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

NCT Number: NCT02658734

Document Date: Protocol Version 2: 12-February-2018

PROTOCOL

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
VERSION NUMBER:	2.0
EUDRACT NUMBER:	2008-005 713-22
IND NUMBER:	71072
TEST PRODUCT:	Trastuzumab emtansine (T-DM1)
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	Roche Products (India) Pvt. Ltd.
DATE AMENDED:	30 Jan 2018

PROTOCOL AMENDMEN[redacted]VAL

Signature with Date:
Name:
Designation:

Dr. [redacted]
Roche Products (India) Pvt. Ltd.

Signature with Date:
Name:
Designation:

Dr. [redacted]
Roche Products (India) Pvt. Ltd.

Signature with Date:
Name:
Designation:

Dr. [redacted]
MakroCare

PROTOCOL

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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DATE AMENDED:	30 Jan 2018

PROTOCOL AMENDMENT APPROVAL

Signature with Date: _____
Name: Dr. [redacted]
Designation: [redacted]
Roche Products (India) Pvt. Ltd.

Signature with Date: _____
Name: Dr. [redacted]
Designation: [redacted]
Roche Products (India) Pvt. Ltd.

Signature with Date: [redacted] JAN 2018
Name: Dr. [redacted]
Designation: [redacted]
MakroCare

PROTOCOL AMENDMENT, VERSION 2.0
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- Pharmacokinetic (PK) objective and endpoint has been removed due to logistic problems in transportation of samples to the central laboratory outside of India. Moreover, the T-DM1 assays are not available in the local laboratories. Therefore, all text pertaining to PK sampling and analysis have been removed.
- It has been clarified that patients who have had HER2 testing done by the same local laboratory for their prior treatment need not undergo re-testing.
- CNS only disease will not be eligible for participation in the study.
- Safety update on hemorrhagic events has been added in the section on Risks Associated with trastuzumab emtansine
- Audio-video consenting is no longer required for this study population as per the communication received from the Health Authority in India.
- The steps to be followed in case of any temperature excursion either during shipment from depot to site or at the site, have been included as an appendix to the protocol.
- Contact details of product complaint have been provided.
- It has been specified that all deaths that occur either during the study period, regardless of relationship to study drug, must be reported to the Sponsor and Health Authorities within 24 hours of the occurrence of the event.
- It has been specified that the investigator must report events that require immediate reporting (e.g. deaths, AESIs, abortions, 9.4.3.4 congenital anomalies etc.) to the Sponsor not more than 24 hours after the occurrence of the event and not more than 24 hours after the Investigator learns of the event as mentioned in the previous version of the protocol.
- The name and contact information of the Medical Monitor and Alternate Medical Monitor has been updated.
- Reference to Appendix 3 RECIST criteria has been added.
- Errors in referencing the safety section have been corrected in the text, wherever applicable.

Recent updates on clinical trial data of trastuzumab emtansine have been added

PROTOCOL AMENDMENT, VERSION 2.0
SUMMARY OF CHANGES

GLOBAL CHANGES

Text and sections on Pharmacokinetic objectives or analysis have been removed throughout the document.

It has been clarified throughout the Safety sections of the document that Serious Adverse Events and Adverse Events of Special Interest should be reported no more than 24 hours of occurrence of the event instead of no more than 24 hours after occurrence/learning of the event.

Name of the Medical Monitor was updated.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 2.1: DESCRIPTION OF THE STUDY

Revised text: The estimated duration of enrollment is 12 months ***or till achievement of enrolment target***.

SECTION 2.3.1 and SECTION 8.1.1 Inclusion Criteria

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 **(*Except for those patients who had HER2 testing done by the same local laboratory for their prior treatment)**

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

SECTION 2.3.2 and SECTION 8.1.2 Exclusion Criteria

9. CNS only disease

SECTION 7.4.1 PRIMARY ANALYSIS

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

SECTION 5.2 BACKGROUND ON TRASTUZUMAB EMTANSINE

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). **The descriptive analysis of the final overall survival data from this trial reported median overall survival of 29.9 months [95% CI 26·3–34·1] with trastuzumab emtansine vs 25.9 months [95% CI 22·7–28·3] with control (Dieras et al, 2017).**

SECTION 8.3.1.1. Trastuzumab emtansine

In case of any temperature excursion either during shipment from depot to site or at the site, the steps outlined in Appendix 5 should be followed. Any damage or product complaints should be reported as follows and as per details in Appendix 5:

Contact details for Product Complaint:

During Office Hours: [redacted]

Mobile [24 x7]: [redacted]

Fax: +91-22-33941054

Product Complaint Mailbox: india.productcomplaints@roche.com

Adverse Event Mailbox: india.drugsafety@roche.com

Reporting Timelines: within ONE business day.

SECTION 8.5.1 Informed Consent Forms and Screening Log

~~Audio visual recordings of w~~**W**ritten informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

SECTION 8.5.4 Vital Signs

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

SECTION 8.5.6.2 Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix ~~3~~**2**). It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study. Performance status will be assessed at baseline, **after** every three cycles of treatment, and at the 28-days post-treatment safety follow-up visit.

SECTION 9.5.7 Laboratory Assessments

HER2 testing: HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site) to be assessed by IHC and/or ISH at a local laboratory that is experienced/certified in HER2- expression testing. **Patients who have had HER2 testing done at the same local laboratory for their prior treatment will not require re-testing.**

~~For sampling procedures, storage conditions, and shipment instructions, please refer to the Sample Handling and Logistics Manual which will be provided separately.~~

~~For sampling procedures, storage conditions, and shipment instructions, please refer to the laboratory manual, which will be provided separately.~~

SECTION 9.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with trastuzumab emtansine in completed and ongoing studies~~.~~ **and knowledge of toxicities related to trastuzumab and maytansine (a parent compound of emtansine and DM1)**. The anticipated important safety risks for trastuzumab emtansine are outlined below. Please refer to the ~~T~~trastuzumab emtansine Investigator's Brochure for a complete summary of safety information.

Dose delays and dose reductions will be allowed for trastuzumab emtansine please refer the tables below (Prescribing Information Trastuzumab emtansine, February 201**7**~~5~~)

SECTION 9.1.1 Risks Associated with Trastuzumab Emtansine

Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia, in others there were no known additional risk factors. Additional monitoring should be considered when concomitant use is medically necessary.

SECTION 9.1.3 Hepatotoxicity

Transaminase elevations were generally transient **with peak elevation at day 8 after therapy and subsequent recovery to Grade 1 or less prior to the next cycle**.

SECTION 9.3.1 Adverse Event Reporting Period

All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. ~~and~~ **All SAEs will be notified as per local regulations in** the Appendix XI Form.

SECTION 9.3.5.8 Deaths

All deaths that occur during the ~~protocol-specified AE reporting~~ **study** period (see Section ~~5~~**9**.3.1),) regardless of relationship to study drug, must be recorded on the Adverse Event eCRF ~~and~~, the Appendix XI Form and ~~immediately~~ reported to the Sponsor **and Health Authorities** (see Section ~~5~~**9**.4.2).) **within 24 hours of occurrence of the event.** This

includes death attributed to progression of HER2-positive unresectable, locally advanced or mBC.

During survival follow-up, **all** deaths should be recorded ~~only on~~ **in** the Survival eCRF **and the Appendix XI Form and reported to the Sponsor and Health Authorities (see Section 9.4.2) within 24 hours of occurrence of the event.**

SECTION 9.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after ***of*** the ~~investigator learns~~ **occurrence** of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours ~~after~~ ***of*** occurrence ~~or learning~~ of the event, regardless of relationship to study drug:

- Serious adverse events (see Section ~~5.4~~**9**.2**.2** for further details)
- Non-serious adverse events of special interest (see Section ~~5.4~~**9**.2**.3** for further details)
- Pregnancies (see Section ~~5~~***9.***4.3 for further details)

SECTION 9.4.1 Emergency Medical Contacts

Medical Monitor contact information for all sites

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Medical Monitor contact information for all sites:

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 10.5.1 Secondary Efficacy Endpoints

To be assigned a status of PR or CR (i.e., a responder~~), changes)~~ **determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (Appendix 3).**

SECTION 13.2 INFORMED CONSENT

~~The Informed Consent Form will contain separate sections for any optional procedures such as PK sampling.~~

~~An audio – visual recording taken with the patient's consent will document the informed consent process and that written informed consent was obtained prior to participation in the study.~~

Appendix 1
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~~14~~]**
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,~~ **serology 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	X	X	

		drug conjugate			
~~PK sampling[11]~~		~~Pre dose and 15 min post infusion~~			
Adverse event reporting[121]	X	X	X	X	X
Administration of trastuzumab emtansine[12]		X			
Pregnancy test[13]	Within 7 days prior to 1st dosing	Every 3 cycles of antibody drug conjugate	X	At 4 and 7 months after the last dose of antibody drug conjugate	
Survival[15]	X	X	X	X	X

Notes:

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 **after** 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

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PROTOCOL ACCEPTANCE FORM

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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IND NUMBER:	71072
TEST PRODUCT:	Trastuzumab emtansine (T-DM1)
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	Roche Products (India) Pvt.Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the local study monitor at Roche Products (India) Pvt. Ltd.

PROTOCOL SYNOPSIS

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
VERSION NUMBER:	2.0
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

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.

1.1 SAFETY OBJECTIVES

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)

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 echocardiogram (ECHO)
- Laboratory results abnormalities
- Incidence of AEs leading to discontinuation, modification, or interruption of study medication
- Exposure to study medication

1.2 EFFICACY OBJECTIVES

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)

2. STUDY DESIGN

2.1 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 or till achievement of enrolment target. 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).

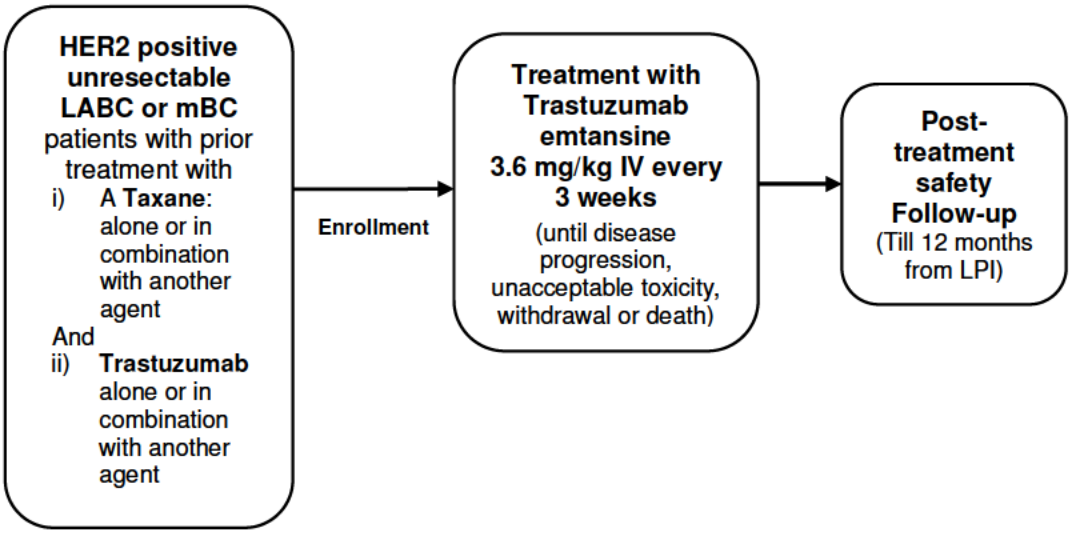
All patients will be followed-up for at least 12 months after the last patient is enrolled; unless they have been lost to follow up, withdrawn consent, or died, or the study is prematurely terminated by the Sponsor.

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 8.3.4

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



2.2 NUMBER OF PATIENTS

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

2.3 TARGET POPULATION

2.3.1 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 (*Except for those patients who had HER2 testing done by the same local laboratory for their prior treatment)
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/mm^3
   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. A signed written informed consent approved by the relevant IRB/EC.

2.3.2 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. CNS only disease
10. History of a decrease in LVEF to < 40% or symptomatic congestive heart failure (CHF) with previous trastuzumab treatment
11. History of symptomatic chronic heart failure (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment
12. History of myocardial infarction or unstable angina within 6 months of enrollment
13. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy
14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
15. Pregnancy or lactation
16. 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 viral load per local guidelines

17. Presence of conditions that could affect gastrointestinal absorption: malabsorption syndrome, resection of the small bowel or stomach, and ulcerative colitis
18. History of intolerance (such as Grade 3-4 infusion reaction) or known hypersensitivity to trastuzumab or murine proteins or any component of the product
19. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

2.4 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)

3. 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 site's 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.

4. STATISTICAL METHODS

4.1 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.

4.2 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

4.3 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADC	Antibody-drug Conjugate
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
aPTT	activated Partial Thromboplastin Time
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
β-HCG	Beta Human Chorionic Gonadotropin
CHF	Congestive Heart Failure
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIBD	Developmental International Birth Date
DLP	Data Lock Point
EC	Ethics Committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FISH	Fluorescence In Situ Hybridization
HER2	Human Epidermal Growth Factor Receptor 2
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IND	Investigational New Drug (application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IV	Intravenous
LABC	Locally Advanced Breast Cancer

LDH	Lactate Dehydrogenase
LPLV	Last Patient, Last Visit
LVEF	Left Ventricular Ejection Fraction
mBC	Metastatic Breast Cancer
NCI	National Cancer Institute
NRH	Nodular Regenerative Hyperplasia
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Standard Deviation
T-DM1	Trastuzumab Emtansine
ULN	Upper Limit Of Normal

5. BACKGROUND

5.1 BACKGROUND ON BREAST CANCER

Breast cancer accounts for nearly one in three cancers diagnosed among women in the United States, and the second leading cause of cancer death around the world (Ferlay et al. 2010; DeSantis et al. 2011). Approximately 20% of breast cancers are characterized by amplification of the human epidermal growth factor receptor 2 (HER2) gene and overexpression of HER2, which functions as a driver oncogene for such tumors (Slamon et al. 1989 and Wolff et al. 2013).

HER2-positive breast cancers have historically been associated with decreased relapse free survival, decreased overall survival (OS) and poorer prognosis (Slamon et al. 1987, 1989; Perou et al. 2000; Sørlie et al. 2001). In contrast to normal cells which express approximately 20,000 HER2 receptors on the cell membrane, each HER2-positive breast cancer cell expresses approximately one to two million HER2 receptors, making HER2 an attractive candidate for targeted therapy (Venter et al., 1987).

The HER tyrosine kinase receptor family is comprised of four receptors: HER1, HER2, HER3, and HER4. These receptors are important mediators of cell growth, survival, and differentiation (Sundaresan et al. 1999). Activation of HER receptors leads to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation.

The development of trastuzumab in the 1990s provided women with HER2-overexpressing tumors with a markedly better outcome than was possible with chemotherapy alone.

Increases in response rate, response duration, and progression-free survival (PFS) were associated with a 5-month survival advantage when trastuzumab was given in the first-line metastatic setting, as demonstrated in the initial Phase III trial (Slamon et al. 2001).

For patients with HER2-positive mBC, the combination of trastuzumab and a taxane is a globally accepted first-line treatment, based on the survival advantage demonstrated in two large pivotal trials (Slamon et al. 2001; Marty et al. 2005). However, virtually all patients with HER2-positive mBC develop progressive disease (PD) and require additional therapies. Importantly, such tumors continue to express high levels of HER2 (Spector et al. 2005), and neither the process of internalization nor the level of surface expression is altered when HER2 is bound by trastuzumab (Austin et al. 2004). HER2-directed combination therapy beyond progression for HER2-positive mBC is an accepted palliative treatment approach.

5.2 BACKGROUND ON TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (also known as T-DM1) the investigational product is a novel antibody-drug conjugate (ADC) that is specifically designed for the treatment of HER2-positive malignancies. Trastuzumab emtansine is composed of trastuzumab (Herceptin®), a humanized monoclonal antibody directed against the extracellular region of HER2 and of DM1 (maytansinoid), an anti-microtubule agent derived from maytansine; and the thioether linker maleimidylmethyl cylcohexane-1-carboxylate (MCC), which is used to conjugate each molecule of DM1 to trastuzumab. DM1 is a highly potent drug synthesized from maytansinol that binds β–tubulin to inhibit tubulin polymerization. It binds to tubulin competitively with vinca alkaloids, but is 20–100 times more potent than vincristine in its cytotoxic effect against tumor cell lines. Its parent molecule, maytansine, has been studied in approximately 800 cancer patients in the 1970s and 1980s, with responses seen in patients with breast and lung cancer (Junttila et al. 2011; Issell and Crooke 1978). However, because of its narrow therapeutic index and the observed gastrointestinal toxicity of the free drug, it was not developed further as a therapeutic option (Cassady et al. 2004; Cabanillas et al. 1979).

Trastuzumab emtansine and trastuzumab recognize the same epitope on HER2 and are binding with a similar affinity. Following antigen specific binding of trastuzumab emtansine to HER2, it is hypothesized that the complex of receptor and ADC is internalized, where upon DM1-containing catabolites are released into the cytosol following proteolytic cleavage of the antibody in lysosomes (Erickson et al. 2006). Binding of these DM1-containing species to β-tubulin inhibits tubulin polymerization resulting in cell death (Cassady et al.2004).

In addition to targeting delivery of DM1 to HER2-overexpressing tumor cells, trastuzumab emtansine retains the anti-tumor activities of trastuzumab, including suppression of HER2 signaling pathways that confer a proliferative and survival advantage to cells, and the flagging of cells for destruction through antibody-dependent cell cytotoxicity (Junttila et al. 2011).

Completed and ongoing Phase I and II single arm studies of trastuzumab emtansine have demonstrated clinical activity. The randomized Phase II study BO21976 which compared single-agent trastuzumab emtansine with trastuzumab plus docetaxel showed a significant improvement in PFS with a HR 0.59 p=0.0353 and a favorable safety profile. 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. (29·9 30.9 months with trastuzumab emtansine vs 25.1 9 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). The descriptive analysis of the final overall survival data from this trial reported median overall survival of 29.9 months [95% CI 26·3–34·1] with trastuzumab emtansine vs 25.9 months [95% CI 22·7–28·3] with control (Dieras et al, 2017).

Based on the data from these 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.

See the trastuzumab emtansine Investigator's Brochure and local prescribing information for trastuzumab emtansine for additional details on nonclinical and clinical studies.

5.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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 as described in section 5.2. 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. (Investigator's Brochure Trastuzumab emtansine, 2014).

According to Periodic Benefit-Risk Evaluation Report, the estimated overall cumulative exposure to trastuzumab emtansine (i.e., from Roche − and Chugai − sponsored clinical trials and from marketing experience) since the Developmental International Birth Date (DIBD) (19 January 2006) until the data lock point (DLP) (21 February 2015) is 28,366 worldwide.

- From the DIBD (19 January 2006), to the DLP (21 February 2015) of this PBRER, an estimated total of 7,157 patients have received trastuzumab emtansine via Roche − and Chugai − sponsored interventional clinical trials participation.

- 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.

6. 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.

6.1 SAFETY OBJECTIVES

6.1.1 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)

6.1.2 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

6.2 EFFICACY OBJECTIVES

6.2.1 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)

7. STUDY DESIGN

7.1 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.

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.

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.

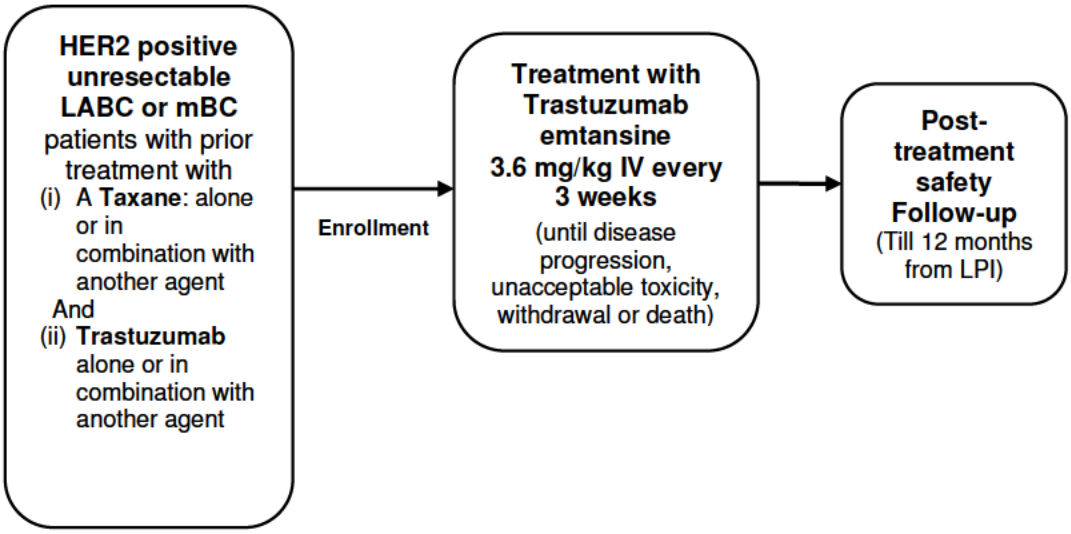
Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 12 months after last patient first visit, whichever occurs first. Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment, see Section 8.3.4

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



7.2 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)

7.3 RATIONALE FOR STUDY DESIGN

In this open-label, multicenter study, the safety of trastuzumab emtansine will be evaluated to gain a better insight into its safety profile in the Indian population to fulfill post-marketing regulatory requirements.

The study design employs standard methods for Phase IV safety studies in patients with cancer.

The primary objective is to assess the safety of trastuzumab emtansine in patients with HER2-positive LABC or mBC. Additionally, the efficacy of trastuzumab emtansine in this patient population will also be determined in this study.

As this is a predominantly safety study, the type of data collected and the frequency with which patients are monitored will ensure the safety of the patients at all times as well as fulfilling local regulatory requirements.

7.3.1 Rationale for Trastuzumab Emtansine Dose and Schedule

Trastuzumab emtansine will be administered intravenously q3w at a dose of 3.6 mg/kg over approximately 90 minutes for the first dose and 30 (±10) minutes for subsequent doses as in the Phase III registration trial (BO21977) (Verma S et al., 2012). The total trastuzumab emtansine dose will be calculated based on the patient's weight on Day 1 (or up to 28 days before) of each cycle with no upper limit.

7.3.2 Rationale for Patient Population

The patient population for this study comprises of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent) which is not amenable to curative resection and has already undergone treatment with trastuzumab and a taxane alone or in combination. Measurement of HER2 gene amplification has traditionally been performed using immunohistochemistry (IHC) and determination by in situ hybridization (ISH) has also proven to be a reliable method for demonstrating HER2-positive status (Press et al. 2005). Therefore, patients' eligibility will be determined at a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay. Good efficacy and a manageable safety profile have been demonstrated in clinical trials of trastuzumab emtansine in this patient population globally.

8. MATERIALS AND METHODS

8.1 PATIENTS

Approximately 70 patients with HER2-positive, unresectable, LABC or mBC who have received prior chemotherapy treatment with a taxane, alone or in combination with another agent and anti-HER2 treatment with trastuzumab, alone or in combination with another

agent. These patients would have progressed on or after the most recent treatment of LABC or mBC, or within 6 months of completing adjuvant trastuzumab and taxane therapy.

8.1.1 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 (*Except for those patients who had HER2 testing done by the same local laboratory for their prior treatment).
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:
    ix. Absolute neutrophil count > 1,500 cells/mm^3
    x. Platelet count > 100,000 cells/mm^3
    xi. Hemoglobin > 9.0 g/dL. Patients will be allowed to be transfused red blood cells to this level
    xii. Albumin ≥ 2.5 g/dL
    xiii. Total bilirubin ≤ 1.5 upper limit of normal (ULN)

xiv. 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

xv. 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)

xvi. 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. A signed written informed consent approved by the relevant IRB/EC

8.1.2 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:
    v. Doxorubicin or liposomal doxorubicin > 500 mg/m^2
    vi. Epirubicin > 900 mg/m^2
    vii. Mitoxantrone > 120 mg/m^2
    viii. 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. CNS only disease
10. History of a decrease in LVEF to < 40% or symptomatic congestive heart failure (CHF) with previous trastuzumab treatment
11. History of symptomatic chronic heart failure (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment
12. History of myocardial infarction or unstable angina within 6 months of enrollment
13. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy
14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
15. Pregnancy or lactation
16. 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 viral load per local guidelines
17. Presence of conditions that could affect gastrointestinal absorption: malabsorption syndrome, resection of the small bowel or stomach, and ulcerative colitis
18. History of intolerance (such as Grade 3-4 infusion reaction) or known hypersensitivity to trastuzumab or murine proteins or any component of the product
19. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

8.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label, single arm study. Therefore, all the enrolled patients fulfilling the eligibility criteria will receive trastuzumab emtansine.

8.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is trastuzumab emtansine.

8.3.1 Formulation, Packaging, and Handling

8.3.1.1 Trastuzumab emtansine

Trastuzumab emtansine will be provided by the Sponsor as a lyophilized product in either 15 mL or 20 mL single-use vials, which contain enough products to deliver 100 mg or 160 mg, respectively, of trastuzumab emtansine. The lyophilized form of the product is provided for reconstitution to a liquid concentrate using sterile water for injection.

All vials of trastuzumab emtansine should be handled by appropriately trained site staff wearing gloves and using appropriate procedures in place at the clinical site for preparation of chemotherapeutic drugs. Vials should be visually inspected upon receipt to ensure that they are intact without exterior contamination. Discard any cracked vials and report vials with surface contamination to the clinical site manager for assessment.

The lyophilized drug product, after reconstitution, contains 20 mg/mL trastuzumab emtansine. The reconstituted product will contain no preservative and should be intended for single use only. Using a new syringe, add 8.0 mL of sterile water for injection to the 20 mL (160 mg) trastuzumab emtansine vial configuration, or 5.0 mL of sterile water for injection to the 15 mL (100 mg) trastuzumab emtansine vial configuration. Swirl gently until completely dissolved (do not shake vigorously). Reconstituted trastuzumab emtansine should be diluted into polyvinyl chloride (PVC), latex-free PVC-free polyolefin bags (PO), polypropylene (PP) or polyethylene (PE) bags containing 0.45% or 0.9% sodium chloride injection (minimum volume of 250 mL). Sodium chloride 0.45% may be used without a 0.2 or 0.22 micron in-line polyethersulfone (PES) filter. If 0.9% sodium chloride is used for infusion, a 0.2 or 0.22 micron in-line PES filter is required.

The stopper of lyophilized product vials should be punctured once to introduce the sterile water for injection and once to remove the constituted product. Vials that have been used for one patient should not be used for any other patient.

For information on the formulation and handling of trastuzumab emtansine see the the current version of the Investigator's Brochure or local prescribing information of trastuzumab emtansine.

In case of any temperature excursion either during shipment from depot to site or at the site, the steps outlined in Appendix 5 should be followed. Any damage or product complaints should be reported as follows and as per details in Appendix 5:

Contact details for Product Complaint:

During Office Hours: [redacted]

Mobile [24 x7]: [redacted]

Fax: +91-22-33941054

Product Complaint Mailbox: india.productcomplaints@roche.com

Adverse Event Mailbox: india.drugsafety@roche.com

Reporting Timelines: within ONE business day.

8.3.2 Dosage, Administration, and Compliance

8.3.2.1 Trastuzumab emtansine

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

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

Trastuzumab emtansine infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Infusions of Trastuzumab emtansine

First Infusion	Subsequent Infusions
• Trastuzumab emtansine will be administered on Day 1 of a 3-week cycle at a dose of 3.6 mg/kg IV • The initial dose will be delivered over 90 ± 10 minutes. Vital signs will be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion associated symptoms	• If the first infusion is tolerated without infusion-associated AEs (fever or chills), the subsequent infusions may be delivered over 30 ± 10 minutes. • Patients who experience an infusion–associated AE may be premedicated for the next infusion, but the infusion time may not be decreased for that infusion. • In the case of infusion-related reactions, consideration for re-treatment should be based on clinical assessment of the severity and pathophysiology of the reaction (specific guidance is provided in study protocols). In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 8.6.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. Section 9.3.5.12 summarizes available safety data related to overdosing of trastuzumab emtansine.

8.3.3 Investigational Medicinal Product Accountability

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 site's 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.

8.3.4 Post-Trial Access to Trastuzumab Emtansine

The Sponsor will offer post-trial access to trastuzumab emtansine free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for HER2-positive unresectable, LABC or mBC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for HER2-positive unresectable, LABC or mBC
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

- http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

8.4 CONCOMITANT THERAPY

Concomitant therapy and premedication are defined as non-IMP. No formal drug-drug interaction studies with trastuzumab emtansine in humans have been conducted. Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient between the 14 days preceding first treatment and the safety follow-up visit.

8.4.1 Permitted Therapy

Premedication is allowed according to standard practice guidelines.

No premedication for the first infusion of trastuzumab emtansine is required; however, premedication is allowed at the investigator’s discretion.

Concomitant use of erythropoiesis-stimulating agents is allowed if clinically indicated in accordance with local prescribing guidelines.

Palliative radiotherapy may be permitted to treat pre-existing bone metastases or to treat brain metastases (for patients who have disease control outside of the brain). Please contact the Medical Monitor for approval. If the Medical Monitor cannot be reached, radiotherapy may be administered, but the Medical Monitor should still be informed.

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

8.4.2 Prohibited Therapy

Use of the following therapies is prohibited:

- Any other systemic anticancer agent or other treatments not part of protocol-specified anticancer therapy
- Any oral, injected, or implanted hormonal methods of contraception
- Any other investigational agent
- Initiation of herbal remedies for cancer treatment. Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy
- Tumor necrosis factor (TNF)-α inhibitors
- Anti-T cell antibodies

Radiotherapy for unequivocal disease progression is not permitted while on study treatment, with the exception of new brain metastases or isolated progression of previously treated brain lesions. Patients who have disease control outside of the brain, defined as continued PR or CR of any duration, or stable disease for ≥ 4 months, but who have developed brain metastases that are treatable with radiation will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain that cannot be treated with additional radiation.

Radiotherapy should be finished at least 7 days before resuming administration of trastuzumab emtansine and all toxicities need to have resolved. The Medical Monitor should be informed before a decision is made to resume study treatment after radiotherapy for brain metastases.

Patients with thrombocytopenia and on anti-coagulant treatment must be monitored closely during treatment with trastuzumab emtansine. Platelet counts will be monitored prior to each trastuzumab emtansine dose.

The above list of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

8.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

8.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse,and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

8.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.5.4 Vital Signs

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

8.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. 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 $\geq$ 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.

8.5.6 Other Disease-Specific Assessments

8.5.6.1 LVEF assessments

LVEF assessments will be performed within 42 days of enrollment and after every 3 treatment cycles by either ECHO scan. For being eligible for this study, LVEF ≥ 50% is required at screening. ECHO should be the method of choice for these assessments. The same method of LVEF assessment must be used for the same patient throughout the study, and to the extent possible, be obtained at the same institution. All pre-study LVEF values during and following trastuzumab adjuvant treatment for all patients will be collected.

8.5.6.2 Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 2). It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study. Performance status will be assessed at baseline, after every three cycles of treatment, and at the 28-days post-treatment safety follow-up visit.

8.5.7 Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's accredited local laboratory for analysis:

- HER2 testing: HER2-positive status on fixed tissue blocks from the primary tumor (and/or metastatic site) to be assessed by IHC and/or ISH at a local laboratory that is experienced/certified in HER2- expression testing. Patients who have had HER2 testing done at the same local laboratory for their prior treatment will not require re-testing.

- Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells])
- Serum chemistry (sodium, potassium, chloride, bicarbonate, magnesium, blood glucose, blood urea nitrogen [BUN] or urea, creatinine, total protein, albumin, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, lactate dehydrogenase [LDH])
- Coagulation (INR, aPTT, and partial thromboplastin time (PTT)

Hematology, biochemistry, and coagulation tests will be done as part of regular safety assessments: at screening/baseline, every treatment cycle, and at the 1-month post-treatment safety follow-up. Assessments must be performed at each cycle within 3 days (with results available) prior to the administration of study medication.

- Viral serology at screening (HIV, hepatitis B surface antigen
- Hepatitis B surface antigen, total Hepatitis B core antibody, Hepatitis C virus antibody)
- Pregnancy test

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 cycles (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.

8.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

8.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as as non-compliance with the study procedures, the schedule of protocol-defined assessments

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

8.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Serious hypersensitivity reaction/anaphylaxis
- Clinical signs and symptoms suggesting CHF
- Changes in LVEF (see Appendix 4)
- Dyspnea or clinically significant hypotension (defined per investigator discretion)
- Details of discontinuation due to toxicity are given in Section 9.1.

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time due to any of the following reasons:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, specifically defined as non-compliance with the study procedures, the schedule of assessments, or the protocol defined timelines

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

8.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

9. ASSESSMENT OF SAFETY

9.1 SAFETY PLAN

Trastuzumab emtansine is approved in India for treatment of patients with HER2-positive, unresectable, LABC or mBC who have received prior treatment with trastuzumab and a taxane. The safety plan for patients in this study is based on clinical experience with trastuzumab emtansine in completed and ongoing studies and knowledge of toxicities related to trastuzumab and maytansine (a parent compound of emtansine and DM1). The anticipated important safety risks for trastuzumab emtansine are outlined below. Please refer to the trastuzumab emtansine Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs. In addition, guidelines for managing AEs, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

An iDMC will review the safety data for interim analysis after approximately 50% patients complete 6 months investigational medicinal product therapy.

The NCI-CTCAE version 4.03 will be used to grade toxicity. Trastuzumab emtansine will be administered as specified in Section 8.3.2.

Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections. Trastuzumab emtansine administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events. Dose delays and dose reductions will be allowed for trastuzumab emtansine please refer the tables below (Prescribing Information Trastuzumab emtansine, April 2017).

Table 2 Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting Dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

9.1.1 Risks Associated with Trastuzumab Emtansine

9.1.1.1 Cardiotoxicity

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including left ventricular ejection fraction (LVEF) of <40%, have been observed infrequently in clinical trials of trastuzumab emtansine.

Patients must meet specified LVEF requirements to be included in this study (see Section 8.1.

Left ventricular function will be monitored by measurement of ejection fraction using echocardiogram (ECHO) as described in Section 8.5 and the schedule of assessments (see Appendix 1).

Guidelines for management of patients who develop left ventricular dysfunction are provided in Table 3.

Table 3 Dose Modifications for Left Ventricular Dysfunction

Symptomatic CHF	LVEF <40%	LVEF 40% to ≤45% and decrease is ≥10% points from baseline	LVEF 40% to ≤45% and decrease is <10% points from baseline	LVEF >45%
Discontinue trastuzumab emtansine	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, discontinue trastuzumab emtansine	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline , discontinue trastuzumab emtansine	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.	Continue treatment with trastuzumab emtansine

9.1.2 Hematologic Toxicity

Thrombocytopenia

Thrombocytopenia, or decreased platelet counts, was reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (≥50,000/mm^3), with the nadir occurring by Day 8 and generally improving to Grade 0 or

1 (≥75,000/mm^3) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including central nervous system hemorrhage, have been reported in clinical trials with trastuzumab emtansine; these events were independent of ethnicity. In some of the observed cases the patients were also receiving anti-coagulation therapy.

Patients with thrombocytopenia (<100,000/mm^3) and patients on anti-coagulant treatment should be monitored closely while on trastuzumab emtansine treatment. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine has not been studied in patients with platelet counts <100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (<50,000/mm^3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥75,000/mm^3).

Table 4 Dose Modification Guidelines for Thrombocytopenia

Grade 3	Grade 4
25,000 to < 50,000/mm^3	< 25,000/mm^3
Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at the same dose level.	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm3), and then reduce one dose level.

Use of erythropoiesis-stimulating agents will be allowed as consistent with prescribing guidelines. Transfusion of red blood cells and/or platelets will be allowed according to and at the discretion of the treating physician.

Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia, in others there were no known additional risk factors. Additional monitoring should be considered when concomitant use is medically necessary.

9.1.3 Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1 – 4 transaminitis), has been observed in patients while on treatment with trastuzumab emtansine in clinical trials. Transaminase elevations were generally transient with peak elevation at day 8 after therapy and subsequent recovery to

Grade 1 or less prior to the next cycle. The incidence of increased AST was substantially higher than that for ALT.

Trastuzumab emtansine has not been studied in patients with serum transaminases >2.5× ULN or total bilirubin >1.5x ULN prior to initiation of treatment. Trastuzumab emtansine treatment in patients with serum transaminases >3x ULN and concomitant total bilirubin >2x ULN should be permanently discontinued.

Dose adjustments for increased transaminases should be done as follows:

Table 5 Dose Modification Guidelines for Increased Transaminases (AST/ALT)

Grade 2 (>2.5 to ≤5× the ULN)	Grade 3 (>5 to ≤20× the ULN)	Grade 4 (>20 × the ULN)
Treat at the same dose level.	Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level	Discontinue trastuzumab emtansine

Rare cases of severe hepatotoxicity, including death due to drug-induced liver injury and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases of acute liver injury may have been confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. An acute severe liver injury (Hy's law) case has the following components:

- Aminotransferase enzymes (ALT/AST) greater than 3'× ULN with concurrent elevation of serum total bilirubin to >2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and serum total bilirubin, such as viral Hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury.
- The finding should be serious as shown by gross jaundice, clinical disability, need for hospital care, and be at least probably drug-induced (by trastuzumab emtansine)

The following are the guidelines for dose modification for hyperbilirubinemia:

Table 6 Dose Modification Guidelines for Hyperbilirubinemia

Grade 2 (>1.5 to ≤3 × the ULN)	Grade 3 (> 3 to ≤10 × the ULN)	Grade 4 (>10 × the ULN)
Do not administer trastuzumab emtansine until total bilirubin recovers to	Do not administer trastuzumab emtansine until total bilirubin recovers to	Discontinue trastuzumab emtansine

Grade ≤1, and then treat at the same dose level.	Grade ≤1 and then reduce one dose level.	

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine and presenting with signs and symptoms of portal hypertension. NRH was also observed in one fatal case of hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology. NRH should be considered in patients who develop clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on CT scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

9.1.4 Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events.

Patients with clinically significant pulmonary symptoms or disease will be excluded from this study (see Section 8.1.2).

Treatment with trastuzumab emtansine has to be permanently discontinued in patients who are diagnosed with ILD or pneumonitis.

9.1.5 Infusion-Related Reactions, Hypersensitivity Reactions

Treatment with trastuzumab emtansine has not been studied in patients who had trastuzumab permanently discontinued due to infusion related reactions (IRR)/hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients.

Infusion related reactions (IRR): IRRs, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia-have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Trastuzumab emtansine treatment should be interrupted in patients with severe IRR. Trastuzumab emtansine treatment should be permanently discontinued in the event of a life threatening IRR.

Hypersensitivity Reactions: Hypersensitivity reactions, including serious, anaphylactic like reactions have been observed in clinical trials with treatment of trastuzumab emtansine. Patients who develop a severe IRR/hypersensitivity, including anaphylaxis, angioedema, or acute respiratory distress syndrome, during an infusion of trastuzumab emtansine should discontinue treatment.

Patients should be observed closely for IRR/hypersensitivity reactions for a minimum of 90 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. In the case of infusion-related reactions, consideration for re-treatment should be based on clinical assessment of the severity and pathophysiology of the reaction. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

9.1.6 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. Treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

9.1.7 Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

9.1.8 Management of Specific Adverse Events

Adverse events of particular relevance include thrombocytopenia and hemorrhage, hepatotoxicity (increases in serum transaminases and nodular regenerative hyperplasia [NRH] of liver), IRR/hypersensitivity, cardiac dysfunction (left ventricular dysfunction), peripheral neuropathy and pulmonary toxicity (ILD).

Please refer to the local prescribing information and section 9.1 for the management of specific AEs are provided.

9.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest, performing protocol-specified safety laboratory

assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 9.4.

9.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 9.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 9.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 9.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 9.4.2 for reporting instructions).

9.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after occurrence of the event; see Section 9.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of severe drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 9.3.5.7). The following laboratory abnormalities define potential Hy's law cases:
    - AST and/or ALT elevations that are >3 × ULN
    - Concurrent elevation of total bilirubin >2 × ULN (or clinical jaundice if total bilirubin measures are not available), except in patients with documented Gilbert's syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin > 2 × ULN should be used instead
- Suspected transmission of an infectious agent by the study drug, as defined below

    Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

9.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 9.2.1 for definition) are recorded on the Adverse Event eCRF and Appendix XI Form and reported to the Sponsor in accordance with instructions provided in this section and in Sections 9.4–9.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 9.2.2 for seriousness criteria), severity (see Section 9.3.3), and causality (see Section 9.3.4).

9.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. All SAEs will be notified as per local regulations in the Appendix XI Form.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 9.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs will be reported until the end of the study **(**as defined in Section 7.1). After this period, the investigator should report SAEs that are believed to be related to prior study drug treatment (see Section 9.6).

9.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (version 4.03) will be used for assessing AE severity. Table 8 will be used for assessing severity for AE that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.03), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE (see Section 9.4.2 for reporting instructions), per the definition of SAE in Section 9.2.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 9.4.2 for reporting instructions), per the definition of SAE in Section 9.2.2.

9.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

9.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF and Appendix XI Form.

9.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

9.3.5.2 Diagnosis versus Signs and Symptoms

For AEs other than infusion-related (see Section 9.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF and the Appendix XI Form rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.3.5.3 Adverse Events That are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

9.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 9.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

9.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as AEs.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 9.3.5.4 for details on recording persistent AEs).

9.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 9.3.5.4 for details on recording persistent AEs).

9.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 9.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours of occurrence of the event), either as a SAE or a non-serious adverse event of special interest (see Section 9.4.2).

9.3.5.8 Deaths

All deaths that occur during the study period (see Section 9.3.1) regardless of relationship to study drug, must be recorded on the Adverse Event eCRF, the Appendix XI Form and reported to the Sponsor and Health Authorities (see Section 9.4.2) within 24 hours of occurrence of the event. This includes death attributed to progression of HER2-positive unresectable, locally advanced or mBC.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of HER2-positive unresectable, locally advanced or mBC, "breast cancer progression" should be recorded in the Adverse Event eCRF.

During survival follow-up, all deaths should be recorded in the Survival eCRF and the Appendix XI Form and reported to the Sponsor and Health Authorities (see Section 9.4.2) within 24 hours of occurrence of the event.

9.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting

condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

9.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 9.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be AE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an AE
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be SAEs, but should be reported as AEs instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

9.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the

associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours of occurrence of the event; see Section 9.4.2).

Adverse events associated with an overdose of trastuzumab emtansine in previous clinical studies include thrombocytopenia or increased ALT. In the few cases of medication error due to confusion between two products and consequent overdose with trastuzumab emtansine to date, events of either thrombocytopenia without hemorrhage or asymptomatic increases in transaminases have been observed. A single case of sudden death after medication error has been reported to date; however, after analysis of this case by the Applicant, a causal relationship to the medication error was considered unlikely. Please refer to Investigator's Brochure for more information on the cases.

9.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours of the occurrence of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours of occurrence of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 9.2.2 for further details)
- Non-serious adverse events of special interest (see Section 9.2.3 for further details)
- Pregnancies (see Section 9.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

9.4.1 Emergency Medical Contacts

Medical Monitor contact information for all sites

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Medical Monitor contact information for all sites:

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

Drug Safety: Contact Information

To ensure the safety reporting, following contact information will be available to all investigators.

Telephone No.: [redacted]

Direct: [redacted]

Fax: +91-22-33941054

E-mail: india.drugsafety@roche.com

9.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

9.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form and the Appendix XI Form as per local regulations provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e, no more than 24 hours of occurrence of the event), either by faxing or by scanning and emailing the Appendix XI Form using the fax number or email address provided to investigators.

9.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and non-serious AEs of special interest will be reported until 12 months after last patient enrolled in the study. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours of occurrence of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours of the occurrence of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study AEs are provided in Section 9.6.

9.4.3 Reporting Requirements for Pregnancies

9.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug.

A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

In order to learn more about the effects of trastuzumab emtansine on pregnancy, Roche Safety will request detailed follow-up information during the pregnancy and during the baby's first year of life, even if the patient has left the study.

9.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months and additional 90 days (a spermatogenesis cycle) after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e. no more than 24 hours after learning of the pregnancy) and submitted via the EDC system.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 9.4.3.1.

In order to learn more about the effects of trastuzumab emtansine on pregnancy, Roche Safety will request detailed follow-up information during the patient's partner's pregnancy and during the baby's first year of life, even if the patient has left the study.

9.4.3.3 Abortions

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF and the Appendix XI Form, and reported to the Sponsor immediately (i.e., no more than 24 hours of occurrence of the event; see Section 9.4.2).

9.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF and the Appendix XI Form and reported to the Sponsor immediately (i.e., no more than 24 hours of occurrence of the event; see Section 9.4.2).

9.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

9.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 9.4.3.1.

9.5.2 Sponsor Follow-Up

For SAEs, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period (defined as section 9.3.1 after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form and the Appendix XI form as per local requirements using the fax number or email address provided to investigators.

9.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the local prescribing information and Investigator's Brochure for trastuzumab emtansine

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

10. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

A total of approximately 70 patients will be enrolled in this study.

10.1 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,

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

Where,

P=Incidence of all AEs

d: Precision

$Z_{\alpha/2}$ $Z_{\alpha/2}$ value: 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

10.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

This is a safety study with the safety populations being the main analysis population. The analysis populations in this study will be as follows:

- **Intent-to-treat (ITT) population**: The ITT population will be defined as all enrolled patients. All baseline summaries and efficacy analyses will be based on the ITT population.

- **Safety population:** The safety population is defined as all enrolled patients who receive at least one dose of study medication.

10.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation [SD], and 25th-75th quartiles for the continuous variables.

10.4 SAFETY ANALYSES

All safety variables will be analyzed for the safety population that will include all patients who receive at least one dose of study medication.

10.4.1 Primary Safety Endpoint

The primary safety endpoint for this study is as follows:

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

10.4.2 Secondary Safety Endpoints

The following variables will be measured as secondary safety 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
- 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

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. Summaries will include: the incidence of AEs and SAEs (overall, by severity using NCI CTCAE version 4.03, by action taken with study drug).

Incidence of CHF and/or significant decline in LVEF: 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.

The number of patients prematurely discontinued from the treatment and the corresponding reasons for discontinuation will be summarized and listed. Laboratory parameters (hematology, serum biochemistry, and coagulation) will be presented by means, standard deviation, minimum, and maximum.

10.5 EFFICACY ANALYSES

Efficacy variables (PFS, ORR, and OS) will be summarized for the intent-to-treat (ITT) population defined as a population that includes all patients enrolled in the study.

10.5.1 Secondary Efficacy Endpoints

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

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

PFS is defined as the time from the date of enrollment until the first documented progression of disease or death from any cause, whichever occurs first. PFS will be obtained by the Kaplan-Meier approach. Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of enrollment plus one day.

OS is defined as the time from the date of enrollment until the date of death, regardless of the cause of death. Patients who are alive at the time of the final analysis will be censored at the date of the last follow-up assessment. OS analysis will be done at 12 months from the last patient enrolled in the study using the Kaplan-Meier estimate.

The analysis of ORR will be based on the best (confirmed) overall response (BOR). Best (confirmed) overall response (BOR) is defined as the best response recorded from the start of trial treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder) determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (Appendix 3). Changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Patients without a post-baseline tumor assessment will be considered to be non-responders. Ninety five percent confidence intervals (calculated using Clopper-Pearson methodology) for this will be provided.

10.6 INTERIM ANALYSIS

10.6.1 Planned Interim Analysis

In addition to the final analysis, there will be interim analysis for safety [refer to safety outcome measures] 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.

11. DATA COLLECTION AND MANAGEMENT

11.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO’s data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor’s standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system’s audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO’s standard procedures.

11.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. Electronic CRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

11.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 11.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

11.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

11.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

12. ETHICAL CONSIDERATIONS

12.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

12.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. As applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

12.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 13.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such

reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

12.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

12.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

13. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

13.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

13.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

13.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

13.4 ADMINISTRATIVE STRUCTURE

The study will have an iDMC and an eCRF. It will be conducted by a CRO together with the Sponsor. Assessment of laboratory test results will be performed locally.

13.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of

the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

13.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Prescribing Information Kadcyla® (Trastuzumab emtansine) revised on April 2017, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report 1063701 for Trastuzumab emtansine. Interval Covered 22 August 2014 to 21 February 2015 (inclusive), released on 22 April 2015

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Appendix 1
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[14]**
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, serology 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	
Adverse event reporting[11]	X	X	X	X	X
Administration of trastuzumab emtansine[12]		X			
Pregnancy test[13]	Within 7 days prior to 1st dosing	Every 3 cycles of antibody drug conjugate	X	At 4 and 7 months after the last dose of antibody drug conjugate	
Survival[15]	X	X	X	X	X

Notes:

17. Signed and dated informed consent in language comprehended by the potential clinical trial subject/Legally acceptable representative
18. 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
19. 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
20. 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

21. Current concomitant medication will be recorded at screening and on an ongoing basis
22. 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
23. 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.
24. 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.
25. ECOG performance status to be recorded after every 3 cycles until disease progression.
26. LVEF ≥ 50% at screening period to be determined by ECHO. To the extent possible, assessment to be obtained at the same institution.
27. 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.
28. 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).
29. 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.
30. 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.
31. 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 2 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

As published in:

Oken, MM, Creech, RH, Tormey, DC, Horton, J, Davis, TE, McFadden, ET, Carbone, PP. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Appendix 3 RECIST Criteria Version 1.1

Response Evaluation Criteria in Solid Tumors (RECIST): An Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with the addition of explanatory text as needed for clarity.[2]

1. Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as discussed below.

i. Measurable

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

ii. Non-Measurable Tumor Lesions

Non-measurable tumor lesions include small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

iii. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as given below.

Bone Lesions

- 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, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions

- 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.

Lesions with Prior Local Treatment

- 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.

iv. Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the follow-up visits. Imaging-based evaluation should always be preferred over clinical examination.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised. However, these techniques can be used to confirm the complete pathological response.

2. Tumor Response Evaluation

i. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as described above.

ii. Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph

nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

iii. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

a. Evaluation of Target Lesions

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20%, the sum must also demonstrate an absolute increase of at least 5mm.
- The appearance of one or more new lesions is also considered progression.

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure: During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

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.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

PD: Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is

no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease.

If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

iv. Evaluation of Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’.

a. Time point Response

It is assumed that at each protocol-specified time point, a response assessment occurs.

Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, **Table 2** is to be used.

Table 1 Time point Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2 Time point Response: Patients with Non-Target Lesions Only

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

CR = complete response; NE = not evaluable; PD = progressive disease.

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

b. 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.

c. Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient’s best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in **Table 3.**

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, or 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.

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective

response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table 1**, **2** and **3**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

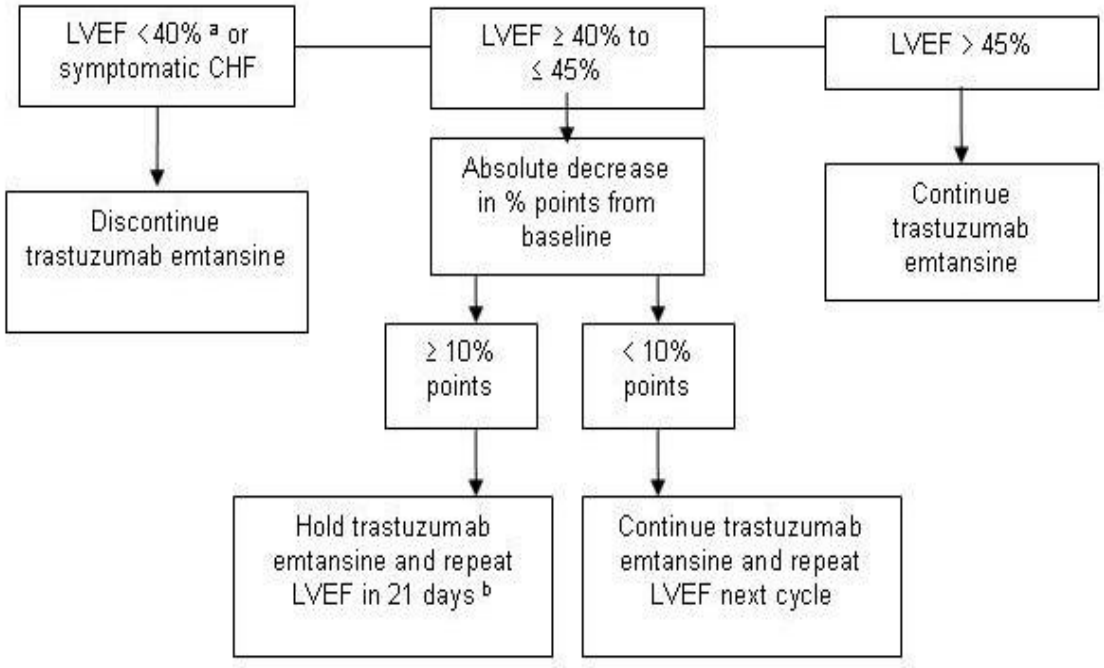
In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

v. Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Appendix 4

Algorithm for Continuation and Discontinuation of Trastuzumab emtansine Based on Left Ventricular Fraction Assessments in Patients



Reference: Prescribing information Kadcyla® (Trastuzumab emtansine) Feb 2015

Appendix 5

Guidance on Temperature Excursion and Product Complaint

In case of a temperature excursion and/or any product complaint noted at the site, the following steps should be followed. The excursion aspect includes shipment excursion from IMP depot to site and excursion noted during IMP storage at site.

TEMPERATURE EXCURSION	
Excursion noted during shipment from depot to site: • Once the temperature excursion is noted upon receipt of the study drug, temperature recording of the temperature logger should be stopped. • The temperature on the IMP receipt form should be recorded. • The affected IMP should be kept in allocated bags and a 'QUARANTINE' label affixed on the bags and stored in the study refrigerator isolated/ separated from the usable stock under protocol mandated temperature conditions and the temperature on the study temperature log should be noted. • The site monitor should be informed of the excursion with details through e-mail communication. • The PD103 form (IMP Deviation Form) should be completed by the Monitor based on information provided by site and the site should be consulted for additional information, if required. • The affected IMP should not be dispensed to any subject till a decision is received in writing from Sponsor. • If approved by Sponsor in writing, the 'QUARANTINE' label should be removed from the affected IMP and released. • If rejected by Sponsor, a "DO NOT USE" label should be affixed on the bags with the affected IMP and not dispensed to any of the subjects and proceeded for destruction of the affected IMP after the approval from Sponsor • The completed PD103 form shared by Monitor, temperature recording logs and related communication from	**Excursion noted at site:** • The deviated temperature (higher/lower) and duration of excursion when the site staff noticed the excursion on the study temperature log should be noted. • The affected IMP should be transferred to another secured, temperature controlled refrigerator under protocol mandated temperature conditions and the temperature and time should be recorded on the study temperature log. • The affected IMP should be kept in allocated bags and affixed a 'QUARANTINE' label on the bags and stored in the study refrigerator isolated/ separated from the usable stock under protocol mandated temperature conditions and the temperature on the study temperature log should be noted. • The site monitor should be informed of the excursion with details through e-mail communication along with relevant temperature recording logs. • The Monitor should complete PD103 form (IMP Deviation Form) based on information provided by site and consult site for additional information, if required • The affected IMP should not be dispensed to any subject till a decision is received in writing from Sponsor. • If approved by Sponsor in writing, the 'QUARANTINE' label from the affected IMP and it may be dispensed to subjects. • If rejected by Sponsor, a "DO NOT USE" label should be affixed on the bags with the affected IMP and should not dispensed it to any of the subjects. • The completed PD103 form shared by Monitor, temperature recording logs and related communication from Sponsor on approval/ rejection, destruction record (where applicable) should be filed in

Sponsor on approval/ rejection, destruction record (where applicable) should be filed in appropriate section of the investigator site file. • The Sponsor has a timeline of 3 working days to provide approval/ rejection decision on the impacted batch of IMP.	appropriate section of the investigator site file. • The reason for temperature excursion should be identified and required assessments and corrections should be performed to avoid recurrence of the same and the details shared with sponsor. • The Sponsor has a timeline of 3 working days to provide approval/ rejection decision on the impacted batch of IMP.

In case of temperature excursions, below are the minimum details of affected IMP to be reported by site:

- Name and number of affected IMP
- Dosage Form (e.g. tablet, syringe, vial)
- Batch number and Expiry Date
- Strength
- Shipment ID (If related to shipment)
- Minimum temperature
- Duration below lower limit
- Maximum temperature
- Duration above upper limit
- Did the concerned IMP have a temperature deviation before?

In case of a product complaint, the following details should be provided:

- Product Name and number of affected IMP
- Dosage Form (e.g. tablet, syringe, vial)
- Batch number and Expiry Date

Examples of Product Complaints include the following, but not limited to:-

- Broken Solvent Vials
- Missing Component
- Unusual Appearance
- Smudging of Batch Number
- Defective Component/Packaging
- Reconstitution Problems
- Discoloration
- Bacterial/microbial contamination
- Size/Shape Variation
- Foreign Matter

Contact details for Product Complaint:

During Office Hours: [redacted]
Mobile [24 x7]: [redacted]
Fax: +91-22-33941054

Product Complaint Mailbox: india.productcomplaints@roche.com

Adverse Event Mailbox: india.drugsafety@roche.com

Reporting Timelines: within ONE business day.

The site monitor should be copied on all e-mail communications. In case of any issues or clarification, please feel free to contact your site monitor.