Official Title: A Multicenter, Open-Label, Single-Arm, Phase IV Study of Trastuzumab Emtansine in Indian Patients With HER2-Positive Unresectable Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Treatment With Trastuzumab and a Taxane

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STATISTICAL ANALYSIS PLAN

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM, PHASE IV STUDY OF TRASTUZUMAB EMTANSINE IN INDIAN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TREATMENT WITH TRASTUZUMAB AND A TAXANE**
PROTOCOL NUMBER:	ML29662
STUDY DRUG:	Trastuzumab emtansine (T-DM1)
VERSION NUMBER:	1.0
IND NUMBER:	71072
EUDRACT NUMBER:	2008-005 713-22
SPONSOR:	Roche Products (India) Pvt. Ltd.
PLAN PREPARED BY:	[redacted]
DATE FINAL:	16-MAY-2018

STATISTICAL ANALYSIS PLAN APPROVAL

[Change to STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL for SAP

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The Study Biostatistician must determine whether formal review and approval is needed for this ISAP per current departmental process.

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1. BACKGROUND

Trastuzumab emtansine is a novel agent that has demonstrated efficacy in the treatment of HER2-positive mBC who progressed on trastuzumab and taxane based treatment. Registration Study TDM4370g/BO21977 met its co-primary endpoints of improving PFS in patients who received trastuzumab emtansine (by Independent Review Committee) and OS compared with those who received the combination of lapatinib and capecitabine. The safety profile of trastuzumab emtansine was consistent with that seen in previous studies.

The safety profile of trastuzumab emtansine in mBC is based on data from 884 patients receiving single-agent trastuzumab emtansine treatment at 3.6mg/kg q3w (Studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976, TDM4370g/BO21977 and TDM4529g/BO25430) and combined treatment with pertuzumab in 87 patients (from Studies TDM4373g/BO22495 and TDM4688g). The most common adverse events (AEs) for trastuzumab emtansine (AEs, in ≥ 25% of patients) were fatigue, nausea, thrombocytopenia, headache, constipation, and epistaxis.

Phase I and II single arm studies of trastuzumab emtansine have demonstrated profound clinical activity. A Phase III study BO21977 compared trastuzumab emtansine to standard of care HER2-targeted combination therapy (capecitabine and lapatinib) for patients with mBC who had received prior trastuzumab and taxane therapies. The study demonstrated a statistically significant and clinically meaningful improvement in both PFS (9.6 months with trastuzumab emtansine vs 6.4 months with lapatinib plus capecitabine) and OS. (30.9 months with trastuzumab emtansine vs 25.1 months with lapatinib plus capecitabine). The patient-reported outcome of time to symptom progression demonstrated an improvement with trastuzumab emtansine (7.1 months) as compared to (4.6 months) treatment with lapatinib plus capecitabine (Verma S et al, 2012).

Based on the data from the above said trials trastuzumab emtansine has been approved as a single agent, for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane in over 70 countries including India.

From the international birth date (February 2013) to January 2015, an estimated cumulative total of 21,209 patients have received trastuzumab emtansine from marketing experience; of which 7,527 patients were estimated to have received trastuzumab

emtansine during the reporting interval. Based on the evaluation of these data, the clinical trial results are consistent with the safety profile observed in the postmarketing setting. Thus, the benefit−risk profile of trastuzumab emtansine remains favorable.

This current Phase IV, single-arm, open-label, multicenter study is planned to be conducted to fulfil a post-marketing regulatory requirement. It is aimed to gain more insights into the safety and efficacy of trastuzumab emtansine for the treatment of Indian patients with HER2-positive advanced (metastatic or locally recurrent) breast cancer.

2. STUDY DESIGN

This is a Phase IV, single-arm, multicenter, open-label clinical trial designed to assess the safety of trastuzumab emtansine in Indian patients with HER2-positive unresectable LABC or mBC who have received prior treatment with trastuzumab and a taxane.

All patients fulfilling the eligibility criteria and willing to provide informed consent will receive intravenous (IV) trastuzumab emtansine 3.6 mg/kg over 30−90 minutes on Day 1 of a 21-day cycle. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death.

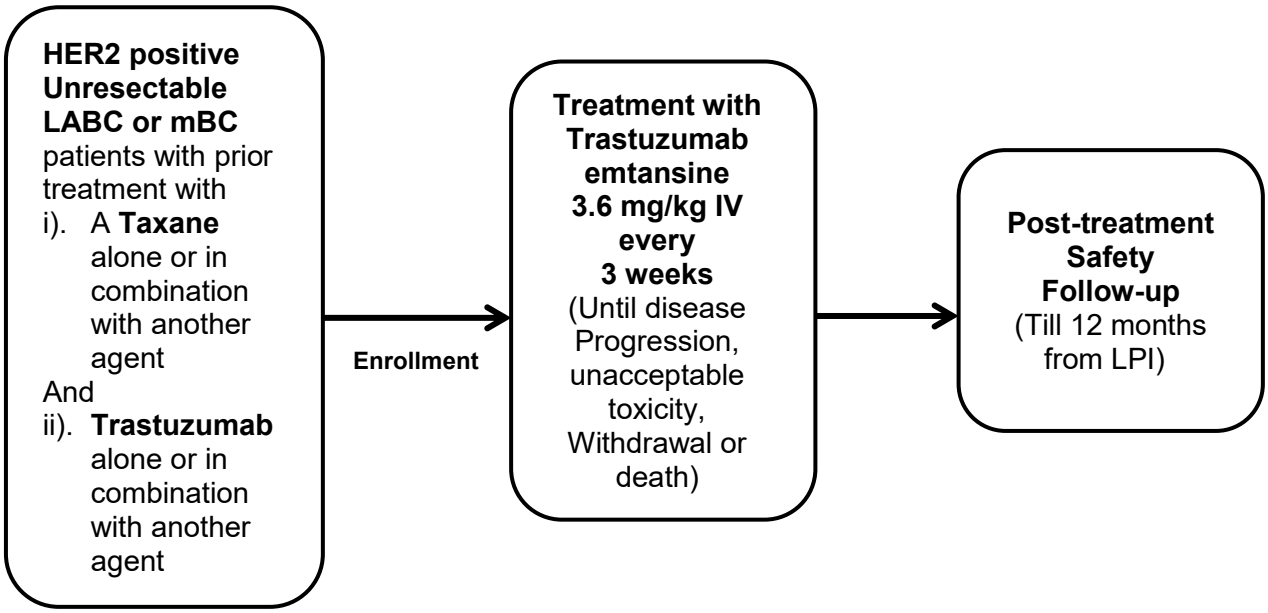
The study will include a screening phase, treatment phase and post-treatment safety follow-up phase for each patient as described in the Study Schema (Figure 1).

All patients will be followed-up for at least 12 months after the last patient is enrolled; unless they have been lost to follow up, withdrawn consent, or died, or the study is prematurely terminated by the Sponsor.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 12 months 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, see Section 4.2.4. An independent data monitoring committee (iDMC) will be formed for this study and will comprise of three members including a statistician. The iDMC will review the safety data for interim analysis after approximately 50% patients complete 6 months investigational medicinal product therapy. See the iDMC charter for further information.

. A schedule of assessments is provided in Appendix 1.

Figure 1. Study Schema



2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 2.

2.2 OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy of trastuzumab emtansine in Indian patients with HER2-positive unresectable locally advanced or metastatic breast cancer (mBC) who have received prior treatment with trastuzumab and a taxane. Specific objectives and corresponding endpoints for the study are outlined below.

2.2.1 Safety Objectives

2.2.1.1 Primary Safety Objective

The primary safety objective for this study is to evaluate the safety of trastuzumab emtansine in Indian patients on the basis of the following endpoint:

- Incidence and severity of AEs as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03)

2.2.1.2 Secondary Safety Objective

The secondary safety objectives for this study are to evaluate the safety of trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of SAEs as per NCI-CTCAE (version 4.03)
- Incidence of non-serious AEs of special interest
- Cases of drug-induced liver injury meeting Hy's law criteria
- Incidence of CHF
- Left Ventricular ejection fraction (LVEF) decrease over the course of the study as measured by ECHO
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Exposure to study medication

2.2.2 Efficacy Objective

2.2.2.1 Secondary Efficacy Objective

The secondary efficacy objectives of this study are to evaluate the efficacy of trastuzumab emtansine in Indian patients with respect to:

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)

2.3 DETERMINATION OF SAMPLE SIZE

For the purpose of the estimation of sample size, the incidence of all grade AEs was chosen as a safety endpoint of primary interest. If the observed incidence of all grade AEs is 95.9% according to the EMILIA study and assuming level of significance 5% (i.e. 95% CI) and precision 5% with drop out of 10%, approximately 70 patients are planned for enrollment this study.

Sample size formula used for estimating proportion is,

$$n = \frac{Z^2_{\alpha/2}\ p * (1-p)}{d^2}$$

Where,

P = Incidence of all AEs

d = Precision

Zα/2value = 1.96 for 95% confidence level

Any AEs				
Incidence of adverse event-AE (p)	Precision (d)	Sample size (n)	After adjusting the dropout rate of	
			10 %	20 %
95.9%	01 %	1511	1679	1889
	02 %	378	420	473
	03 %	168	187	210
	04 %	95	106	119
	05 %	61	68	77
	06 %	42	47	53
	07 %	31	35	39
	08 %	24	27	30
	09 %	19	22	24
	10 %	16	18	20

2.4 ANALYSIS TIMING

In addition to the final analysis, there will be interim analysis for safety when approximately 50% patients will complete 6 months investigational medicinal product therapy.

An independent Data Monitoring Committee (iDMC) will be formed which will include a statistician. An iDMC will perform the review of this interim analysis of efficacy and safety and subsequent safety reviews as described in the iDMC Charter.

3. STUDY CONDUCT

This study is planned to be conducted in 70 patients across 12-15 centers in India.

Enrollment is estimated to take 12 months. All patients fulfilling the eligibility criteria and willing to provide informed consent will receive intravenous (IV) trastuzumab emtansine 3.6 mg/kg over 30−90 minutes on Day 1 of a 21-day cycle. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death.

3.1 RANDOMIZATION ISSUES

This is an open-label non randomized study.

3.2 DATA MONITORING

An independent data monitoring committee (iDMC) will be formed for this study and will comprise of three members including a statistician. The iDMC will review the safety data for interim analysis after approximately 50% patients complete 6 months investigational medicinal product therapy. Details of the iDMC roles and process will be in separate charter.

3.3 ASSESSMENT OF RECIST VISIT RESPONSES

For all subjects, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST version 1.1. It will also be used to determine if and when a subject has progressed in accordance with RECIST and also their best overall response.

Baseline radiological tumour assessments are to be performed no more than 28 days before the start of study medication. Tumour assessments are then performed every 3 cycles following study medication administration until disease progression.

Response will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) scans, and other modalities (e.g., MRI, brain scans, bone marrow examinations), using the RECIST criteria 1.1. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator as far as possible to ensure internal consistency across visits.

Measurable disease:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable disease:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions
- Skin lesions assessed by clinical examination
- Brain metastasis

Special cases:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
- Blastic lesions are considered non-measurable.
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target lesions

A subject can have a maximum of 5 measurable lesions recorded at baseline and these are referred to as the target lesions. If more than one baseline scan is recorded, then measurements from the one that is closest to start of study medication will be used to define the baseline sum of TLs.

The baseline assessment is the assessment recorded before, or on the day of study medication and is that which is closest to the day of study medication will be used as long as it is not after the date of first dose.

Note: For patients who do not have measurable disease at entry (i.e. no TLs), evaluation of overall visit responses will be based on the overall non-target lesion (NTL) assessment and the absence/presence of new lesions. Note that if a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 1 TL visit responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	All target lesion measurements are missing and sum of diameters of non-missing target lesions does not qualify for PD.
Not applicable (NA)	No target lesions are recorded at baseline

Lymph nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are

< 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL too small to measure:

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation/ curative surgery), should be treated as missing and should be handled as specified as above. in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours.

Lesions That Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Change in method of assessment of target lesions:

If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment is required while response derivation.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

Non-Target Lesions and new lesions

Non-target lesion response will be derived based on the Investigator's overall assessment of NTLs as follows:

Progressive disease:	Unequivocal progression of existing NTLs, which may be due to an important progression in one lesion only or in several lesions.
Complete response:	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10mm short axis).
Non-CR/Non-PD:	Persistence of one or more NTLs with no evidence of progression.
Not evaluable:	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment.
Not applicable:	Only relevant if there are no NTLs at baseline.

New lesions will be identified via a Yes/No tick box. A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Were there any new lesions (since baseline) at this timepoint?' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

Overall visit response

Table 3 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 2 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR (or NA)	No	CR
CR	Non-CR/Non-PD or NE	No (or NE)	PR
PR	Non-PD or NE	No (or NE)	PR
SD	Non-PD or NE	No (or NE)	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
NA	CR	No	CR
NA	Non-CR/Non-PD	No	Non-CR/non-PD [a]
NA	NE	No (or NE)	NE
NA	Non-PD	NE	SD

[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.

Best Overall Response When Confirmation Is Required

Best (confirmed) overall response (BOR) is defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death. The best overall response can be interpreted as in Table 4. Complete or partial responses may be claimed as Best Overall Response only if the following criteria met.

CR: Overall visit response of CR confirmed at least 4 weeks (28 days) later by another overall visit response of CR (intervening responses of NE are possible and are acceptable but PD is not)

PR: Overall visit response of PR confirmed at least 4 weeks (28 days) later by an overall visit response of at least PR (i.e CR/PR) (with no intervening response of PD)

SD>= 54 days: Stable disease recorded at least 54 days after start of treatment

Table 3 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, PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration 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.

4. STATISTICAL METHODS

4.1 GENERAL PRINCIPLES

The below mentioned general principles will be followed throughout the study:

- All summaries (safety) will be presented at each schedule time point, wherever applicable.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Study day: Study day for given reference point (such as AE start date, visit date or ECG date) will be calculated as number of days from date of first administration of study medication, i.e.,

  - Study day = Reference date – study medication administration start date, if visit date is before the study medication administration date. OR

  - Study day = Reference date – study medication administration start date + 1, if visit date is on or after the study medication administration date.

    If the study medication administration start date or reference date is missing then study day will be set as missing.

- Descriptive statistics will include number of non-missing subject (n), mean, standard deviation (SD), 25th quartile, median,75th quartile, minimum and maximum values for continuous variables, and for categorical variables the frequencies and percentages of subjects will be presented. For baseline and demographic characteristic data in addition to above statistics range will also be presented.
- For continuous safety data, mean, median and quartiles will be rounded to 1 additional decimal place, standard deviation (SD) will be rounded to 2 additional decimal places compared to the original data and minimum and maximum will be displayed with the same precision as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- For laboratory values below or above the limit of quantification (e.g., value reported by the laboratory as ‘<0.10’or ‘>2.90’), a numeric value (i.e. 0.10 or 2.90) equal to the reported quantification limit will be imputed in a manner consistent with the corresponding laboratory flags and limits, and the imputed values will be utilized in data summaries and the imputed values along with corresponding symbol (‘<’ or ‘>’) will be listed.

- All study data will be included in study data listings. In general, all data will be listed by time point within subject.
- SAS® version 9.2 or higher will be used for all analyses.

4.2 ANALYSIS POPULATIONS

4.2.1 Intent-to-treat Population

The Intent-to-treat (ITT) population is defined as all enrolled patients regardless of whether or not study medication was administered. All baseline summaries and efficacy analysis will be based on ITT population.

4.2.2 Safety Population

The safety population is defined as all enrolled patients who have received at least one dose of study medication. All safety endpoints will be analyzed based on safety population.

4.3 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized.

Screened patients are defined as any patient who signed the informed consent.

Enrolled patients are defined as any patient who met all eligibility criteria.

For patient study status, the total number of patients in each of the following categories will be presented in summary table:

- Screened patients
- Enrolled patients
- Enrolled and treated patients
- Patients who completed the treatment
- Patients who discontinued the treatment
- Reasons for premature treatment withdrawal
- Patients who completed the study
- Patients who discontinued the study
- Reasons for premature study withdrawal

Screen failed patients and screen failure reasons will be summarized separately.

Major protocol deviations will be listed and summarized for their potential effects on the interpretation of study results.

4.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS AND SUBJECT DISPOSITION

Characteristics of the patients, including inclusion in analysis populations, age, sex, self-reported race/ethnicity, ECOG performance status, Breast cancer history, previous cancer therapy, radiotherapy, medical history, surgical history and concomitant medications will be listed for each patient and summarized.

Previous anti-cancer treatments at baseline and concomitant medication will be summarized and listed as appropriate. Disallowed concomitant medications, post-study medication will also be listed. Systemic anti-cancer treatments received prior/post to progression by line may be summarized. Height, weight and BMI will be listed for each patient and summarized.

4.5 SAFETY ANALYSIS

Safety data will be summarized and listed only, as appropriate. No formal statistical analyses will be performed on the safety data. All safety data will be summarized including patients who have dose reduction. However, some listings such as AEs listings will display the actual dose the patient received at onset of an AE. Data from all cycles of initial treatment will be combined in the presentation of safety data.

The following sections describe the planned safety summaries. However, additional safety tables may need to be produced to aid interpretation of the safety data.

4.5.1 Primary and Secondary Safety Endpoints

4.5.1.1 Adverse events

Data from all cycles of initial treatment will be combined in the presentation of safety data. All adverse events will be listed individually for each patient and summarized according to the system organ class (SOC) and preferred term (PT) assigned to the event using the MedDRA. AEs will be graded according to the NCI CTCAE version 4.03 for AEs. The

CTCAE grade will be assigned by the investigator. MedDRA version 18.0 or higher will be used for coding.

Any AEs occurring after the first dose of study treatment and within 35 days of the last dose of study treatment will be included in the AE summaries. AEs occurring before the first dose of study treatment or more than 35 days after the last dose of study treatment will not be included in AE summaries but will be included and presented in the patient listings.

AEs will be categorized into one or more of the following categories depending on the type of events reported:

- All AEs
- All AEs (by episode)
- All AEs by severity (CTCAE grade)
- All AEs with by relationship to the study medication
- All AEs related to study medication by severity
- All serious adverse events (SAEs)
- All SAEs by severity (CTCAE grade)
- All SAEs with by relationship to the study medication
- All SAEs related to study medication by severity
- AE leading to interruption of study medication
- AE leading to dose reduction of study medication
- AEs leading to discontinuation of study medication
- AEs leading to discontinuation of study medication, causally related to study medication
- AEs with an outcome of death
- AEs with an outcome of death, causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to study medication
- Summary of cause of Serious Adverse Events
- Summary of Outcome of Adverse Events
- Summary of Outcome of study medication related Adverse Events
- Summary of Outcome of Serious Adverse Events

- Summary of Outcome of study medication related Serious Adverse Events

An overall summary of the number and percentage of patients in each category will be presented, as well an overall summary of the number of events in each category.

The number and percentage of patients reporting adverse events in each category above will be summarized by MedDRA system organ class and preferred term.

AEs will be assigned a CTCAE version 4.03 grade and summaries of the number and percentage of patients will be provided by worst CTCAE grade, preferred term

All adverse event data will be listed for all patients. Investigator terms with their MedDRA preferred terms will be listed for each patient. Listings will include the last dose for the patient along with the number of days since last dose. In addition, serious adverse events, other significant adverse events, adverse events that led to withdrawal, adverse events with causality trastuzumab emtansine and adverse events of special interest will be listed. Adverse events that occur after the last trastuzumab emtansine dose and within 30 days of the last trastuzumab emtansine dose will be attributed to the visit in which the last dose was given.

The summary of death will be categorized as follows,

- AEs with outcome= death by system organ class (SOC) and preferred term (PT)
- AEs with outcome= death, causally related to study medication, system organ class (SOC) and preferred term (PT)
- Number (%) of patients who died by the end of study period (on-study, post-study) and reasons for death

On-study period is from first dose of study treatment and till 35 days of the last dose of study treatmentAdverse events of special interest

AESI will be identified using CRF

Grouped summary tables of certain preferred terms will be produced. For each 'grouped' term, the number (%) of patients experiencing any of the specified terms will be presented by maximum CTCAE grade. A listing of the preferred terms in each grouping will be provided. Changes observed in CTCAE grade during study will be listed only.

Additional summaries of the above-mentioned grouped AE categories will include number (%) of patients who have:

- At least adverse event of special interest presented by outcome
- At least one adverse event of special interest by CTCAE grade
- At least one adverse event of special interest causally related to study medication
- At least one adverse event of special interest leading to discontinuation of study medication.

4.5.1.2 Exposure:

Total duration of exposure of study medication in weeks will be calculated as:

(minimum of date of progression or date of discontinuation - Date of first dose of study medication + 1)/7

Exposure to investigational product i.e., total amount of study medication received will be listed for all patients and summarized.

Total exposure, total time on study and total number of cycles administered per patient will be summarized by mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption and at least one dose reduction will be presented separately, if appropriate.

4.5.1.3 Laboratory Data

Blood sample for the determination of Hematology, biochemistry, and coagulation tests will be done as part of regular safety assessments: at screening/baseline, every treatment cycle, and at the 28 days (±7 days) from last treatment cycle/dose. Assessments must be performed at each cycle within ±3 days (with results available) prior to the administration of study medication.

The baseline value is the last value observed prior to first administration of study medication on cycle 1 and any information taken after first administration of study medication is regarded as post baseline information. When there are multiple observations within a nominal visit, most extreme value will be taken for continuous variables and worse value will be taken for categorical variables.

All laboratory data is to be collected and reported in SI units

All laboratory data (result) and change from baseline values will be summarized using descriptive statistics at each scheduled assessment time. For categorical data, shift from baseline will be summarised using frequency and proportion at each assessment time. Numerical summaries should provide the mean, median and lower and upper quartile (25th and 75th), in addition to other statistics, for visit based tabular summaries.

Shift tables for laboratory values by worst Common toxicity criteria (CTC) grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypo-directionality of change will be produced. For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided (i.e. on-treatment is defined as data collected up until the last dose of study medication).

Results along with reference ranges will be listed. All laboratory summaries and listings will be presented by parameter.

Other summaries will include number (%) of patients who have:

- Elevated Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and elevated bilirubin during the study
    - ALT <= 1x , > 1x – 3x, > 3x – 5x, > 5x – 10x, > 10x – 20x and > 20x ULN during the study
    - AST <= 1x, > 1x – 3x, > 3x – 5x, > 5x – 10x, > 10x – 20x and > 20x ULN during the study
    - Total bilirubin <= 1x, > 1x - 1.5x, > 1.5x – 2x, > 2x ULN during the study

Individual patient data where ALT or AST plus bilirubin are elevated at any time will be listed.

Box-plots of absolute values and change from baseline in Hemoglobin, Neutrophils, Potassium, AST, ALT and Total bilirubin will be presented. Shift plots comparing baseline to minimum value for hemoglobin, neutrophils and potassium while shift plots comparing baseline to maximum value for potassium, AST, ALT and total bilirubin will be provided.

4.5.1.4 Vital Signs

Vital signs will be assessed before treatment on Day 1 of every treatment cycle, recorded again after infusion during the observation period. Vital signs will include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and oral or axillary temperature.

The baseline value is the last value observed prior to first administration of study medication on cycle 1. The change from baseline is defined as the post-baseline value minus the baseline value. There will not be any imputation for missing values.

Vital signs (SBP, DBP respiratory rate, and pulse rate) will be summarized over time in terms of absolute values and changes from baseline at each scheduled measurement Box plots of change from baseline in SBP, DBP, respiratory rate, and pulse will be presented.

All data will be listed individually

4.5.1.5 LVEF Assessments

Echocardiogram (ECHO) will be performed to assess left ventricular ejection fraction (LVEF) at screening (baseline), every three cycles of treatment, and at the 28-days post-treatment safety follow-up visit.

The incidence of CHF and/or significant decline in LVEF will be summarized using number (n) and percentage. LVEF over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time.

4.5.1.6 Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 3). Performance status will be assessed at baseline, every three cycles of treatment, and at the 28-days post-treatment safety follow-up visit.

ECOG performance status at will be summarized by frequency counts and percentage at each scheduled visit and listed individually. Also a change from Baseline in ECOG performance status at last available visit will be summarized using shift table.

4.6 EFFICACY ANALYSIS

The primary objective for this study is to assess the safety of trastuzumab emtansine and efficacy is being the secondary objective. There will be no formal statistical hypothesis testing performed for secondary efficacy endpoints. All the secondary efficacy endpoint (PFS, ORR, and OS) data will be summarized and listed based on ITT population.

4.6.1 Secondary Efficacy Endpoints

The following variables will be measured as secondary efficacy endpoints:-

- Progression free survival (PFS)
- Overall response rate (ORR)
- Overall survival (OS)

4.6.1.1 Progression-free Survival (PFS)

PFS is defined as the time from the date of enrollment until the date of first documented progression of disease or the date of death (by any cause in the absence of progression) whichever happens first regardless of whether the subject withdraws from study medication or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the last evaluable tumour assessment. However, if the subject progresses or dies after two or more missed visits (18 weeks), the subject will be censored at the time of the latest evaluable RECIST assessment.If the subject has no evaluable post-baseline visits or does not have baseline data they will be censored at 01 days. The number of subjects who were censored at time 01 day will be reported.

PFS will be calculated using the objective tumour assessment collected on CRF form RECIST 1.1 - Response Assessment

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

The progression status of patients at the time of analysis will be summarized. This will include the number (%) of patients who have a progression event along with the type of progression event (i.e. RECIST progression or death). The reasons that patients were

censored at the time of analysis will also be presented with appropriate reasons listed as Alive at time of analysis in the absence of RECIST progression, no baseline RECIST assessment, no evaluable post-baseline assessment.

The treatment status at progression of patients at the time of analysis will also be summarized. This will include the number (%) of patients who were on study treatment at the time of progression, the number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment. Number of days prior to progression for the patients who have discontinued treatment will be presented descriptively.

Point estimates of median PFS (in months), 25th and 75th percentile will be presented and PFS will be displayed graphically using Kaplan-Meier plots. Kaplan-Meier estimates of survival at 3 months, 6 months and 12 months, as appropriate, will be tabulated.

4.6.1.2 Objective Response Rate (ORR)

The analysis of ORR will be based on the best (confirmed) overall response (BOR). ORR is defined as the number (%) of subjects with confirmed complete response (CR) or partial response (PR) where the confirmation should be performed no less than 4 weeks after the criteria for response are first me. Data obtained up until progression or death, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. This will be irrespective of whether or not subjects discontinued treatment or received a subsequent therapy prior to progression. The denominator for ORR will be the ITT population. Patients without a post-baseline tumor assessment will be considered to be non-responders.

A summary of best response (CR, PR, SD, PD, NE) will be reported at the time of the tumour size analysis and a summary of best overall response will be produced at the time of the PFS analysis. These summaries will be presented in terms of the number and percentage of patients for each category. In addition, ninety five percent confidence intervals (95% CI) for the responder patients will be calculated by using Clopper- Pearson methodology, where the confidence interval for the Clopper-Pearson method can be written as

$$\{\theta|\mathrm{P}[\mathrm{Bin}(\mathrm{n},\theta) \leq \mathrm{X}] > \frac{\alpha}{2}]\} \cap \{\theta|\mathrm{P}[\mathrm{Bin}(\mathrm{n},\theta) \geq \mathrm{X}] > \frac{\alpha}{2}]\}$$

Where X is the number of responders and the Bin (n, θ) represents a binomial variable with n being the number of subjects and θ being the probability of success.

The following SAS code may be used to calculate the Clopper-Pearson CI for responders:

```
proc freq data=<<data>>;
    tables CPCI/ nocum norow binomial;
    exact binomial;
run;
```

4.6.1.3 Overall survival

Overall survival is defined as the time from the date of enrollment until the date of death due to any cause. Any patient not known to have died at the time of final analysis will be censored based on the last recorded date on which the subject was known to be alive.

Overall survival will be summarized and graphically displayed at the time of final analysis (12 months from the last patient enrolled in the study). Overall survival will be displayed graphically using a Kaplan-Meier plot. Kaplan-Meier estimates of survival at 3 months, 6 months and 12 months, as appropriate, will be tabulated.

A summary of survival status at the time of final analysis will be produced. This will summarize the number of patients who have died, still in survival follow-up, are lost to follow-up (LTFU) and have withdrawn consent.

Survival data will be listed for all enrolled patients.

4.6.1.4 Duration of Response

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a subject does not progress following a response, then their duration of response will use the PFS censoring time.

Duration of response will be summarized for responder patients using the Kaplan-Meier method.

4.7 INTERIM ANALYSES

In addition to the final analysis, there will be interim analysis for safety once approximately 50% patients complete 6 months investigational medicinal product therapy.

An independent Data Monitoring Committee (iDMC) will be formed which will include a statistician. An iDMC will perform the review of this interim analysis of efficacy and safety and subsequent safety reviews as described in the iDMC Charter. The list of Tables, Listings and figures for interim analysis is given in Appendix 4.

5. REFERENCES

Not Applicable.

Appendix 1

Protocol Synopsis

TITLE	:	**A MULTICENTER, OPEN-LABEL, SINGLE-ARM, PHASE IV STUDY OF TRASTUZUMAB EMTANSINE IN INDIANPATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TREATMENT WITH TRASTUZUMAB AND A TAXANE**
PROTOCOL NUMBER	:	ML29662
VERSION NUMBER	:	1
EUDRACT NUMBER	:	2008-005 713-22
IND NUMBER	:	71072
TEST PRODUCT	:	Trastuzumab emtansine (T-DM1)
PHASE	:	IV
INDICATION	:	HER2-positive unresectable locally advanced or metastatic breast cancer
SPONSOR	:	Roche Products (India) Pvt.Ltd

5.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, of trastuzumab emtansine in Indian patients with HER2-positive unresectable locally advanced or metastatic breast cancer (mBC) who have received prior treatment with trastuzumab and a taxane. Specific objectives and corresponding endpoints for the study are outlined below.

5.1.1 SAFETY OBJECTIVES

5.1.1.1 Primary Safety Objective

The primary safety objective for this study is to evaluate the safety of trastuzumab emtansine in Indian patients on the basis of the following endpoint:

- Incidence and severity of AEs as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03)

5.1.1.2 Secondary Safety Objectives

The secondary safety objectives for this study are to evaluate the safety of trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of SAEs as per NCI-CTCAE (version 4.03)
- Incidence of non-serious AEs of special interest
- Cases of drug-induced liver injury meeting Hy's law criteria
- Incidence of CHF
- Left Ventricular ejection fraction (LVEF) decrease over the course of the study as measured by ECHO
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Exposure to study medication

5.1.2 EFFICACY OBJECTIVES

5.1.2.1 Secondary Efficacy Objectives

The secondary efficacy objectives of this study are to evaluate the efficacy of trastuzumab emtansine in Indian patients with respect to:-

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)

6. STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a Phase IV, single-arm, multicenter, open-label clinical trial designed to assess the safety of trastuzumab emtansine in Indian patients with HER2-positive unresectable LABC or mBC who have received prior treatment with trastuzumab and a taxane.

The estimated duration of enrollment is 12 months. All patients fulfilling the eligibility criteria and willing to provide informed consent will receive intravenous (IV) trastuzumab emtansine 3.6 mg/kg over 30−90 minutes on Day 1 of a 21-day cycle. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death.

The study will include a screening phase, treatment phase and post-treatment safety follow-up phase for each patient as described in the Study Schema (Figure 1).

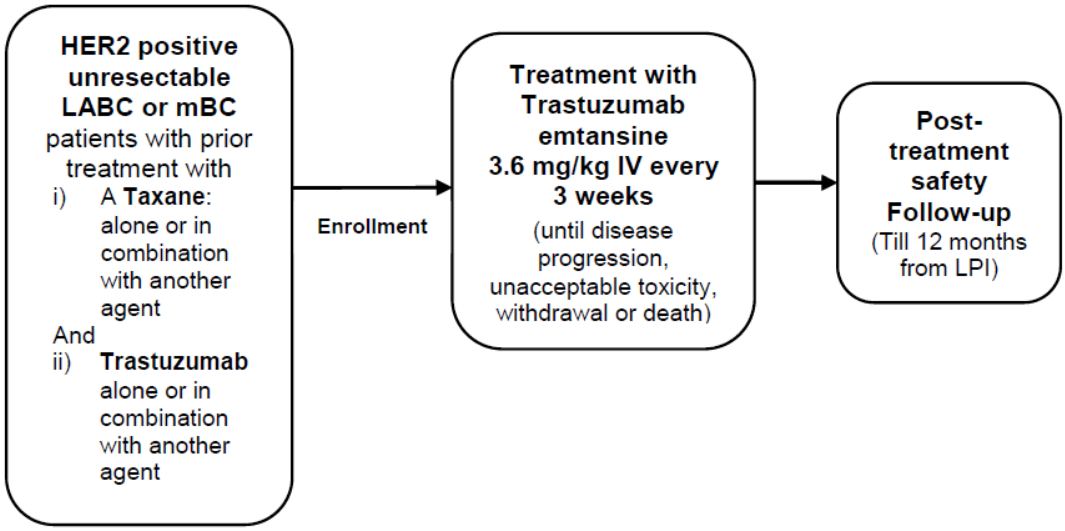
All patients will be followed-up for at least 12 months after the last patient is enrolled; unless they have been lost to follow up, withdrawn consent, or died, or the study is prematurely terminated by the Sponsor.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 12 months 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, see Section 4.2.4

An independent data monitoring committee (iDMC) will be formed for this study and will comprise of three members including a statistician. The iDMC will review the safety data for interim analysis after approximately 50% patients complete 6 months investigational medicinal product therapy. See the iDMC charter for further information.

A schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



6.2 NUMBER OF PATIENTS

This study is planned to be conducted in 70 patients across 12-15 centers in India.

6.3 TARGET POPULATION

6.3.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:-

1. Male or female of age ≥ 18 years

2. Prospectively confirmed HER2-positive (i.e., IHC 3+ or IHC 2+ and gene-amplified by fluorescence in situ hybridization [FISH] positive) as assessed on primary tumor and/or metastatic site if primary tumor not available (ISH positivity is defined as a ratio of 2.0 or greater for the number of HER2 gene copies to the number of signals for CEP17, or for single probe tests, a HER2 gene count greater than 4) as determined in a local

laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay

3. Histologically or cytologically documented invasive breast cancer: unresectable, LABC or mBC

4. Prior treatment for breast cancer in the adjuvant, unresectable, locally advanced, or metastatic setting must include:-

   i. A taxane, alone or in combination with another agent, AND
   ii. Trastuzumab, alone or in combination with another agent in the adjuvant, unresectable, locally advanced, or metastatic setting

5. Documented progression of unresectable, locally advanced, or mBC, determined by the investigator; progression must occur during or after most recent treatment for LABC/mBC or within 6 months after completing adjuvant therapy

6. Measurable and/or non-measurable disease

7. LVEF ≥ 50% by echocardiogram (ECHO)

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

9. Adequate organ function, evidenced by the following laboratory results within 30 days of enrollment:

   i. Absolute neutrophil count > 1,500 cells/mm3
   ii. Platelet count > 100,000 cells/mm^3
   iii. Hemoglobin > 9.0 g/dL. Patients will be allowed to be transfused red blood cells to this level
   iv. Albumin ≥ 2.5 g/dL
   v. Total bilirubin ≤ 1.5 upper limit of normal (ULN)
   vi. Serum glutamic oxaloacetic transaminase (SGOT) or aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT) or alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤2.5 × ULN with the following exception: Patients with bone metastases: ALP ≤ 5 × ULN
   vii. Creatinine clearance > 50 mL/min based on Cockroft-Gault glomerular filtration rate estimation: (140 − Age) × (weight in kg) × (0.85 if female)/(72 × serum creatinine)

viii. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) < 1.5 × ULN (unless on therapeutic coagulation)

10. A negative serum β-Human Chorinic Gonadotropin (β-HCG) test for women of childbearing potential (premenopausal or not meeting the definition of postmenopausal i.e. ≥ 12 months of amenorrhea), and women who have not undergone surgical sterilization (i.e., absence of ovaries and/or uterus) within 7 days prior to the first dose of study treatment with the result available prior to first dosing

11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate non-hormonal methods of contraception, including at least one method with a failure rate of □□1% per year, during the treatment period and for at least 7 months after the last dose of study drug

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Barrier methods must always be supplemented with the use of a spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months plus 90 days (a spermatogenesis cycle) after the last dose of study drug. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 7 months after the last dose of study drug.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

12. An audio-visual recording of the informed consent process and a signed written informed consent approved by the relevant IRB/EC

6.3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Prior treatment with trastuzumab emtansine

2. Prior treatment with lapatinib or lapatinib with capecitabine or non-comparable biologic or biosimilar of trastuzumab

3. Peripheral neuropathy of Grade ≥ 3 per NCI CTCAE (version 4.03)

4. History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive breast cancer, or cancers with a similar curative outcome as those mentioned above

5. History of receiving any anti-cancer drug/biologic or investigational treatment within 21 days prior to enrollment except hormone therapy, which can be given up to 7 days prior to enrollment; recovery of treatment-related toxicity consistent with other eligibility criteria

6. History of exposure to the following cumulative doses of anthracyclines:
   i. Doxorubicin or liposomal doxorubicin > 500 mg/m^2
   ii. Epirubicin > 900 mg/m^2
   iii. Mitoxantrone > 120 mg/m^2
   iv. If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin

7. History of radiation therapy within 14 days of enrollment. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to enrollment.

8. Brain metastases that are untreated, symptomatic, or require therapy to control symptoms, as well as a history of radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 2 months (60 days) before enrollment

9. History of a decrease in LVEF to < 40% or symptomatic congestive heart failure (CHF) with previous trastuzumab treatment

10. History of symptomatic chronic heart failure (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment

11. History of myocardial infarction or unstable angina within 6 months of enrollment

12. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy

13. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)

14. Pregnancy or lactation

15. Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus (HIV) or active hepatitis B and/or hepatitis C. For patients who are known carriers of hepatitis B virus (HBV), active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV DNA 5viral load per local guidelines

16. Presence of conditions that could affect gastrointestinal absorption: malabsorption syndrome, resection of the small bowel or stomach, and ulcerative colitis

17. History of intolerance (such as Grade 3-4 infusion reaction) or known hypersensitivity to trastuzumab or murine proteins or any component of the product

18. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

6.4 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the safety follow-up is received from the last patient, whichever occurs later. The LPLV is to occur 12 months after the last patient is enrolled; unless they have

been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 to 3 years.

Following the completion of the study, Roche will continue to provide study medication to all the patients:-

- who are still receiving the study medication and have not progressed on study medication at the end of the study
- and who are willing to continue study medication
- and are considered suitable by the investigator to continue receiving study medication till progression of the disease and signed written post trial access consent form, approved by the relevant Institutional Review Board (IRB)/Ethics Committee (EC)

7. INVESTIGATIONAL MEDICINAL PRODUCTS

All investigational medicinal products (IMPs) required for completion of this study (trastuzumab emtansine) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study sites institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

8. STATISTICAL METHODS

8.1 PRIMARY ANALYSIS

The primary safety objective for this study is to evaluate the safety of trastuzumab emtansine in Indian patients on the basis of the following endpoint:

- Incidence and severity of AEs as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03)

The primary analyses will be conducted on the safety population that will include all enrolled patients who receive at least one dose of study medication.

The incidence of AEs and SAEs will be summarized according to the primary system organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

8.2 DETERMINATION OF SAMPLE SIZE

For the purpose of the estimation of sample size, the incidence of all grade AEs was chosen as a safety endpoint of primary interest. If the observed incidence of all grade AEs is 95.9% according to the EMILIA study and assuming level of significance 5% (i.e. 95% CI) and precision 5% with drop out of 10%, approximately 70 patients are planned for enrollment this study.

Any AEs				
Incidence of adverse event-AE (p)	**Precision (d)**	**Sample size (n)**	**After adjusting the dropout rate of**	
			10 %	**20 %**
95.9%	01 %	1511	1679	1889
	02 %	378	420	473
	03 %	168	187	210
	04 %	95	106	119
	05 %	61	68	77
	06 %	42	47	53
	07 %	31	35	39
	08 %	24	27	30
	09 %	19	22	24
	10 %	16	18	20

8.3 INTERIM ANALYSIS

In addition to the final analysis, there will be interim analysis for safety once approximately 50% patients complete 6 months investigational medicinal product therapy.

An independent Data Monitoring Committee (iDMC) will be formed which will include a statistician. An iDMC will perform the review of this interim analysis of efficacy and safety and subsequent safety reviews as described in the iDMC Charter. The list of Tables, Listings and figures for interim analysis is given in Appendix 4.

Appendix 2

Schedule of Assessments

VISIT	Screening Visit	Treatment Visits	Post-Treatment Safety Follow-Up After Study Treatment Termination		
Day/Month	Day -28 to Day 1	Day 1 of each treatment cycle	28 days from last Treatment cycle/dose	Every 3 months	End of Study visit[15]
Window Period		± 3 days	± 7 days	± 7 days	± 7 days
Informed consent[1]	X				
Demographics and medical history	X				
Physical examination	X	X	X	X	X
Vital signs and blood pressure	X	X	X	X	X
Height	X				
Weight	X	X	X		
Concomitant medication[5]	X	X	X	X	X

HER2 reports review for eligibility[6]	**X**				
Tumor evaluation[7]	**X**	Every 3 cycles of antibody drug conjugate	If disease progression not yet established	If disease progression not yet established	
Laboratory Investigations (Hematology and serum chemistry)[8]	**X**	**X**	**X**		
ECOG performance status[9]	**X**	Every 3 cycles of antibody drug conjugate	**X**		**X**
LVEF[10]	**X**	Every 3 cycles of antibody drug conjugate	**X**	**X**	
PK sampling[11]	**X**	Pre-dose and 15 min post-infusion			
Adverse event reporting[12]	**X**	**X**	**X**	**X**	**X**
Administration of trastuzumab emtansine[13]		**X**			

Pregnancy test[14]	Within 7 days prior to 1st dosing				
Survival[16]	**X**	**X**	**X**	**X**	**X**

1. Signed and dated informed consent in language comprehended by the potential clinical trial subject/Legally acceptable representative
2. Complete medical history and demographics (i.e. age, sex, race, and ethnicity, if applicable) and all medications taken during the last 28 days prior to screening visit will be collected
3. Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF
4. Vital signs will be assessed before treatment on Day 1 of every treatment cycle, recorded again after infusion during the observation period. Vital signs include respiratory rate, pulse rate, and systolic, and diastolic blood pressure while the patient is in a seated position, and oral or axillary temperature
5. Current concomitant medication will be recorded at screening and on an ongoing basis
6. HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site, if primary tumor not available) to be assessed by IHC and/or FISH at a local laboratory
7. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. A CT or MRI and (if indicated) isotope bone scan (evaluation according to RECIST criteria) should be performed at screening and as clinically indicated. Scans at screening should not be older than 28 days prior to first study medication administration. NB: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. Tumor assessment ± 3 days of planned scheduled visit. At the end of study visit, if a patient does not fit into the end of study definition, then tumor assessment to be done as per institutional criteria and routine clinical practice.
8. Laboratory assessment as per routine standard of care must be performed within 3 days (with results available) prior to the administration of study medication. Hematology, as per routine standard of care, may include hemoglobin, hematocrit, platelet count, RBC, WBC with

differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells). Serum chemistry, as per routine standard of care, may include sodium, potassium, calcium, chloride, magnesium, BUN (urea), uric acid, total protein, albumin, alkaline phosphatase, ALT, AST, lactate dehydrogenase (LDH), total bilirubin, creatinine, and blood glucose and calculated creatinine clearance at baseline. Coagulation tests will consist of international normalized ratio (INR) and aPTT or PTT.

9. ECOG performance status to be recorded every 3 cycles until disease progression.
10. LVEF ≥ 50% at screening period to be determined by ECHO. To the extent possible, assessment to be obtained at the same institution
11. Blood and serum samples will be collected pre-dose on Cycle 1, 2, and 3 and post-infusion on Cycle 1 and 3 only from patients that have signed the PK substudy informed consent form
12. After informed consent and prior to dosing, SAEs considered related to a study mandated procedure are reportable. As of cycle 1 all AEs and SAEs considered will be collected. AEs and SAEs to be monitored and continuously collected till end of study visit and to be recorded with grading according to NCI-CTCAE version 4.03
13. The initial dose of trastuzumab emtansine will be administered over 90 minutes and if well tolerated subsequent infusions may be administered over 30 min (±10 min)
14. For women of childbearing potential, serum β-HCG test must be performed within 7 days prior to the first dose of study treatment with the result available prior to first dosing. Urine β-HCG test must be performed within 7 days prior to every 3rd cycle (with results available prior to treatment), at the safety follow up visit, and at 4 and 7 months after the last dose of study treatment. All positive urine pregnancy tests must be confirmed by a serum β HCG test
15. Patients who complete the study or discontinue from the study early will be asked to return to the hospital within 28 days after the last dose of study drug for the end of the study visit
16. Survival status will be recorded during the treatment period and every 3 months after the one month post-treatment safety follow up visit until 12 months after the last patient enrolled in study or lost to follow up, withdrawn consent, or died, or if the study is prematurely terminated by Roche, whichever occurs first. Patients who are alive at the time of the analysis will be censored at the date of the last follow up assessment

Appendix 3

Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 4

Data Display for Interim Analysis

The following data but not limiting to will be reviewed and discussed by IDMC at interim analysis.

Baseline Tables

- Subject Disposition
- Subject Disposition by Visit
- Summary of Demographics and Baseline characteristics
- Summary of significant medical history
- Summary of Prior Systemic Cancer Therapy
- Summary of Prior Systemic Cancer Therapy by different factors
- Summary of Prior Radiotherapy
- Summary of Prior Radiotherapy by different factors
- Summary of Prior Concomitant Medications
- Summary of Concomitant Medications
- Summary of Dose of Trastuzumab emtansine by Visit

Efficacy Tables

- Summary of Progression free survival (PFS) using Kaplan Meier estimates
- Kaplan Meier graph for progression free survival – Total
- Summary of Overall survival using Kaplan Meier estimates

- Kaplan Meier graph for Overall survival – Total
- Analysis of Duration of Response
- Analysis of Overall Response
- Summary of Progression free survival (PFS) using Kaplan Meier estimates by disease status
- Kaplan Meier graph for progression free survival by disease status
- Summary of Overall survival using Kaplan Meier estimates by disease status
- Kaplan Meier graph for Overall survival by disease status
- Summary of Progression free survival (PFS) using Kaplan Meier estimates by disease location
- Kaplan Meier graph for progression free survival by disease location
- Summary of Overall survival using Kaplan Meier estimates by disease location
- Kaplan Meier graph for Overall survival by disease location
- Summary of Progression free survival (PFS) using Kaplan Meier estimates by disease evaluation
- Kaplan Meier graph for progression free survival by disease evaluation
- Summary of Overall survival using Kaplan Meier estimates by disease evaluation
- Kaplan Meier graph for Overall survival by disease evaluation
- Distribution of site and location of Target Lesions
- Summary of target lesions
- Analysis of Target Lesions-Diameter

Safety Tables

- Summary of Adverse Events

- Summary of Adverse Events by severity (CTCAE grade)
- Summary of Adverse Events by Relationship to the study medication
- Summary of Adverse Events related to study medication by severity
- Summary of Serious Adverse Events
- Summary of Serious Adverse Events by severity
- Summary of Serious Adverse Events by Relationship to the study medication
- Summary of study medication related Serious Adverse Events by severity
- Summary of Outcome of Adverse Events
- Summary of Outcome of study medication related Adverse Events
- Summary of Outcome of Serious Adverse Events
- Summary of Outcome of study medication related Serious Adverse Events
- Summary of cause of Serious Adverse Events
- Summary of number of cycles and duration of treatment
- Summary of Deaths
- Summary of LVEF change in Baseline
- Summary of Physical Examination
- Summary of Vital Signs Measurements
- Summary of Other Lab tests
- Summary of ECOG performance status
- Analysis of ECOG performance status –Change from Baseline