤ 1/6 patients at that dose level)
  b) If 1 of the initial 3 patients (1/3) experiences a DLT, an additional 3 patients should be enrolled and treated at the same dose, i.e., Dose Level 1
  c) If no additional patients experience a DLT (1/6), the MTD will be established as the current dose level
  d) If 1 or more additional patients experience a DLT (> 1/6), the dose will be de-escalated to the next lowest dose level. If no more than 1 patient experiences a DLT (≤ 1/6) after dose de-escalation, the dose will be considered the MTD and, following independent data monitoring committee (IDMC) recommendation, will be further explored in the Randomized Phase II part of the study. Dose re escalation will not be allowed. If 2 or more patients experience a DLT (> 1/6) after dose de-escalation, de-escalation should continue to the next lowest dose level. Based on the DLT findings, the next dose level may be considered the MTD and, following IDMC recommendation, be further explored in the Randomized Phase II part of the study or the study may be terminated if DLTs occur in > 1/6 patients at Dose Level -2.

In order to define the dose for the Randomized Phase II Exploration of Efficacy and Safety part of the study, evaluation will include not only the DLTs during Cycle 1 but also all available safety information during the subsequent cycles. The dose level considered optimal will be the dose level selected to proceed to the Phase II and LA/mGC parts of the study (the IDMC will be involved in this decision).

Once the appropriate dose of study medication is established, the Randomized Phase II part of the study and Phase I, Cohort 2 will open.

After review of safety data from Part 1, cohort 1, the IDMC recommended a regimen of capecitabine 700 mg/m^2 bid days 1–14 in combination with trastuzumab emtansine 3.6 mg/kg q3w for further evaluation. The Phase II part of the study will explore the efficacy and safety of this recommended regimen compared with trastuzumab emtansine alone in patients with HER2-positive mBC.

Approximately 160 additional patients with HER2-positive mBC will be randomized into the Phase II part of the study. Patients in the Phase I part of the study will not contribute to the Phase II part of the study; however, they will be followed-up until EOS.

Cohort 2 will enroll patients with HER2-positive LA/mGC. Trastuzumab emtansine will be administered weekly (qw) at a fixed dose of 2.4 mg/kg and capecitabine will be started at 700 mg/m^2 bid, the MTD defined for patients with mBC in Cohort 1.

Cohort 2 will open with a 3 plus 3 classical design to investigate the feasibility of combination therapy of capecitabine and trastuzumab emtansine in up to 12 patients with

LA/mGC. The capecitabine dose will be de-escalated from the starting dose of 700 mg/m^2 bid (the MTD recommended in Cohort 1).

The dose levels for de-escalation of capecitabine will be the same as described for Cohort 1, except for Dose Level 1, which will not be explored in patients with mGC.

If Dose Level -1 (700 mg/m^2 bid, the MTD recommended in cohort 1) is well tolerated (DLT in ≤ 1/6), this dose will be established as the MTD for LA/mGC.

- If Dose Level -1 is not tolerated in Cohort 2 (DLT in > 1/3 or > 1/6 patients), de-escalation will be to Dose Level 2.
- If Dose Level 2 is not tolerated in Cohort 2 (DLT in > 1/6), the combination will be considered not feasible in LA/mGC and Cohort 2 will be terminated. Patients who, at that time, experience response according to RECIST v.1.1 will be offered the possibility to continue on trastuzumab emtansine as a single agent, or with the combination, based on risk-benefit balance and agreement with the Steering Committee (SC).

This is a multicenter, international study. Between 6 and 18 patients will be enrolled into Phase I, Cohort 1. A total of approximately 160 patients with mBC will be randomized in Phase II. 3–12 patients will be enrolled into Phase I, Cohort 2.

3.2 Study Treatment

3.2.1 Patients with mBC

Trastuzumab emtansine will be administered on Day 1 q3w at a dose of 3.6 mg/kg intravenously (IV) (see Appendix 1 of the protocol). The total dose will be calculated based on the patient's weight on Day 1 of each cycle (or up to 3 days before) with no upper limit.

Capecitabine will be administered twice a day, orally for 14 days followed by a 7-day rest period at the Dose Levels described in Section 3.1. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Capecitabine doses can be delayed for up to 4 hours, while keeping the minimal interval of 8 hours between the doses.

Rounding of the dose, based on 150 and 500 mg strength tablets, will be allowed to the nearest dose per patient body surface area (BSA).

3.2.2 Patients with LA/mGC

Trastuzumab emtansine will be administered on Day 1 qw at a dose of 2.4 mg/kg IV (see Appendix 1 of the protocol). The total dose will be calculated based on the patient's weight on Day 1 of each cycle (or up to 3 days before) with no upper limit.

Capecitabine will be administered at a starting dose of 700 mg/m^2 bid, orally, for 14 days followed by a 7-day rest period (the dose level determined as the MTD in cohort 1). Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Capecitabine doses can be delayed for up to 4 hours, while keeping the minimal interval of 8 hours between the doses.

3.3 Study Schedule

The schedules of assessments for each phase/cohort can be found in Appendix 1 of the protocol.

3.4 Concomitant Medication

The use of permitted and prohibited therapy is described in Section 4.4 of the protocol.

3.5 Study Analysis Populations

3.5.1 Phase I

For Phase I, two populations are defined:

3.5.1.1 DLT-evaluable Population

The main analysis population for Phase 1 (Cohort 1 and Cohort 2) will be the DLT-evaluable population. The DLT-evaluable population is defined as all enrolled and treated patients who have not experienced any major protocol deviation (including violation of the inclusion and exclusion criteria) and completed Cycle 1.

3.5.1.2 Safety Population

The safety population (SP) will include all patients who received at least one dose of study medication during Phase I. Safety endpoints will be summarized by dose level, where dose level is defined as the first dose level the patient received (regardless of whether the dose was subsequently decreased).

3.5.2 Phase II

For the randomized Phase II part of the study, three populations are defined:

3.5.2.1 Intent-to-Treat Population

The main analysis population for the efficacy analysis will be the intent-to-treat population (ITT), which will include all patients in the Randomized Phase II part of the study.

3.5.2.2 Per Protocol Population

The per protocol (PP) population will include all ITT patients who have at least one post-baseline tumor assessment during the Phase II part and no major protocol deviations (see Section 4.17).

3.5.2.3 Safety Population

The SP will include all patients who received at least one dose of study medication during the Randomized Phase II part of the study. Safety endpoints will be summarized by treatment group based on the actual treatment received by the patient (i.e. if a patient was randomized to the T-DM1 alone arm but also received Capecitabine they will be summarized in the T-DM1 + Capecitabine arm).

3.6 Patient Discontinuation

Patients have the right to withdraw from the study at any time for any reason. Further information regarding withdrawing from the study can be found in Section 4.6 of the protocol.

3.7 Randomization

Not applicable for Phase I (Cohort 1 and 2).

In the Randomized Phase II part of the study, patients will be randomized to receive either the combination of trastuzumab emtansine and capecitabine or trastuzumab emtansine alone in a 1:1 ratio. Patients will be stratified according to the number of prior lines of treatment for metastatic disease (≤1 or >1, excluding single-agent therapy).

3.8 Blinding

This is an open-label randomized study; therefore, no blinding will be used. However, no by treatment summaries will be provided to any of the core study team prior to database lock in order to minimize any bias.

3.9 Sample Size

3.9.1 Phase I, Cohort 1: Patients with mBC

This part will be based on a classical 3 plus 3 Phase I design. A minimum of 6 and up to 18 patients will be enrolled into Cohort 1. There is no formal sample size estimation for this part.

3.9.2 Randomized Phase II: Patients with mBC

The sample size for the primary endpoint ORR is based on a Fisher's exact test with an alpha level of 5% (one-sided)[1, 2] power of 70% and the clinical assumption of an ORR of 43% with trastuzumab emtansine alone and 62.5% with the combination of trastuzumab emtansine and capecitabine. Approximately 160 patients (approximately 80 patients in each treatment group), including a 15% withdrawal rate, will be randomized with a 1:1 ratio to trastuzumab emtansine alone or the combination of trastuzumab emtansine and capecitabine.

An expected ORR of 43.6% [95% confidence interval (CI): 38.6%–48.6%] for patients receiving trastuzumab emtansine alone was chosen based on previously published data for T-DM1 in patients with unresectable, locally advanced or mBC previously treated with a taxane and trastuzumab (EMILIA study)[3].

The ORR for patients treated with the combination of T-DM1 and capecitabine were chosen based on recent results from other combination studies of T-DM1 plus chemotherapy or trastuzumab plus capecitabine. Response rates were based on those observed in patients with HER2-positive mBC in a Phase Ib/IIa study (BP22752) that compared the combination of trastuzumab emtansine with docetaxel, with or without pertuzumab (ORR: 76% [95% CI: 53%–92%]), and also in a Phase II study that compared the combination of trastuzumab with docetaxel, with or without capecitabine (ORRs: 72.7% [95% CI: 63.4%–80.8%] and 70.5% [95% CI: 61.2%–78.8%]).

Increased ORRs for the combination treatment compared with single-agent trastuzumab emtansine are in line with previously published results of a randomized Phase III study in

patients with locally advanced or mBC treated with the combination of trastuzumab with capecitabine versus capecitabine alone (ORR: 48.1% versus 27.0%, odds ratio = 2.50, p = 0.0115)[5].

The estimation of sample size was performed by Nquery® and EAST® programs.

Stratification Factors

The following stratification factor will be implemented:

- Number of prior lines of treatment for metastatic disease (≤1 or >1; excluding single-agent hormones)

A treatment line is any regimen given to a patient from treatment initiation until confirmed PD.

3.9.3 Phase I, Cohort 2: Patients with LA/mGC

This part will be based on a classical 3 plus 3 Phase I design. From 3 to 12 patients might be enrolled into Cohort 2. There is no formal sample size estimation for this part.

4 Statistical Methodology

4.1 Planned Analyses

Summary statistics will be presented for continuous variables; by way of number of observations (n), mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Percentages will be calculated using the total number of patients in each dose level (Phase I) or each treatment group (Phase II) except for ECOG data where the number of patients with the ECOG assessment performed in each dose level/treatment group will be used instead.

For Phase I, demographics and baseline characteristics will be summarized using the DLT-evaluable and safety populations. Medical history will be summarized using the DLT-evaluable population. Efficacy analyses will be carried out using the DLT-evaluable population. Summaries of DLT data will be carried out on the DLT-evaluable population. Safety analyses will be carried out on the safety population.

For Phase II, demographics and baseline characteristics will be summarized using the ITT, PP and safety populations. Medical history will be summarized using the ITT population. Efficacy analyses will be carried out using the ITT and PP populations. Safety analyses will be carried out on the safety population. P-values/confidence intervals (where presented) are two-sided.

Statistics will be displayed for the following:

Phase I, Cohort I: Patients with mBC:

- Dose Level 1
- Dose Level -1
- Overall (not applicable for efficacy output).

Phase II, mBC:

- T-DM1 + Capecitabine
- T-DM1 Alone
- Overall (not applicable for efficacy outputs).

Phase I, Cohort 2: Patients with LA/mGC:

- Dose Level -1
- Dose Level -2 (will be displayed only if patients are enrolled at this dose level)
- Overall (will be displayed only if patients are enrolled at dose level -2).

Notes:

- Where a change from baseline is presented, baseline is defined as the last non-missing value obtained prior to first dose of any study treatment.
- All data will be listed.

4.2 Interim Analysis

There is no formal efficacy interim analysis for any phase/cohort.

However, an IDMC will recommend whether the Randomized Phase II part of the study can commence. The IDMC will also monitor safety outcomes after 25, 75, and 150 patients have received at least 3 cycles (Cycle 3 Day 21) of treatment in the Randomized Phase II part of the study. Afterwards, the IDMC will monitor accumulating patient safety data every 6 months during the course of the Randomized Phase II of the study or as requested.

Efficacy data will be provided only if required by the IDMC to estimate the risk-benefit balance for the patients. Further details on the function and logistics of the IDMC are provided in the IDMC Charter.

4.3 Disposition of Patients

The number of patients who were enrolled, randomized (Phase II only), randomized in each strata (Phase II only), included in each analysis population, who completed the study and the reasons for any premature discontinuation from the study will be presented by dose level (Phase I) or treatment group (Phase II). The reasons for discontinuing each treatment will also be presented.

Major protocol deviations which lead to exclusion from the PP population will be summarized by treatment group for Phase II only and deviation category (overall and by site) using the ITT Population.

4.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarized by dose level (Phase I) or treatment group (Phase II).

Demographic characteristics include race, ethnicity, gender, child-bearing potential (females only), age and age group.

Baseline characteristics include height, weight, ECOG status, smoking status and alcohol and drug abuse history.

Medical history will be summarized separately for past (resolved) conditions and active (ongoing) conditions.

For Phase I, mBC and Phase II, previous disease history includes:

- Location of tumor
- Histology at time of diagnosis
- Time since diagnosis (years)
- TNM classification at diagnosis
- Tumor stage
- Time from first metastases to randomization (Phase II) or first treatment (Phase I) (years)
- Metastatic sites
- Time from first diagnosis to first metastases (years)
- Cancer grade
- Estrogen/progesterone responsiveness
- Current status

- Visceral disease involvement
- HER2 details [Immunohistochemistry (IHC) and *In Situ* Hybridization (ISH) results for archival primary tissue and mBC tissue plus overall HER2 positivity].

For Phase I, Cohort 2: Patients with LA/mGC, previous disease history includes:

- Extent of disease
- Primary site
- Type of gastric cancer (based on pathology)
- Measurability
- Time since diagnosis (years)
- Time from locally advanced/metastatic diagnosis to first treatment (years)
- Time from first diagnosis to locally advanced/metastatic diagnosis (years)
- HER2 details (IHC and ISH results for archival tumor from primary or metastatic, invasive tumor tissue or FFPE tissue block with at least 5 mm of invasive tumor) plus overall HER2 positivity).

For Phase I, mBC and Phase II, previous anti-cancer therapy includes:

- Number and percentage of patients with previous systemic therapy (overall and neo-adjuvant, adjuvant and treatment for metastatic disease), radiotherapy and surgery as well as combinations of systemic therapy, radiotherapy and surgery and with each number of lines of metastatic treatment
- Number and percentage of patients with previous chemotherapy, trastuzumab therapy, hormone therapy and other therapy (overall and neo-adjuvant, adjuvant and treatment for metastatic disease). Note that hormone therapy is defined as any therapy with a code beginning with H.

For Phase I, cohort 2, previous anti-cancer therapy includes:

- Number and percentage of patients with previous systemic therapy (overall and xeloda and anthracyclines), radiotherapy and surgery as well as combinations of systemic therapy, radiotherapy and surgery.

Notes:

- Age will not be recalculated, the value recorded in the eCRF will be used
- Age groups are defined as:
  - < 40 years
  - ≥ 40 years and < 50 years
  - ≥ 50 years and < 60 years
  - ≥ 60 years and < 65 years
  - ≥ 65 years and < 70 years
  - ≥ 70 years and < 75 years
  - ≥ 75 years.

- Non-visceral disease includes metastatic sites of bone, chest wall, lymph nodes, opposite breast and skin. All other metastatic sites are classed as visceral disease. Patients with tumors in multiple locations that cover both visceral and non-visceral disease are classed as having visceral disease
- Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The version of the dictionary used will be updated throughout the study. Time since diagnosis (years) = (date of randomization - date of initial diagnosis + 1)/365.25
- Time from first metastases to randomization (years) = (date of randomization – date of first metastatic diagnosis + 1)/365.25
- Time from first diagnosis to first metastases (years) = (date of first metastatic diagnosis – date of initial diagnosis + 1)/365.25
- HER2 positivity is defined as IHC 3+ or gene amplification by ISH.

4.5 Prior and Concomitant Medication

Incidence of prior and concomitant medication will be presented by treatment (dose level in Phase I and treatment group in Phase II), International Non-Proprietary Name (INN) and preferred drug name. Summaries will be produced using the safety population only (in all phases/cohorts).

Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose.

Where a medication start 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.

Notes:

- Medications are coded using Roche's INN Drug Terms and Procedures dictionary.

4.6 Prior and Concomitant Radiotherapy

Prior and concomitant radiotherapy will be listed. Prior radiotherapy will also be summarized with previous disease history (Section 4.4).

Prior radiotherapies are those that started and stopped before exposure to study medication; concomitant radiotherapies are those performed during the study period.

4.7 Anti-Cancer Therapy

Anti-cancer therapy will be listed. Prior anti-cancer therapy will be flagged in the listing. The date of first **new** anti-cancer therapy (i.e. treatment started after first dose of study medication) will be used in the efficacy analysis.

4.8 Exposure

For mBC (Phase I, Cohort 1 and Phase II), trastuzumab emtansine dose delays and dose reductions and withdrawal will be summarized by the number and percentage of patients experiencing any dose delay, a dose delay of < 1 week, 1 to 2 weeks, 2 to 3 weeks, 3 to 4

weeks, 4 to 5 weeks, 5 to 6 weeks and > 6 weeks and the number and percentage of patients receiving a dose reduction to 3.0 mg/kg q3w, 2.4 mg/kg q3w and < 2.4 mg/kg q3w. Dose delays of > 6 weeks (42 days) or dose reductions to < 2.4 mg/kg q3w will result in patients being withdrawn from the study.

For patients with LA/mGC (Phase I, Cohort 2), trastuzumab emtansine dose delays and dose reductions and withdrawal will be summarized by the number and percentage of patients experiencing any dose delay, a dose delay of < 1 week, 1 to 2 weeks, 2 to 3 weeks, 3 to 4 weeks, 4 to 5 weeks, 5 to 6 weeks and > 6 weeks and the number and percentage of patients receiving a dose reduction to 2.0 mg/kg qw and < 2.0 mg/kg qw. Dose delays of > 6 weeks (42 days) or dose reductions to < 2.0 mg/kg qw will result in patients being withdrawn from the study.

An overall summary of exposure during the entire study will also be provided. The following will be presented:

- Capecitabine exposure during the entire study in months (i.e. last dose of capecitabine – first dose of capecitabine + 1)/30.4375
- Trastuzumab emtansine exposure during the entire study in months (i.e. last dose of trastuzumab emtansine – first dose of trastuzumab emtansine + 1)/30.4375
- Overall exposure in months (i.e. last dose of any study drug – first dose of any study drug + 1)/30.4375.

Summaries will be provided using the safety population only (in all phases/cohorts).

4.9 Efficacy Analysis

4.9.1 Phase I, Cohort 1: Patients with mBC

4.9.1.1 Main Efficacy Endpoint

ORR, as a main efficacy endpoint, will be assessed via BOR. The BOR is defined as the best response recorded from the date of enrollment until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first.

BOR and ORR will be derived according to RECIST 1.1 (see Appendix 3 of the protocol) and with clarifications from a conference paper[6] (points of note from paper are included below).

In solid tumors, tumor response measures the changes in tumor mass, growth (progression) or shrinkage (response) and it is often assessed using the RECIST criteria. Although it is still the object of criticism (e.g. the definition of cut-off used to define the response and the progression), RECIST provides a simplified set of criteria for evaluating tumors response via an anatomical approach using a unidimensional measure of tumor burden.

In RECIST tumor lesions are classified as being target (or measurable) or non-target (or not measurable). Each existing lesion is identified prior to study entry (baseline) and classified accordingly and lesions characteristics such as location, measures (mm) and method used to assess the lesion are collected. Then, at regular time-points during the study, lesions assessed prior to study entry are re-evaluated (measured) and any new identified lesion are also evaluated (new with respect to baseline assessment).

Then, based on all lesions assessed, target, non-target and new lesions at each time-point (if any), the (overall) response is evaluated by looking at either progression (increase in sum of all target lesions or increase in size in any of the non-target lesions or any new lesion detected) or response (decrease in the sum of all target lesions with respect to baseline and

disappearance of all non-target lesions). As per RECIST, latest version 1.1, the overall tumor response at each time-point is defined as follows:

Complete Remission or Response (CR)

- Disappearance of all lesions (target and non-target)
- No new lesions diagnose
- Sustained at least four weeks, when confirmation is required.

Partial Remission or Response (PR)

- Greater than 30% decrease in the sum of the longest diameters of target lesions taking the baseline sum as reference
- No evidence of progression in any of the non-target lesions diagnosed at baseline
- No new lesions diagnosed.

Progressive Disease (PD)

- Greater than 20% increase in the sum of the longest diameters of target lesions taking the smallest sum as reference, where the smallest sum should be more than 5mm or
- The progression of a non-target lesion or
- The appearance of a new lesion.

In all other cases the tumor response, if evaluable, is defined as Stable (SD).

Then the Best Overall Response (BOR) is defined as follows:

- For randomized trials the BOR is the best among all overall responses (CR is better than PR that is better than SD)
- For non-randomized trials a confirmation is required within a pre-defined time-frame, for example 6 weeks (this needs to be defined in the protocol).

Of note the confirmation was required for any kind of trial in RECIST version 1.

Table 1 summarizes the criteria for confirmation (when required):

Overall Response at Previous Time-point	Overall Response at Current Time-point	Best Overall Response
CR	CR	CR
CR/PR	PD	SD provided that criteria for minimum SD duration are met. Otherwise PD.

Overall Response at Previous Time-point	Overall Response at Current Time-point	Best Overall Response
PR	CR	PR
PR	PR	PR
SD	CR/PR	SD
SD	Any	SD provided that criteria for minimum SD duration are met. Otherwise PD or NE.

Table 1: Criteria for Best Overall Confirmation with RECIST 1.1.

Of note Table 1 is a revised version of the table reported in the paper presenting RECIST 1.1 as it does not include other combinations such as CR followed by a PR or SD, PR followed by SD; such a combination where for example initial CR are 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, may require the change of previous CR assessment and therefore should not be considered as a confirmation without further checks (when confirmation is required).For Phase I, no confirmation of response is required and the BOR is the best overall response regardless of the subsequent response.

Responders are classed as patients with a BOR of either CR or PR. Non-responders are all other patients.

Overall RECIST responses at each visit, BOR and responder status will be listed by dose level.

BOR will be summarized for each dose level by the number and proportion of patients with each BOR.

The number and proportions of responders and non-responders (based on BOR) will be presented for each dose level.

Due to the small number of patients no statistical analysis will be performed.

Summaries will be based on the DLT-evaluable population.

4.9.1.2 Secondary Efficacy Endpoints

Due to the small number of patients and the design of this part of the study, no secondary efficacy endpoints will be investigated.

4.9.2 Randomized Phase II: Patients with mBC

All summaries/analyses will be based on ITT and PP populations.

4.9.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint for the Randomized Phase II part of the study is the ORR as assessed via BOR. The BOR is defined as the best response recorded from the start or randomization into the Phase II part of the study and until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. ORR is the rate of patients with BOR equal to PR or CR. 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 28 days after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR.

BOR will be derived (as described in Section 4.9.1) at each visit. In order to be assigned a BOR of CR, PR or SD a patient must have the response confirmed at a subsequent visit (as per Table 3 in Appendix 3 of the protocol). For SD, the minimum duration is defined as 6 weeks from randomization.

Responders are classed as patients with a BOR of either CR or PR. Non-responders are all other patients. Patients with no tumor assessment after the start of study treatment are to be considered as non-responders.

Overall RECIST responses at each visit, BOR and responder status will be listed by treatment group.

BOR will be summarized for each treatment group by the number and proportion of patients with each BOR. 90 and 95% Clopper-Pearson CIs will also be displayed.

The primary hypothesis of interest when comparing ORR – as assessed via BOR – between the two treatment groups (combination of trastuzumab emtansine and capecitabine versus trastuzumab emtansine alone) is:

- H0: $\pi_{\text{trastuzumab emtansine}} = \pi_{\text{trastuzumab emtansine + capecitabine}}$
- H1: $\pi_{\text{trastuzumab emtansine}} \neq \pi_{\text{trastuzumab emtansine + capecitabine}}$

where $\pi_{\text{trastuzumab emtansine}}$ is ORR (=BOR responders rate) in T-DM1 trastuzumab emtansine alone and $\pi_{\text{trastuzumab emtansine + capecitabine}}$ is ORR in trastuzumab emtansine + capecitabine.

The number and proportions of responders and non-responders (based on BOR) together with 90 and 95% Clopper-Pearson CIs will be presented for each treatment group. The difference in ORR (responders vs non-responders) between treatment groups will be displayed with associated 90 and 95% CIs using the Hauck-Anderson approach and p-values for the Fisher's exact test.

4.9.2.1.1 Logistic Analysis of ORR

Logistic analysis will be used to assess the influence of the stratification factor (number of lines of previous treatment: <=1, > 1) and baseline covariates on response (responders vs non-responders) in an exploratory manner. The following covariates will be included:

- Age
- Sex
- ECOG performance status at Screening
- Estrogen/progesterone responsiveness (positive if either estrogen or progesterone is positive, negative if both are negative or both are not done)
- Number of metastases (for advanced breast cancer).

P-values for the covariates will be displayed in addition to the odds ratio (T-DM1 + Capecitabine / T-DM1 Alone), corresponding 90 % CI and p-value for the treatment effect.

4.9.2.2 Secondary Endpoints

The secondary efficacy endpoints for the Randomized Phase II will be:

- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

TTR is defined as the time from randomization to first documentation of confirmed PR or CR (whichever occurs first) (in months). Only patients with a BOR of CR or PR (i.e., responders) will be included in the analysis of TTR.

DoR is defined as the period from the date of first recorded PR or CR until the date of PD or death from any cause (in months). Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR. The method for handling censoring is the same as described for PFS below. Only patients with a BOR of CR or PR (i.e., responders) will be included in the analysis of DoR.

TTP is defined as time from randomization to the first occurrence of PD (in months). Patients who have not progressed at the time of study completion (including patients who have died before PD) or who are lost to follow-up are censored at the date of the last tumor assessment.

TTF is defined as time from randomization until treatment failure (in months), i.e., to PD, death, withdrawal due to AE or laboratory abnormality, or refusal of treatment. Patients who do not experience any of the above events while on study will be censored on the day of their last tumor assessment.

PFS is defined as the time from randomization until the first documented progression of disease or death from any cause, whichever occurs first (in months). Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no post-baseline tumor assessment will be censored at the time of randomization plus 1 day.

OS is defined as the time from randomization until the date of death, regardless of the cause of death (in months). Patients who are alive at the time of data cut-off will be censored at the date of the last follow-up assessment. Patients who are lost-to-follow-up will be censored at the date of last contact.

TTR will be summarized descriptively (n, mean, SD, median, minimum, maximum, 25th and 75th percentiles) for each treatment group. The survivor function will be displayed graphically using a Kaplan-Meier curve however no censoring will be included since only responders are included in the analysis.

Estimates for the survivor function of both treatment groups for DoR, TTP, TTF, PFS and OS will be obtained by using the Kaplan-Meier method. Estimates of the median 'time' and the corresponding 90% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

Hazard ratios (HRs), associated 90% CIs and p-values will be estimated from non-stratified and stratified (based on the stratification factor) Cox regression models. Kaplan-Meier plots will be presented for each variable.

CBR includes patients whose best (confirmed) response was PR, CR or SD that lasted at least 6 months. CBR will be summarized in a similar way to the primary efficacy endpoint, ORR as assessed by BOR.

4.9.3 Phase I, Cohort 2: Patients with LA/mGC

4.9.3.1 Main Efficacy Endpoint

ORR, as a main efficacy endpoint, will be assessed via BOR. The BOR is defined as the best response recorded from the date of enrollment until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first.

BOR will be derived (as described in Section 4.9.1) at each visit. For Phase I, no confirmation of response is required and the BOR is the best overall response regardless of the subsequent response.

Responders are classed as patients with a BOR of either CR or PR. Non-responders are all other patients.

Overall RECIST responses at each visit, BOR and responder status will be listed by dose level.

BOR will be summarized for each dose level by the number and proportion of patients with each BOR.

The number and proportions of responders and non-responders (based on BOR) will be presented for each dose level.

Due to the small number of patients no statistical analysis will be performed.

Summaries will be based on the DLT-evaluable population.

4.9.3.2 Secondary Efficacy Endpoints

Due to the small number of patients and the design of this part of the study, no secondary efficacy endpoints will be investigated.

4.10 Dose Limiting Toxicities

DLTs will be summarized by dose level using the DLT-evaluable population.

4.10.1 Phase I, Cohort 1: Patients with mBC

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4 of the protocol. The number and percentage of patients with DLTs for this part of the study will be summarized by dose level and visit. As the definition of DLTs differed slightly between dose level 1 and dose level -1, the summaries of DLTs will be presented in separate tables for each dose level. Only visits during Cycle 1 and where at least one DLT occurred will be presented.

4.10.2 Randomized Phase II: Patients with mBC

Not applicable.

4.10.3 Phase I, Cohort 2: Patients with LA/mGC

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4 of the protocol. The number and percentage of patients with DLTs for this part of the study will be summarized by dose level and visit. Only visits during Cycle 1 and where at least one DLT occurred will be presented.

4.11 Safety Analysis

Safety parameters will include:

- AEs
- SAEs
- AEs leading to discontinuation of study and/or study treatment
- Grade ≥3 AEs
- AESIs (as per section 5.2.3 of the protocol)
- Fatal AEs
- Events to monitor (based on AEGT specifications)
- Laboratory parameters
- LVEF
- ECOG performance status
- Physical examination
- Body weight.

4.11.1 Phase I, Cohort 1: Patients with mBC

Safety parameters for this part of the study will be summarized by dose level using the safety population.

4.11.1.1 Adverse Events

Overall summaries of adverse events and serious adverse events will be presented separately by dose level by presenting the number and percentage of patients having any event, having a related event, having an event leading to discontinuation from study and/or study treatment, having an AESI, having a fatal AE, having an event to monitor (based on AEGT specifications), having each initial severity and maximum severity (Grades 1 to 5) and each outcome. Number of events will also be presented. Missing severity, relationship or outcome will be classed as unknown.

The incidence of AEs, SAEs, AEs grade 3 and above, AEs leading to discontinuation of study and/or study treatment, AESIs and fatal AEs will be summarized according to the primary system organ class (SOC) and, within each SOC, by MedDRA preferred term. The incidence of events to monitor (based on AEGT specifications) will be summarized according to the adverse event category and, within each category, by MedDRA preferred term.

A patient with more than one occurrence of the same adverse event in a particular SOC or adverse event category will be counted only once in the total of those experiencing adverse events in that particular SOC or adverse event category. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of any AESI will also be summarized via Kaplan-Meier estimates [median time to onset and the corresponding 90% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum)]. Time to onset of the first episode is defined as:

- Time to onset (months) is defined as (start date of the first AESI – date of first dose of any study medication + 1)/30.4375.

For patients with no AESI, time to onset will be censored at the date of last study treatment + 42 days (i.e. after the safety follow-up period during which AEs are still recorded).

Patients who died will be listed together with the cause of death.

All other information collected (e.g. action taken) will be listed as appropriate.

Only treatment emergent adverse events (commencing after exposure to study treatment) will be included in summaries. Non-treatment emergent events (starting prior to exposure to study treatment) and AEs starting after the reporting period (last study treatment + 42 days) will be included in the patient listings and flagged but not included in the above summaries. 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 that it is.

Notes:

- Tables presented will contain both counts of patients and events. Patients who have multiple events in the same system organ class and preferred term will be counted only once in the patient counts.
- AEs will be coded using MedDRA. The version of the dictionary used will be updated throughout the study.

4.11.1.2 Laboratory Findings

Results from the following laboratory parameters, recorded at Screening, Day 1, 8 and 15 of Cycles 1 to 3, Day 1 of Cycle 4 onwards and at the safety follow-up visit will be listed by dose level.

Shift tables of NCI-CTC grade at baseline (last non-missing value prior to first dose) versus worst grade during treatment will be presented by dose level and overall.

Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, and white blood cell (WBC) count with differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils).
Biochemistry: Sodium, potassium, chloride, calcium, magnesium, glucose, blood urea nitrogen (BUN)/urea, creatinine, uric acid, total protein, albumin, alkaline phosphatase, Alanine Transaminase/Serum Glutamic Pyruvic Transaminase [ALT (SGPT)], Aspartate Transaminase/Serum Glutamic Oxaloacetic Transaminase [AST (SGOT)], Gamma-Glutamyl Transferase (G-GT), Lactate Dehydrogenase (LDH), total bilirubin [and direct bilirubin where total bilirubin > upper limit of normal (ULN)]. Direct bilirubin will be listed only since it is not recorded in all patients at all visits.

In addition, the following urinalysis and coagulation parameters will be recorded at Screening and the safety follow-up visit as well as at point during the study if clinically indicated:

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

Coagulation: Activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR).

Urinalysis and coagulation results will be listed only.

A serum beta-human chorionic gonadotrophin (β-HCG) test will be performed at Screening. Urine β-HCG test will be performed on Day 15 of every third cycle and at 3 and 6 months after the safety follow-up visit for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal. All positive urine pregnancy tests must be confirmed by a serum β-HCG test. Pregnancy test results will be listed only.

Abnormal laboratory values will be listed.

Notes:

- Laboratory results from local laboratories will be converted to International Standard (SI) units prior to summarizing. Only the SI results (i.e. not the original results) will be listed unless conversion to SI units was not possible – in such cases, the reported results will be listed and flagged.
- All results outside predefined normal ranges will be flagged in the listings.
- Repeat laboratory results within a visit will replace the original value. Unscheduled results will be listed only.
- CTC grades are assigned to the laboratory data based on the CTCAE Version 4.03.

4.11.1.3 LVEF

Cardiac monitoring will be performed at Screening, between Day 15 and 21 of Cycles 1 to 3, between Day 15 and 21 of every third cycle thereafter and at the safety follow-up visit. The resulting LVEF values will be summarized by dose level and visit. Changes from baseline (last non-missing value prior to first dose of study medication) to each post-dose visit will also be summarized by dose level. Results will be presented graphically (mean and 95% CIs). All visits with at least one LVEF assessment performed will be included in both summaries and plots however 95% Cis will not be included on plots if there are less than 5 patients with data at a visit.

4.11.1.4 ECOG Performance Status

ECOG performance status will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit. ECOG performance status will be summarized over time by dose level and the percentage of patients in different categories will be presented by bar charts.

4.11.1.5 12-Lead ECG

A 12-lead electrocardiogram (ECG) will be performed at Screening. ECG data will be listed.

4.11.1.6 Physical Examination

A complete physical examination will be performed at Screening with limited examinations being performed at Day 1 of each cycle and at the safety follow-up visit. Physical examination data will be listed.

4.11.1.7 Body Weight

Body weight will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit. Body weight data will be listed.

4.11.2 Randomized Phase II: Patients with mBC

Safety parameters for this part of the study will be summarized by treatment group.

4.11.2.1 Adverse Events

Overall summaries of adverse events and serious adverse events will be presented separately by treatment group by presenting the number and percentage of patients having any event, having a related event, having an event leading to discontinuation from study and/or study treatment, having an AESI, having a fatal AE, having an event to monitor (based on AEGT specifications), having each initial severity and maximum severity (Grades 1 to 5) and each outcome. Number of events will also be presented. Missing severity, relationship or outcome will be classed as unknown.

The incidence of AEs, SAEs, AEs grade 3 and above, AEs leading to discontinuation of study and/or study treatment, AESIs and fatal AEs will be summarized according to the primary SOC and, within each SOC, by MedDRA preferred term. The incidence of events to monitor (based on AEGT specifications) will be summarized according to the adverse event category and, within each category, by MedDRA preferred term.

A patient with more than one occurrence of the same adverse event in a particular SOC or adverse event category will be counted only once in the total of those experiencing adverse events in that particular SOC or adverse event category. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of any AESI will also be summarized via Kaplan-Meier estimates [median time to onset and the corresponding 90% CI will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum)]. Time to onset of the first episode is defined as:

- Time to onset (months) is defined as (start date of the first AESI – date of first dose of any study medication + 1)/30.4375.

For patients with no AESI, time to onset will be censored at the date of last study treatment + 42 days (i.e. after the safety follow-up period during which AEs are still recorded).

Patients who died will be listed together with the cause of death.

All other information collected (e.g. action taken) will be listed as appropriate.

Only treatment emergent adverse events (commencing after exposure to study treatment) will be included in summaries. Non-treatment emergent events (starting prior to exposure to study treatment) and AEs starting after the reporting period (last study treatment + 42 days) will be

included in the patient listings and flagged but not included in the above summaries. 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 that it is.

Notes:

- Tables presented will contain both counts of patients and events. Patients who have multiple events in the same system organ class and preferred term will be counted only once in the patient counts.
- AEs will be coded using MedDRA. The version of the dictionary used will be updated throughout the study.

4.11.2.2 Laboratory Findings

Results from the following laboratory parameters, recorded at Screening, Day 1, 8 and 15 of Cycles 1 to 3, Day 1 of Cycle 4 onwards and at the safety follow-up visit will be listed by treatment group.

Shift tables of NCI-CTC grade at baseline (last non-missing value prior to first dose) versus worst grade during treatment will be presented by treatment group and overall.

Hematology: Hemoglobin, hematocrit, RBC count, platelet count, and WBC count with differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils).

Biochemistry: Sodium, potassium, chloride, calcium, magnesium, glucose, BUN/urea, creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), G-GT, LDH, total bilirubin (and direct bilirubin where total bilirubin > ULN). Direct bilirubin will be listed only since it is not recorded in all patients at all visits.

In addition, the following urinalysis and coagulation parameters will be recorded at Screening and the safety follow-up visit as well as at point during the study if clinically indicated:

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

Coagulation: aPTT and INR.

Urinalysis and coagulation results will be listed only.

A serum β-HCG test will be performed at Screening. Urine β-HCG test will be performed on Day 15 of every third cycle and at 3 and 6 months after the safety follow-up visit for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal. All positive urine pregnancy tests must be confirmed by a serum β-HCG test. Pregnancy test results will be listed only.

Abnormal laboratory values will be listed.

Notes:

- Laboratory results from local laboratories will be converted to International Standard (SI) units prior to summarizing. Only the SI results (i.e. not the original results) will be listed.
- All results outside predefined normal ranges will be flagged in the listings.
- Repeat laboratory results within a visit will replace the original value. Unscheduled results will be listed only.
- CTC grades are assigned to the laboratory data based on the CTCAE Version 4.0.

4.11.2.3 LVEF

Cardiac monitoring will be performed at Screening, between Day 15 and 21 of Cycles 1 to 3, between Day 15 and 21 of every third cycle thereafter and at the safety follow-up visit. The resulting LVEF values will be summarized by treatment group and visit. Changes from baseline (last non-missing value prior to first dose of study medication) to each post-dose visit will also be summarized by treatment group. Results will be presented graphically (mean and 95% CIs). All visits with at least one LVEF assessment performed will be included in both summaries and plots however 95% Cis will not be included on plots if there are less than 5 patients with data at a visit.

4.11.2.4 ECOG Performance Status

ECOG performance status will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit. ECOG performance status will be summarized over time by treatment group and the percentage of patients in different categories will be presented by bar charts.

4.11.2.5 12-Lead ECG

A 12-lead ECG will be performed at Screening. ECG data will be listed.

4.11.2.6 Physical Examination

A complete physical examination will be performed at Screening with limited examinations being performed at Day 1 of each cycle and at the safety follow-up visit. Physical examination data will be listed.

4.11.2.7 Body Weight

Body weight will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit. Body weight data will be listed.

4.11.3 Phase I, Cohort 2: Patients with LA/mGC

Safety parameters for this part of the study will be summarized by dose level using the safety population.

The analysis will be the same as for Phase I, Cohort 1: Patients with mBC (section 4.11.1)

4.11.3.1 Adverse Events

The analysis of AEs will be the same as for Phase I, Cohort 1: Patients with mBC (section 4.11.1).

4.11.3.2 Laboratory Findings

Results from the following laboratory parameters, recorded at Screening, Day 1, 8 and 15 of all cycles and at the safety follow-up visit will be listed by dose level.

The analysis of laboratory data will be the same as for Phase I, Cohort 1: Patients with mBC (section 4.11.1).

4.11.3.3 LVEF

Cardiac monitoring will be performed at Screening, between Day 15 and 21 of Cycles 1 to 3, between Day 15 and 21 of every third cycle thereafter and at the safety follow-up visit.

The analysis of LVEF data will be the same as for Phase I, Cohort 1: Patients with mBC (section 4.11.1).

4.11.3.4 ECOG Performance Status

ECOG performance status will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit.

The analysis of ECOG performance status data will be the same as for Phase I, Cohort 1: Patients with mBC (section 4.11.1).

4.11.3.5 12-Lead ECG

A 12-lead ECG will be performed at Screening. ECG data will be listed.

4.11.3.6 Physical Examination

A complete physical examination will be performed at Screening with limited examinations being performed at Day 1 of each cycle and at the safety follow-up visit. Physical examination data will be listed.

4.11.3.7 Body Weight

Body weight will be recorded at Screening, Day 1 of each cycle and at the safety follow-up visit. Body weight data will be listed.

4.12 Pharmacokinetic Analysis

4.12.1 Phase I, Cohort 1: Patients with mBC

PK samples for Capecitabine and 5-FU will be taken at the following time points:

- Cycle 1, Day 1: Pre-capecitabine dose and 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 4 h and 6 h post-capecitabine dose
- Cycle 1, Day 2: Pre-capecitabine dose and 30 min, 2 h and 6 h post-capecitabine dose
- Cycle 2, Day 1: 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 4 h and 6 h post-capecitabine dose

Trastuzumab emtansine, total trastuzumab and DM1 PK samples will be taken at the following time points:

- Cycle 1, Day 2/3/9: Pre-trastuzumab emtansine dose, 15-30 min after end of the trastuzumab emtansine infusion, 24 h (± 2 h) after the end of the trastuzumab emtansine infusion, 7 days (± 1 day) after end of trastuzumab emtansine infusion
- Cycle 2, Day 1/2/7: Pre-capecitabine and trastuzumab emtansine dose, 15-30 min after end of the trastuzumab emtansine infusion, 24 h (± 2 h) after the end of the

trastuzumab emtansine infusion, 7 days (± 1 day) after end of trastuzumab emtansine infusion

- Cycle 3, Day 1: Pre-trastuzumab emtansine dose.

DM1 will not be analyzed at 7 days post-trastuzumab infusion or at pre-dose in Cycles 2 or 3.

The analysis of the PK data will be performed by Genentech and will be described in a separate document.

4.12.2 Randomized Phase II: Patients with mBC

No PK samples will be taken in the randomized Phase II part of the study.

4.12.3 Phase I, Cohort 2: Patients with LA/mGC

PK samples will be taken at the same time points as specified in Section 4.12.1. The analysis of the PK is not covered by this SAP (see above).

4.13 Biomarker Data

HER2 data from the central laboratory ([redacted]) will be listed for each cohort and will be used in subgroup analyses of demographic and efficacy data (see Section 4.15).

The central HER2 status will be compared to the local HER2 status (for each cohort separately) by:

- summarizing the number of enrolled patients locally assessed by HER2 IHC and by central IHC testing done at [redacted].
- summarizing the number of enrolled patients locally assessed by HER2 ISH and by central ISH testing done at [redacted].
- summarizing the number of enrolled patients locally assessed by the HER2 IHC/ISH combi test and IHC/ISH testing done at [redacted]. The number patients who would not have been eligible for the study according to the [redacted] result will also be presented.
- the discordance will also be displayed in shift tables (1 table per type of test: IHC, ISH, IHC/ISH).

4.14 Other Data

All other data recorded in the eCRF will be listed only.

4.15 Subgroup Analyses

The following subgroups are defined based on the central HER2 data:

- Centrally confirmed HER2 positive: All
- Centrally confirmed HER2 positive: IHC2+
- Centrally confirmed HER2 positive: IHC3+
- IHC2+

- IHC3+.

Demographics will be summarized by HER2 subgroup for Phase II only using the ITT population.

ORR will be summarized/analyzed by HER2 subgroup for Phase II only using the ITT population.

For Phase I (mBC and LA/mGC) numbers are too small to perform a formal analysis, in these cohorts the no subgroup analyses will be performed.

4.16 Adjustment for Covariates

For the randomized Phase II part of the study the stratification factor (number of lines of previous treatment) will be included in the analysis. The following covariates will also be included in the exploratory logistic regression:

- Age
- Sex
- ECOG performance status at Screening
- Estrogen/progesterone responsiveness (positive if either estrogen or progesterone is positive, negative if both are negative or both are not done)
- Number of metastases (for advanced breast cancer).

4.16.1 Center Effects

This study will be conducted at approximately 40 study sites in 12 countries. Patients from all centers will be pooled. No adjustment for center will be carried out.

4.17 Protocol Deviations

If major protocol deviations do occur as outlined in the criteria below, then the data from complete individual patients, individual visits or individual evaluations will be excluded from this analysis. The finalization of major protocol deviations and excluded data will be made prior to the database lock.

4.17.1 Major Protocol Deviations

Major protocol deviations will be recorded on an ongoing basis throughout the study, initially using the PD99 form and subsequently in the protocol deviation management system (PDMS) and the information recorded in this system will be used in the listing of protocol deviations. Patients who meet the criteria detailed in MO28230_Major Protocol Deviation List_Final_v3_09Oct2014 and MO28230_Protocol_Violation_Tracking_Sheet_08Apr2014 be listed and presented in the clinical study report (CSR).

All identified major protocol deviations will be reviewed prior to database lock by the statistician and the sponsor. Roche will approve the list of major protocol deviations which impact the efficacy. These deviations will be summarized as described in Section 4.3.

Patients with at least one major protocol deviation that have an impact on efficacy will be excluded from the per protocol population. These can fall into the next categories:

- Any disease/condition/treatment that interferes with study
- Patient with non-measurable disease per RECIST at baseline
- Patient who did not receive any dose of study medication
- Patient who received incorrect study treatment
- Treatment compliance issues
- Expired IMP
- Patient who received/took prohibited concomitant medication
- Any other major deviation regarding efficacy
    - No baseline or post baseline tumor assessment
    - Omission of 2 consecutive tumor assessments
- Patients that missed 2 consecutive tumor assessments followed by a PD
- Patients who violate efficacy related inclusion/exclusion criteria
- Change in tumor assessment method without medical justification.

Each deviation resulting in exclusion from the PP population will be assigned to one of the above categories and this assignment will be defined in the analysis set specification (i.e. the recorded categories will not be used).

4.17.2 Minor Protocol Deviations

Other deviations from the protocol which are entered on PDMS but do not result in exclusion from the PP analysis will also be listed.

4.18 Missing Values – Missing Visits

There is no intention to implement any procedure for replacing missing data.

4.19 Deviations from SAP

Any deviations from the original SAP will be described and justified in the final CSR.

4.20 Changes in Conduct or Planned Analyses from the Protocol

Not applicable.

4.21 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 exact 90/95% Clopper-Pearson CIs:**

DATA DSET1;
SET DSET;
n = number of patients in the population;
m = number of patients with events;
per = m/n;
alpha=0.05 or 0.1;
** exact CI - Pearson Clopper *;*
*f1 = FINV(alpha/2,2*m,2*(n-m+1));*
f2 = FINV(1-alpha/2,2(m+1),2*(n-m));*
*lower_ex = (m*f1)/(n-m+1+m*f1);*
*upper_ex = ((m+1)*f2)/(n-m+(m+1)*f2);*
RUN;

- **Tables that require logistic model, including 90/95% CIs of odds ratios:**

PROC GENMOD data = dataset;
CLASS treatment covar1 covar2 ... covarn;
MODEL response = treatment covar1 covar2...covarn / dist=binomial wald type3
alpha=0.05 or 0.1;
ESTIMATE 'A vs B' treatment 1 -1 / exp;
RUN;

- **Tables that present Fisher's Exact or CMH:**

PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2/CMH score=MODRIDIT EXACT alpha=0.05 or 0.1;*
OUTPUT OUT=outname CMH EXACT;
RUN;

- **Tables that present Hauck-Anderson CIs:**

PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2/RISKDIFF (method=HA) alpha=0.05 or 0.1;*
OUTPUT OUT=outname RISKDIFF;
RUN;

- **Tables that need life table with estimates of survival, with CIs and log rank test:**
  PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
  *TIME duration*censor (0 or 1);*
  ID patient;
  STRATA treatment / logrank alpha=0.05 or 0.1;
  RUN;
- **Tables that need hazard ratios and CIs:**
  PROC PHREG DATA=dset;
  class treatment / param=ref ref=last;
  *MODEL time*cens (1) = treatment / RISKLIMITS alpha= 0.05 or 0.1;*
  RUN;

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.2 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 1.9cm 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 patient's record has been continued to the next page, an appropriate identification (e.g., the patient 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 phase/cohort, dose level or treatment group, patient and visit and have the source data

received by data management referenced in a footnote. All tables, listings and figures will be converted into Microsoft Word documents and collated into three complete documents.

5.3 Tables

Table 14.1.1.1	Patient Disposition - Phase I, Cohort 1: Patients with mBC (All Patients)
Table 14.1.1.2	Patient Disposition – Randomized Phase II: Patients with mBC (All Patients)
Table 14.1.1.3	Patient Disposition - Phase I, Cohort 2: Patients with LA/mGC (All Patients)
Table 14.1.1.4	Major Protocol Deviations Leading to Exclusion from the Per Protocol Population – Randomized Phase II: Patients with mBC (ITT Population)
Table 14.1.2.1.1	Demography - Phase I, Cohort 1: Patients with mBC (DLT-evaluable Population)
Table 14.1.2.1.2	Demography - Phase I, Cohort 1: Patients with mBC (Safety Population)
Table 14.1.2.2.1	Demography – Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Table 14.1.2.2.2	Demography - Randomized Phase II: Patients with mBC (Per Protocol Population)
Table 14.1.2.2.3	Demography - Randomized Phase II: Patients with mBC (Safety Population)
Table 14.1.2.2.4	Demography by HER2 Subgroups – Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Table 14.1.2.3.1	Demography - Phase I, Cohort 2: Patients with LA/mGC (DLT-evaluable Population)
Table 14.1.2.3.2	Demography - Phase I, Cohort 2: Patients with LA/mGC (Safety Population)
Table 14.1.3.1.1	Baseline Characteristics - Phase I, Cohort 1: Patients with mBC (DLT-evaluable Population)
Table 14.1.3.1.2	Baseline Characteristics - Phase I, Cohort 1: Patients with mBC (Safety Population)
Table 14.1.3.2.1	Baseline Characteristics – Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Table 14.1.3.2.2	Baseline Characteristics - Randomized Phase II: Patients with mBC (Per Protocol Population)
Table 14.1.3.2.3	Baseline Characteristics - Randomized Phase II: Patients with mBC (Safety Population)
Table 14.1.3.3.1	Baseline Characteristics - Phase I, Cohort 2: Patients with LA/mGC (DLT-evaluable Population)
Table 14.1.3.3.2	Baseline Characteristics - Phase I, Cohort 2: Patients with LA/mGC (Safety Population)
Table 14.1.4.1.1	Past Medical History - Phase I, Cohort 1: Patients with mBC (DLT-evaluable Population)
Table 14.1.4.1.2	Active Medical History - Phase I, Cohort 1: Patients with mBC (DLT-evaluable Population)
Table 14.1.4.2.1	Past Medical History – Randomized Phase II: Patients with mBC

5.4 Listings

Listing 16.2.2	Major Protocol Deviations
Listing 16.2.3	Analysis Populations
Listing 16.2.4.1	Patient Demography
Listing 16.2.4.2	Baseline Characteristics
Listing 16.2.4.3	Medical History
Listing 16.2.4.4.1.1	Previous Breast Cancer History
Listing 16.2.4.4.1.2	Previous Breast Cancer History: HER2 Details
Listing 16.2.4.4.2.1	Previous Gastric Cancer History
Listing 16.2.4.4.2.2	Previous Gastric Cancer History: HER2 Details
Listing 16.2.4.5.1.1	Previous Treatment for Breast Cancer – Part I
Listing 16.2.4.5.1.2	Previous Treatment for Breast Cancer – Part II
Listing 16.2.4.5.2.1	Previous Treatment for Gastric Cancer – Part I
Listing 16.2.4.5.2.2	Previous Treatment for Gastric Cancer – Part II
Listing 16.2.4.6.1	Surgical Resection of Primary Cancer (Breast)
Listing 16.2.4.6.2	Surgical Resection of Primary Cancer (Gastric)
Listing 16.2.4.7.1	Prior and Concomitant Radiotherapy (Breast)
Listing 16.2.4.7.2	Prior and Concomitant Radiotherapy (Gastric)
Listing 16.2.4.8	Prior Medications
Listing 16.2.4.9	Concomitant Medications
Listing 16.2.4.10	Anti-Cancer Therapy
Listing 16.2.5.1	Capecitabine Drug Administration
Listing 16.2.5.2	Trastuzumab Emtansine Drug Administration
Listing 16.2.5.3	Study Drug Exposure
Listing 16.2.5.4	Visit Dates
Listing 16.2.6.1.1	Target Lesions, Non-Target Lesions and Summary of Lesions - Part I
Listing 16.2.6.1.2	Target Lesions, Non-Target Lesions and Summary of Lesions - Part II
Listing 16.2.6.2	RECIST Responses
Listing 16.2.6.3	Derived Efficacy Variables
Listing 16.2.6.4.1	HER2 Results from Central Laboratory (Breast)
Listing 16.2.6.4.2	HER2 Results from Central Laboratory (Gastric)
Listing 16.2.7.1	Dose Limiting Toxicities
Listing 16.2.7.2	Adverse Events
Listing 16.2.7.3	Serious Adverse Events
Listing 16.2.7.4	Adverse Events Leading to Discontinuation from Study or Study Treatment
Listing 16.2.7.5	Adverse Events of Special Interest
Listing 16.2.7.6	Time to Onset (months) of Adverse Events of Special Interest
Listing 16.2.7.7	Adverse Events of Grade 3 and Above
Listing 16.2.7.8	Fatal Adverse Events
Listing 16.2.7.9	Events to Monitor (Based on AEGT Specifications)
Listing 16.2.8.1	Laboratory Results: Hematology
Listing 16.2.8.2	Laboratory Results: Biochemistry

5.5 Figures

	(Safety Population)
Figure 14.3.2.3	LVEF Values Over Time – Phase I, Cohort 2: Patients with LA/mGC (Safety Population)
Figure 14.3.3.1	ECOG Performance Status – Phase I, Cohort 1: Patients with mBC (Safety Population)
Figure 14.3.3.2	ECOG Performance Status – Randomized Phase II: Patients with mBC (Safety Population)
Figure 14.3.3.3	ECOG Performance Status – Phase I, Cohort 2: Patients with LA/mGC (Safety Population)

Tables, Listings, and Figures will follow the format of: MO28230_Version_2_Final_ _07Sep2017.

5.6 Appendices

The following appendices are for internal use only and not for inclusion into the CSR. {**Note**: ALL analyses will require raw SAS output}

Appendix 14.2.2.2.1	Summary and Analysis of Overall Response Rate - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.2.2	Summary and Analysis of Overall Response Rate - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix 14.2.2.2.3	Summary and Analysis of Overall Response Rate by HER2 Subgroups - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix 14.2.2.2.4	Logistic Regression Analysis of Overall Response Rate - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.2.5	Logistic Regression Analysis of Overall Response Rate - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix 14.2.2.2.6	Logistic Regression Analysis of Overall Response Rate by HER2 Subgroups - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.4.1	Summary and Analysis of Duration of Response (months) - Randomized Phase II: Patients with mBC (Intent-to-Treat Population – Responders Only)
Appendix 14.2.2.4.2	Summary and Analysis of Duration of Response (months) - Randomized Phase II: Patients with mBC (Per Protocol Population – Responders Only)
Appendix 14.2.2.5.1	Summary and Analysis of Time to Progression (months) - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.5.2	Summary and Analysis of Time to Progression (months) - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix 14.2.2.6.1	Summary and Analysis of Time to Treatment Failure (months) - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.6.2	Summary and Analysis of Time to Treatment Failure (months) - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix 14.2.2.7.1	Summary and Analysis of Progression Free Survival (months) - Randomized Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix 14.2.2.7.2	Summary and Analysis of Progression Free Survival (months) - Randomized Phase II: Patients with mBC (Per Protocol Population)
Appendix	Summary and Analysis of Overall Survival (months) - Randomized

14.2.2.8.1	Phase II: Patients with mBC (Intent-to-Treat Population)
Appendix	Summary and Analysis of Overall Survival (months) - Randomized
14.2.2.8.2	Phase II: Patients with mBC (Per Protocol Population)
Appendix	Summary and Analysis of Clinical Benefit Rate - Randomized Phase II:
14.2.2.9.1	Patients with mBC (Intent-to-Treat Population)
Appendix	Summary and Analysis of Clinical Benefit Rate - Randomized Phase II:
14.2.2.9.2	Patients with mBC (Per Protocol Population)
Appendix	Time to Onset (months) for Adverse Events of Special Interest – Phase I,
14.3.1.2.8	Cohort 1: Patients with mBC (Safety Population)
Appendix	Time to Onset (months) for Adverse Events of Special Interest –
14.3.1.3.8	Randomized Phase II: Patients with mBC (Safety Population)
Appendix	Time to Onset (months) for Adverse Events of Special Interest – Phase I,
14.3.1.4.8	Cohort 2: Patients with LA/mGC (Safety Population)

5.7 References

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