Official Title: An Indian Multicentric Open Label Prospective Phase IV Study to Evaluate Safety and Efficacy of Trastuzumab in Her2 Positive, Node Positive or High Risk Node Negative Breast Cancer as Part of a Treatment Regimen Consisting of Doxorubicin, Cyclophosphamide, With Either Docetaxel or Paclitaxel (AC-TH) or Docetaxel and Carboplatin (TCH)

NCT Number: NCT02419742

Document Date: Protocol Version 1: 29-July-2013

CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER ML28714

AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE PHASE IV STUDY TO EVALUATE SAFETY AND EFFICACY OF TRASTUZUMAB IN HER2 POSITIVE, NODE POSITIVE OR HIGH RISK NODE NEGATIVE BREAST CANCER AS PART OF A TREATMENT REGIMEN CONSISTING OF DOXORUBICIN, CYCLOPHOSPHAMIDE, WITH EITHER DOCETAXEL OR PACLITAXEL(AC→TH) OR DOCETAXEL AND CARBOPLATIN (TCH)

PROTOCOL APPROVAL

Protocol Number :	ML28714
Version No:	1.0
Date: (DD-MMM-YYYY)	29-JUL-2013

Protocol approved by:

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

Signature

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

Signature

[redacted] - **Statistician**
MakroCare Clinical Research Limited

Signature

Confidentiality Statement

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PROTOCOL ACCEPTANCE FORM

STUDY TITLE : **AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE PHASE IV STUDY TO EVALUATE SAFETY AND EFFICACY OF TRASTUZUMAB IN HER2 POSITIVE, NODE POSITIVE OR HIGH RISK NODE NEGATIVE BREAST CANCER AS PART OF A TREATMENT REGIMEN CONSISTING OF DOXORUBICIN, CYCLOPHOSPHAMIDE, WITH EITHER DOCETAXEL OR PACLITAXEL(AC→TH) OR DOCETAXEL AND CARBOPLATIN (TCH)**

PROTOCOL NUMBER : ML28714

VERSION NUMBER : 1.0

EUDRACT NUMBER: NA

IND NUMBER : NA

TEST PRODUCT : Trastuzumab (Ro 45-2317)
Made for *F. Hoffmann-La Roche Ltd*

MEDICALMONITOR: 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 return a copy of the form as instructed by your local study monitor.

Please retain the original for your study files.

PROTOCOL SYNOPSIS	
TITLE:	**AN INDIAN MULTICENTRIC OPEN LABEL PROSPECTIVE PHASE IV STUDY TO EVALUATE SAFETY AND EFFICACY OF TRASTUZUMAB IN HER2 POSITIVE, NODE POSITIVE OR HIGH RISK NODE NEGATIVE BREAST CANCER AS PART OF A TREATMENT REGIMEN CONSISTING OF DOXORUBICIN, CYCLOPHOSPHAMIDE, WITH EITHER DOCETAXEL OR PACLITAXEL (AC→TH) OR DOCETAXEL AND CARBOPLATIN (TCH)**
PROTOCOL NUMBER:	ML28714
VERSION NUMBER:	1.0
EUDRACT NUMBER:	NA
IND NUMBER:	NA
TEST PRODUCT:	Trastuzumab
PHASE:	IV Post marketing study
INDICATION:	HER2 positive early breast cancer
SPONSOR:	Roche Products India Pvt. Ltd. The View, 2nd floor, 165, Dr Annie Besant Road, Worli, Mumbai-400018, India

Objectives:

Primary Objectives:

The primary objective for this study is as follows:

- To evaluate the safety of Trastuzumab for the treatment of HER2-positive node positive or high risk node negative breast cancer patients with regimen consisting of doxorubicin and cyclophosphamide followed by either paclitaxel or docetaxel (AC→TH) or a regimen consisting of docetaxel and carboplatin (TCH) in Indian population.

Secondary Objectives:

The secondary objectives for this study are as follows:

- To determine the disease free survival (DFS)
- To determine the overall survival (OS)

Study Design:

Description of Study

This is a prospective, phase IV, multi-center, single arm, open-label, interventional study in patients with HER2-positive node positive or high risk node negative breast cancer. A total of approximately 109 patients will be enrolled at approximately 10 sites across India. Patients eligible as per the inclusion and exclusion criteria will be treated with either AC→TH or TCH treatment regimens.

The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigators' discretion referring the local prescribing document of Trastuzumab.

AC→TH regimen:

- Every 3 weeks for 4 cycles, patients in the AC→TH regimen will be receiving 60 mg/m2 doxorubicin as a 5 to15 minute I.V. bolus injection followed by 600 mg/m2 cyclophosphamide as a 5 to 60 minute I.V. bolus injection.
- On Day 1 of Cycle 5, 4-mg/kg Trastuzumab loading dose will be administered as a 90 minute I.V. infusion as a weekly regimen OR 8-mg/kg Trastuzumab loading dose will be administered as a 90-minute I.V. infusion as a 3 weekly regimen at Investigator's discretion.
- If weekly regimen of Trastuzumab is selected, on Day 8 of Cycle 5, 2 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion and 2mg/ kg every week as a weekly regimen will be given OR beginning on Day 1 of Cycle 6, Trastuzumab 6 mg/kg will be administered as a 30-minute I.V. infusion every 3 weeks as a 3 weekly regimen for four cycles.

- Docetaxel 100 mg/m^2 or Paclitaxel 175 mg/m^2 (at investigator's discretion) will be administered as a 1 hour I.V. infusion every 3 weeks for four cycles, beginning on Day 1 of Cycle 5 and continued for up to Cycle 8.
- Three weeks after the last treatment with docetaxel/paclitaxel (i.e., on Day 1 of Cycle 9), 6 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion every 3 weeks. Trastuzumab treatment will be continued up to cycle 22 (completing a total 52 week trastuzumab therapy).

TCH regimen:

- Trastuzumab will be given intravenously at a dose of 4 mg/kg loading dose administered as a 90 minute I.V. infusion followed by 2 mg/kg administered as a 30 minute I.V. infusion weekly as a weekly regimen or 8-mg/kg Trastuzumab loading dose administered as a 90 minute I.V. infusion followed by 6 mg/kg administered as a 30 minute I.V. infusion 3 weekly as a 3 weekly regimen during chemotherapy from cycle 1 to 6 at Investigator's discretion.

- Every 3 weeks for six cycles, patients in the TCH regimen will be receiving 75 mg/m^2 docetaxel as a 60-minute I.V. bolus injection followed by AUC 6 x (GFR + 25) carboplatin as a 30 to 60 minute I.V. bolus injection.

- After completion of chemotherapy, Trastuzumab will be administered at a dose of 6 mg/kg every 3 weeks up to cycle 18 (completing total 52 week trastuzumab therapy)

The patient will be followed up for duration of 12 months from the last dose of Trastuzumab. All adverse events occurring during treatment and this follow up period will be captured.

Number of Patients

A total of approximately 109 patients will be enrolled at approximately 10 sites across India.

Target Population

Patients must meet the following criteria for study entry:

Inclusion criteria:

- Able and willing to give written informed consent and comply with the requirements of the study protocol
- Adult female patients, ≥18 years of age
- Histologically confirmed early invasive HER2 positive, node positive or high risk node negative breast cancer with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage I to IIIA that is eligible for adjuvant treatment with Trastuzumab

- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- HER2 over-expression/amplification defined as either IHC3+, or IHC2+ and FISH-positive as determined in a central laboratory.
- At time of starting Trastuzumab therapy, Left ventricular ejection fraction (LVEF) measured by echocardiography.
- Screening left ventricular ejection fraction (LVEF) ≥ 55%
- Adequate bone marrow, renal, and hepatic function
- Agreement to use an adequate, non-hormonal means of contraception by women of childbearing potential.

Exclusion Criteria:

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

- Any contraindication to Trastuzumab
- Previous adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
- History of other malignancy, except for curatively treated carcinoma in situ of the cervix or basal cell carcinoma and patients with other curatively treated malignancies who have been disease-free for at least 5 years
- Past history of ductal carcinoma in situ and/or lobular carcinoma that has been treated with any systemic therapy or with radiation therapy to the ipsilateral breast where the invasive cancer subsequently develops
- Locally advanced (stage IIIB and IIIC) and Metastatic disease (stage IV)
- Clinically relevant cardiovascular disorder or disease
- Uncontrolled hypertension, or history of hypertensive crisis or hypertensive encephalopathy
- History of severe allergic or immunological reactions, e.g. difficult to control asthma
- Pregnant or lactating women

Length of Study

The study is estimated to last approximately 4 years, based on an expected 18-month recruitment, 12 months of study treatment and 12 months of follow-up after the treatment.

End of Study

End of study is defined as the last patient last visit in the follow-up period. The study will end when all patients have been followed for at least 12 months after their last study treatment, or if withdrawal from the study, lost to follow up or death. The final analysis of OS and DFS will be conducted and updated safety parameters will be summarized at this stage.

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Disease free survival rate (DFS) and Overall Survival rate (OS).

As per institutional practice or American Society of Clinical Oncology (ASCO) adjuvant follow-up guidelines 2006, Breast cancer assessments for DFS and OS are to be reported for every 6 months.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All Adverse Event (AE) and Serious Adverse Event (SAE) as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

- Cardiac function will be evaluated by measuring LVEF by echocardiography. Symptomatic left ventricular dysfunction (congestive heart failure [CHF]) will be graded according to the New York Heart Association functional classification.

- AEs and SAEs related to Trastuzumab will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or greater.

- Patients will undergo a Safety Follow-up, 4 weeks after their last dose of study treatment.

- Cardiac function will be evaluated by measuring LVEF by echocardiography. Symptomatic left ventricular dysfunction (congestive heart failure [CHF]) will be graded according to the New York Heart Association functional classification.

- AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all adverse events and adverse events related to study drug.

- Adverse events will also be summarized by toxicity grade, outcome, seriousness and action taken to the study medication.

Investigational Medicinal Products

Not Applicable as the test product is licensed for use in the study disease and will be used in the same form and dose as approved.

Test Product

Trastuzumab- Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2).

Test drug administration: Trastuzumab will be administered as weekly or 3 weekly regimens at the investigator's discretion.

Weekly regimen:

Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes followed by subsequent dose of 2 mg/kg as an intravenous infusion over 30 minutes every week.

Three weekly regimen:

Initial dose of 8 mg/kg as an intravenous infusion over 90 minutes followed by subsequent dose of 6 mg/kg as an intravenous infusion over 30 minutes every three weeks.

Non-Investigational Medicinal Products

Anthracycline based therapy (AC→TH protocol)

Doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles, followed by docetaxel (100 mg/m^2 every 3 weeks for 4 cycles) or paclitaxel (175 mg/m^2 every 3 weeks for 4 cycles). Trastuzumab is started concurrently with docetaxel or paclitaxel and continued to complete 52 weeks therapy. Dose and frequency of administration of taxanes is at investigator's discretion.

Non-anthracycline based therapy (TCH protocol)

Docetaxel (75 mg/m^2) and carboplatin (AUC, 6 mg/ml/min x (GFR + 25)) every 3 week for 6 cycles will be given along with adjuvant therapy of Trastuzumab to complete 52 weeks therapy.

All the chemotherapeutic agents will administered as per the local prescribing information.

Comparator

There is no comparator as it is a single arm interventional trial.

Statistical Methods

Descriptive statistics will be calculated in the analysis for all safety, efficacy and laboratory parameters at defined courses, specified in the study schedule assessment.

Safety Analysis

- Safety measurements include adverse events, laboratory tests (hematology and biochemistry), vital signs, electrocardiograms, physical examinations, and toxicity evaluations.

- Toxicities will be evaluated at each course of therapy using the NCI-CTCAE version 4.0 or a non-CTC grading scale for toxicities that are not covered by the NCI CTC.

- Adverse Event (AE) and Serious Adverse Event (SAE) related to Trastuzumab will be summarized by using number and percentage (Incidence of AEs and SAEs). AEs and SAEs related to Trastuzumab will be coded using MedDRA, version 15.1 or greater.

- AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all adverse events and adverse events related to study drug. Adverse events will also be summarized by toxicity grade, outcome, seriousness and action taken to the study medication.

- All the Laboratory evaluations (hematology & biochemistry) will be considered at baseline and completion/early termination visits. Change from Baseline will be calculated for all the available hematology and biochemistry parameters as specified in the CRF pages.

- ECOG performance status will be collected at baseline and every 4 Cycles during treatment period. Counts and percentages will be reported in the results.

- Patient data will be analyzed for evidence of cumulative toxicity with repeated courses of therapy. Summary of ECG status will be evaluated at all visits. Counts and percentages will be reported in the results.

- HER-2 testing will be collected at Baseline/Screening.

- LVEF will be collected for every 3 months or and percentage change from baseline will be reported for every 3 months.

Efficacy analysis

- Efficacy measurements include Disease free survival and Overall survival.

- DFS is defined as time from the date of first study treatment to the date of local, regional or distant recurrence, contra-lateral breast cancer or death due to any cause.

- OS is defined as time from the date of first study treatment until date of death, regardless of the cause of death.

- These variables will be summarized by the Kaplan Meier method, and KM plots will be provided.

Determination of Sample Size

A total of approximately 109 subjects will be required to conduct a phase IV study to evaluate safety and efficacy of Trastuzumab in HER2 positive node positive or high risk node negative breast cancer by assuming level of significance 5%, incidence of adverse event 65.9%, precision 10% and dropout rate 20%.

Justification for Sample size

Incidence of adverse event in AC→TH group with Grade 3 or 4 hematologic events such as neutropenia, leucopenia, febrile neutropenia, neutropenic infection, anemia, thrombocytopenia, leukemia were 71.5%, 60.3 %, 10.9%, 11.9%, 3.1%, 2.1% and 0.1% respectively. In TCH group incidence of adverse event with Grade 3 or 4 hematologic events such as neutropenia, leucopenia, febrile neutropenia, neutropenic infection, anemia, thrombocytopenia, leukemia were 65.9%, 48.2 %, 9.6 %, 11.2%, 5.8%, 6.1% and 0.1% respectively.[1]

While considering the 71.5%, the highest incidence of adverse event in AC→TH group, sample size of 99 patients will be required. Similarly, by considering the highest incidence of adverse event 65.9% in TCH group, sample size of 109 patients will be required. Also considered the incidence of 68.7% (i.e. mean of 71.5% and 65.9%), 104 patients will be required. The above three calculations, assumed a 5% level of significance, 10% precision and 20% dropout rate. Considering all the above calculation, it is suggested that approximately 109 patients will be required for the proposed study.

Interim Analyses
No Interim Analysis Planned for this study.

Procedures (Summary)

During screening and baseline phase following assessments will be carried to evaluate the subject eligibility:

Informed consent, allocation of subject number, demographics, physical examination, vital signs, inclusion and exclusion criteria, relevant medical history, previous and concomitant medication details, confirmation of early breast cancer disease by histology, radiography (mammogram), (tumor size < 5 cm and < 4 positive lymph nodes), CT/MRI, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), measurement of LVEF by echocardiography, haematology and biochemistry assessment.

HER2-positive status on fixed tissue blocks from the primary tumor assessed by IHC (immuno histochemistry) and/or FISH (fluorescence insitu hybridisation) according to institutional criteria.

Administration of treatment regimen:

The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigators' discretion.

Order of administration in **AC→TH protocol** : Post AC therapy, Trastuzumab first followed by docetaxel/paclitaxel.

Drug	Dose	Administration Guideline
Cycles* 1-4		
Doxorubicin	60 mg/m^2	Administered as I.V. bolus over 5 to15 min.
Cyclophosphamide	600 mg/m^2	Administered I.V. over 5 to 60 min. (use non-PVC equipment).
Cycles 5-8		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week or 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 weeks	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 90 minutes post infusion • Maintenance dose: I.V. in 250 mL NS over 30 min on all the doses, observe for 30 minutes post infusion.
Taxane	Docetaxel (100 mg/m^2) or Paclitaxel (175 mg/m^2)	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Cycles 9 to 22		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 week	I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

<u>Order of administration in TCH protocol:</u> Trastuzumab first, docetaxel second, carboplatin third.

Drug	Dose	Administration Guideline
Cycle* 1-6		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week or 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 week	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 1 hour post-infusion • Maintenance dose: I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.
Docetaxel	75 mg/m^2	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Carboplatin	Dose = AUC 6 x (GFR + 25)	Administered I.V. in 500 mL D5W over 30 to 60 min
Cycle 7 to 18		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 weeks	• I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

As per institutional practice or American Society of Clinical Oncology (ASCO) adjuvant follow-up guidelines 2006, Breast cancer assessments for DFS and OS are to be reported for every 6 months.

American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

- History/physical examination - every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually.
- Mammography - first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.

- Pelvic examination - regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI) and tumor marker assessments (CA 15-3, CA 27.29, and CEA).

However, bone scan, liver imaging, and brain CT scan will be performed if clinically indicated.

During treatment period

- Safety parameters will be assessed for every cycle.
- Vital signs, physical examination and treatment compliance will be performed for every cycle and subject safety will be evaluated.
- LVEF and ECG will be assessed for every 3 months (4 cycles) to evaluate cardiac safety of the patients.
- ECOG will be assessed for every 3 months (4 cycles) to evaluate performance status of the patients.
- Hematology and biochemistry assessments will also be performed during the study if clinically indicated.
- Routine breast cancer follow up is done at cycle 9 and 17. History/physical examination, mammography and pelvic examination will be carried out.

Follow-up Phase:

Thereafter during follow up period of one year, cardiac assessments at 6 and 12 months following treatment cessation will be done. Survival follow-up can be performed by regular telephonic calls and/or clinic visits every 6 months.
Please see Appendix 1 and 2 for schedule of assessments.

Appendix 1- Schedule of Assessments (AC→TH protocol)

	Screening and baseline	Treatment Period (Cycle/Week)																						Unplanned Visit [a]	Completion/Early Termination Visit [b]	Follow-Up [c]
Week	–2 to –1	1	4	7	10	13	16	19	22	25	28	31	34	37	40	43	46	49	53	56	59	62	65			
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22			
Informed consent	X																									
Inclusion & Exclusion Criteria	X																									
Demographic data	X																									
General medical history and baseline conditions	X																									
Vital signs [d]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	X																									
Physical examination [e]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [f]	X																								x	
Histology	X																									
Radiography (mammogram)	X																								x	
CT/MRI	X																								x	
Biochemistry [g]	X																								x	
LVEF(measured by Echocardiography)	X					x				x				x				x				x			x	x
12 Lead ECG	X					x				x				x				x				x			x	x

HER2 testing	X																									
ECOG	X					x				x				x				x				x			x	x
Chemotherapy [h]		x	x	x	x	x	x	x	x																	
Trastuzumab administration [i]						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Routine Breast Cancer follow up [j]	X									x								x							x	
Treatment compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Survival																										x

eCRF = electronic Case Report Form.

Notes: All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Visit not specified by the protocol.

[b] Patients who complete the study or discontinue from the study early will be asked to return to the clinic 4 weeks after the last dose of study drug for a follow-up visit.

[c] Follow-up information will be collected via telephone calls and/or clinic visits every 6 months until death, loss to follow-up, or study termination by the Sponsor.

[d] Respiratory rate, pulse rate, temperature, systolic and diastolic blood pressure, before and after trastuzumab infusion.

[e] Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.

[f] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells). Hematology assessment will also be performed during the study, if clinically indicated.

[g] Includes sodium, potassium, chloride, bicarbonate, fasting glucose, BUN or urea, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus, magnesium, LDH, creatine phosphokinase, uric acid. Biochemistry assessment will also be performed during the study, if clinically indicated.

[h] Doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles (Cycles 1 to 4), followed by docetaxel (100 mg/m^2) or paclitaxel (175 mg/m^2 every 3 weeks for 4 cycles (Cycles 5 to 8).

[i] The selection of the dosage regimen from cycle 5 to 8 (weekly or 3 weekly) at investigators' discretion. After completion of chemotherapy, Trastuzumab will be administered every 3 weeks from cycle 9 to cycle 22 (so as to complete total of 52 week Trastuzumab therapy).

[j] History/physical examination, mammography and pelvic examination will be carried out during the routine breast cancer follow-up.

Appendix 2 - Schedule of Assessments (TCH protocol)

	Screening and baseline	Treatment Period (Cycle/Week)																		Unplanned Visit [a]	Completion/Early Termination Visit [b]	Follow-Up [c]
Week	–2 to –1	1	4	7	10	13	16	19	22	25	28	31	34	37	40	43	46	49	53			
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			
Informed consent	X																					
Inclusion & Exclusion Criteria	X																					
Demographic data	X																					
General medical history and baseline conditions	X																					
Vital signs [d]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	X																					
Physical examination [e]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [f]	X																				x	
Histology	X																					
Radiography (mamogram)	X																				x	x
CT/MRI	X																				x	x
Biochemistry [g]	X																				x	
LVEF (measured by Echocardiography)	X					x				x				x				x			x	x
12 Lead ECG	X					x				x				x				x			x	x
HER2 testing	X																					
ECOG	X					x				x				x				x			x	x

Chemotherapy [h]		x	x	x	x	x	x															
Trastuzumab administration [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Routine Breast Cancer follow up [j]	X									x								x			x	
Treatment compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Survival																						x

eCRF = electronic Case Report Form.

Notes: All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Visit not specified by the protocol.

[b] Patients who complete the study or discontinue from the study early will be asked to return to the clinic 4 weeks after the last dose of study drug for a follow-up visit.

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[e] Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.

[f] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells). Hematology assessment will also be performed during the study, if clinically indicated.

[g] Includes sodium, potassium, chloride, bicarbonate, fasting glucose, BUN or urea, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus, magnesium, LDH, creatine phosphokinase, uric acid. Biochemistry assessment will also be performed during the study, if clinically indicated.

[h] Docetaxel (75 mg/m2) and carboplatin (AUC, 6 mg/ml/min x (GFR + 25)) every 3 week for 6 cycles.

[i] The selection of the dosage regimen from cycle 1 to 6 (weekly or 3 weekly) at investigators' discretion. After completion of chemotherapy, Trastuzumab will be administered every 3 weeks from cycle 7 to cycle 18 (so as to complete 52 week Trastuzumab therapy).

[j] History/physical examination, mammography and pelvic examination will be carried out during the routine breast cancer follow-up.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation		Definition
AC→TH		Regimen consisting of Doxorubicin and Cyclophosphamide followed by either Paclitaxel or Docetaxel
ADCC		Antibody-Dependent Cell-Mediated Cytotoxicity
AE		Adverse Event
AGC		Advanced Gastric Cancer
ALT		Alanine aminotransferase
ASCO		American Society of Clinical Oncology
AST		Aspartate aminotransferase
BWFI		Bacteriostatic Water For Injection
CHF		Congestive Heart Failure
CHO		Chinese Hamster Ovary
CISH		Chromogenic in situ Hybridization
CRF		Case Report Form
CTCAE		Common Terminology Criteria for Adverse Events
CMF		Cyclophosphamide plus Methotrexate plus Fluorouracil
DCIS		Ductal Carcinoma in situ
DFS		Disease Free Survival
DR		Duration of Response
EC		Ethics Committee
ECG		Electrocardiogram
ECOG		Eastern Cooperative Oncology Group
eCRF		electronic Case Report Form
EGFR		Epidermal Growth Factor Receptor
EFS		Event-Free Survival
FDA		Food and Drug Administration
FISH		Fluorescence in situ Hybridization
HER2		Human Epidermal growth factor Receptor 2

HERA		Herceptin Adjuvant Trial
HIPAA		Health Insurance Portability and Accountability Act
HR		Hazard Ratio
ICH		International Conference on Harmonisation
ICMR		Indian Council of Medical Research
IHC		Immuno Histo Chemistry
IMP		Investigational Medicinal Product
IND		Investigational New Drug (application)
IRB		Institutional Review Board
IxRS		Interactive Voice and Web Response System
LPLV		Last patient, Last visit
LVEF		Left Ventricular Ejection Fraction.
MBC		Metastatic Breast Cancer
mEDC		MakroCare Electronic Data Capture
NCI		National Cancer Institute
NSCLC		Non-Small Cell Lung Cancer
OS		Overall Survival
ORR		Objective Tumor Response Rate
PBCR		Population-Based Cancer Registries
pCR		pathological Complete Response
PD		Pharmacodynamic
PK		Pharmacokinetic
SAE		Serious Adverse Event
SWFI		Sterile Water For Injection
TCH		Regimen consisting of Docetaxel and Carboplatin
TTP		Time to disease Progression
UICC		International Union Against Cancer
ULN		Upper Limit of Normal
VEGF		Vascular Endothelial Growth Factor

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer (BC) is the most common cancer in women (23% of all cancers), with a global prevalence of more than 1 million patients and an annual mortality rate of approximately 450,000 deaths (American Cancer Society). Breast cancer has a widely variable incidence between countries and regions. The developed countries with a small proportion of the world population account for almost 50% of breast cancers diagnosed worldwide.[2] The lowest breast cancer incidence is reported from Far Eastern and South-East Asian countries.[3,4] In the developing countries of Asia, the health care burden on account of breast cancer has been steadily mounting. It is expected that in the coming decades, these countries would account for majority of new breast cancer patients diagnosed globally. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India.[5] As per the Indian Council of Medical Research (ICMR)- population-based cancer registries (PBCR) data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum where it constitutes > 30% of all cancers in females. In the rural PBCR of Barshi, breast cancer is the second commonest cancer in women after cancer of the uterine cervix.[6] In Europe and North America, most breast cancers are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread, and can be treated with curative intent. In Europe, around 79% are potentially operable (stage T1-3/N0/+M0), 7% are locally advanced (T4/Nx/M0), and 6% are metastatic (M1) at diagnosis.[7,8]

According to a study conducted in four major cities (Mumbai, Trivandrum, Chennai and Lucknow) of India, the percentage incidence in various stages of Early Breast cancer was, stage I - 7.8%, 4.4%, 1% and 4%; stage II – 57.4%, 42.3%, 23% and 33%; stage III – 28.9%, 40.5%, 52% and 47%).[9] In another study done in a large cohort of patients managed over a long time period at a New Delhi hospital, it was noted that the percentage incidence of stage III-a (27%) predominated, followed by II-b (16%) and stage I (1.4%).[10] The etiology of breast cancer is unclear, although it is likely that hormonal and genetic factors play a role.[11] The incidence of breast cancer increases with age, doubling every year up until menopause.[12] Risk factors include early age of first menarche, later age of first full term pregnancy, late menopause and a family history of breast cancer.[13]

1.1.1 Role of Human Epidermal Growth Factor Receptors (HER2) status

The human epidermal growth factor receptor 2 (HER2, HER2/neu, c-erbB-2) gene, first discovered in 1984,[14] is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein that is a member of the epidermal growth factor receptor (EGRF), or HER, family.[15] This HER family of four receptors mediates the growth, differentiation and survival of cells.[16,17,18] The evidence that increased expression and activity of HER2 induces cell transformation and tumorigenesis is overwhelming. In BC, unlike a variety of other epithelial malignancies, HER2 gene amplification is uniformly associated with HER2 (p185neu) protein overexpression.

HER2 gene amplification and/or protein overexpression has been associated with aggressive tumor behaviour, including increased cell proliferation, cell motility, tumor invasiveness, progressive regional and distant metastases, accelerated angiogenesis, and reduced apoptosis and poor prognosis.[15,19,20,21,22,23] A review of 107 studies involving 39,730 BC patients found that in the majority (88%) of the studies, either HER2 gene amplification or HER2 (p185neu) protein overexpression predicted BC outcome by either univariate or multivariate analysis.[17] The frequency of HER2-positivity in these studies ranged from 9% to 74% (mean 22.2%). However, in current practice, most investigators report that the true HER2-positive rate is in the range of 15%–20%.[17,24] The major slide-based HER2 testing approaches include immunohistochemistry (IHC), fluorescence in situ hybridization, and chromogenic in situ hybridization. Her2/neu positivity was present in 27.10 % of cases in a study done in south Indian population[25] and 29% of HER2+ subtype in another study.[26] Studies have shown that women whose tumors exhibit either amplification of the HER2 gene or overexpression of its encoded protein have a more aggressive form of BC that is associated with significantly shortened disease-free and overall survival (OS) compared with women whose tumors do not over express HER2.[27]

1.1.1.1 Treatment Options For early Breast Cancer

Breast cancer prognosis and treatment options are generally based on AJCC staging/ TNM classification. Surgery is the main modality of local treatment for early breast cancer (eBC) and (with or without radiotherapy) can control loco-regional disease in the majority of patients. However, a significant percentage of patients relapse after loco-regional treatment and develop metastases. Systemic chemotherapy or endocrine therapy in hormone receptor-positive patients reduce the risk of relapse and are given either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy). In recent decades, the use of adjuvant systemic therapies in eBC has increased extensively and has most likely contributed to the substantial decline in BC mortality observed in the U.S. and in some European countries.[28,29,30]

In the last few years, there has been accelerated progress in the treatment of eBC, with the introduction of taxanes and aromatase inhibitors, and, most impressively, trastuzumab (a humanized anti-ERBB2 monoclonal antibody) to the adjuvant portfolio.[29] Cytotoxic chemotherapy, endocrine therapy, radiotherapy, and molecular targeted therapies currently represent the backbone of modern systemic BC treatment. Several targeted drugs with different molecular pathways have received approval for metastatic breast cancer (mBC), but trastuzumab is the only such therapy that is currently approved for adjuvant treatment of eBC.[31] The use of trastuzumab in the adjuvant setting is also supported by international treatment guidelines for women with HER2 positive BC.[32,33] The introduction of trastuzumab last decade has particularly improved the outcome for eBC patients with HER2-positive disease.

1.2 BACKGROUND ON TRASTUZUMAB

1.2.1 Trastuzumab IV

Trastuzumab is produced by a genetically engineered Chinese hamster ovary (CHO) cell line grown in large scale, which secretes Trastuzumab into the culture medium. The antibody is then purified extensively using standard chromatographic and filtration methods.

Trastuzumab for intravenous (IV) administration is supplied commercially as a lyophilized preparation in either single-use (150 mg) or multi-dose (440 mg) vials. It is formulated in histidine/histidine-HCl, α,α-trehalose dihydrate, and polysorbate 20. Following reconstitution in either sterile water for injection (SWFI) or bacteriostatic water for injection (BWFI), it is further diluted in 250 mL 0.9% sodium chloride solution for administration.

The addition of trastuzumab to standard chemotherapy increases time to progressive disease or the length of progression-free survival (PFS), and improves survival when given with chemotherapy to women with HER2-positive BC.[29,34] Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, graded 3+ by IHC, and/or with HER2 gene amplification (see Trastuzumab Summary of Product Characteristics, 2012).

Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy.[34,35] The most significant adverse event (AE) observed in patients who received trastuzumab was cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic congestive heart failure (CHF). Risk factors for cardiac failure in the setting of trastuzumab treatment include co administration with anthracycline-based chemotherapy, increasing age, declining LVEF during treatment to below the lower limit of normal, and the use of anti hypertensive medications.[36]

The efficacy and safety of trastuzumab IV have been well characterized. Trastuzumab IV is administered to eBC patients for a total duration of one year. Adjuvant trastuzumab IV may be given as monotherapy, starting after completion of adjuvant chemotherapy, or in combination with the taxane component of adjuvant chemotherapy (followed by trastuzumab monotherapy).

1.2.1.1 Clinical Pharmacokinetics of Trastuzumab

In a study of Early Breast Cancer (HERA/BO16348), using a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg q3W, a t1/2 of 16.2 days was observed (range 11.0-22.8 days).[37] Steady-state concentrations were achieved by Week 37, with mean trough and peak concentrations of 63 µg/mL and 216 µg/mL, respectively. A population PK (PPK) analysis of data from the single-agent trials (H0407g, H0551g, and H0649g) showed that the mean t1/2 of Trastuzumab is 28.5 days (95% confidence interval [CI] 25.5-32.8 days).[38] These data are supported by a later PPK analysis in 194 patients using data from four Phase I and II trials (BO15935, WO16229, BO15899 and M77004) in which the typical population PK parameter values reported were clearance (CL) = 0.226 L/day and volume of distribution of the central compartment (Vc) = 3.17 L,[39] which supported the 3-weekly dosing regimen. An update to this PPK analysis which added data from 71 patients in the intensive loading dose regimen (MO16892), confirmed the primary PK parameter values as CL = 0.241 L/day, Vc = 3.02 L and terminal half-life of about 3 weeks.[40]

When Trastuzumab was administered in combination with: paclitaxel, docetaxel, paclitaxel plus doxorubicin, cisplatin and either capecitabine or 5-fluorouracil, Trastuzumab did not alter the plasma concentrations of the chemotherapeutic agents or the metabolites that were analyzed. In addition, Trastuzumab serum concentrations were not altered by the chemotherapeutic agents that were given in combination with it for the treatment of breast cancer patients.

1.2.2 Efficacy of trastuzumab in Early Breast Cancer (Adjuvant setting)

Six phase III multi-centre randomized controlled trials investigated the efficacy and safety of adjuvant trastuzumab IV in combination with or after standard adjuvant chemotherapy in the treatment of early breast cancer:

- Herceptin Adjuvant (HERA, BO16348) trial.[41,30,42]
- North Central Cancer Treatment Group trial (NCCTG) N9831 trial.[29,43,44,45]
- National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31.[46,44,45]
- Breast Cancer International Research Group (BCIRG-006) study.[1,47]
- Protocol Adjuvant dans le Cancer du Sein (PACS04) trial.[48]
- Finland Herceptin (FinHer) trial.[49]

Together, these trials accrued more than 15,000 women with node-positive or high-risk node-negative BC and used a variety of cytotoxic agents in various combinations, doses, and orders of administration. Four of these trials (HERA, N9831, B31 and BCIRG-006) are considered pivotal.

In the HERA study, trastuzumab treatment was started following completion of an approved neoadjuvant or adjuvant chemotherapeutic regimen (and radiotherapy as indicated) and continued for one or two years. In studies B31, N9831 and BCIRG-006, trastuzumab started after completion of four cycles of doxorubicin/cyclophosphamide and was administered for one year, either concurrently with four cycles of taxane chemotherapy (B31, N9831), or concurrently with six cycles of a non-anthracycline-containing taxane-based regimen (BCIRG-006), or after completion of chemotherapy.

The Breast Cancer International Research Group 006 (BCIRG-006) conducted a randomized trial on 3222 women with HER2-positive, invasive, high-risk, node-negative or node-positive adenocarcinoma (stage T1, T2, or T3) from 41 countries to receive a standard adjuvant anthracycline–taxane chemotherapy regimen, the same regimen plus trastuzumab, or a new non-anthracycline, trastuzumab-based regimen.

All four pivotal randomized controlled trials (HERA, N9831, B31 and BCIRG-006) demonstrated significantly improved DFS, and three (HERA, B31 and BCIRG-006) demonstrated significantly improved OS. The DFS benefits were observed regardless of age, nodal status, hormonal status, or tumor size in all trials.[1,47,50] Importantly, the most recent follow-up data from the HERA trial[29] and the combined analysis of the NCCTG N9831 and NASBP B-31 trials[47] both demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over a median follow-up of 8 years. Further, the significant benefits in DFS and OS were maintained over a median follow-up of approximately 5½ years in the BCIRG-006 study,[1] which is the longest follow-up reported to date. The long-term clinical benefits of one-year trastuzumab treatment clearly continue to outweigh the risks of adverse effects[47] and the regimen is considered standard of care with support from all major treatment guidelines.[32,33]

Of the four pivotal randomized trials, the N9831 study was the only one to directly compare the concurrent and sequential use of trastuzumab. This study identified a strong trend for a 25% reduction in the risk of an outcome event when trastuzumab is started concurrently as compared to sequentially after paclitaxel.[45] Therefore, based on a positive risk/benefit ratio, the authors recommended that trastuzumab be incorporated in a concurrent fashion when administered with paclitaxel,[45] which also resulted in the approval of the concurrent use of trastuzumab and chemotherapy.

For further details, refer to the current Herceptin (Ro 45-2317, Trastuzumab) IB.

1.2.3 Safety of Trastuzumab IV

1.2.3.1 Cardiac Safety of Trastuzumab IV

The most clinically relevant AE associated with trastuzumab IV is left ventricular cardiac dysfunction (e.g. CHF). In patients with HER2-positive eBC enrolled in pivotal clinical trials, trastuzumab treatment for 1 year (administered concurrently or sequentially with chemotherapy) appeared to be associated with a decrease in LVEF, an increase in the incidence of CHF (where specified, this was severe [New York Heart Association or NYHA] class III or IV or grade 3 or 4 or symptomatic CHF) and discontinuation of treatment as a result of cardiac Aes.[51] Cardiac toxicity described as NYHA class III/IV CHF occurred in 0%–0.9% of patients in the control arms and in 0%–3.8% of patients in the trastuzumab-containing arms of the four pivotal trials (HERA, N9831, B31 and BCIRG-006). However, the cardiotoxicity observed with concurrent or sequential trastuzumab treatment appeared to be mostly reversible following trastuzumab discontinuation, and no significant increase in cardiac death was reported.[51]

An overview of cardiac safety data from selected trials of trastuzumab in combination with a taxane after anthracyclines for HER2-overexpressing eBC shows rates of symptomatic or severe CHF of < 4% and asymptomatic declines in left ventricular ejection fractions of > 10 points in ≤ 30% of patients. However, inter-study comparisons of chemotherapy-induced cardiac dysfunction are difficult because of the use of different definitions of cardiac dysfunction and different parameters for assessing cardiac safety.[52] These levels were considered below safety cut-off points set by the individual studies' independent data monitoring committees.[53]

The NeoALTTO trial recorded no major cardiac dysfunction, with only one patient having a left ventricular ejection fraction of less than 50% and a decrease of more than 10% from baseline in trastuzumab group.[54]

The NSABP B-31 trial determined the 5-year cumulative cardiac event rate (NYHA class III or IV CHF or cardiac death) to be 3.8% in patients randomly assigned to trastuzumab versus 0.9% in patients who received chemotherapy alone.[55,56] In the NCCTG N9831 trial, the incidence of CHF was 0% in the chemotherapy-alone arm, 2.2% in patients who received sequential chemotherapy and trastuzumab, and 3.3% in patients who received concurrent chemotherapy and trastuzumab. An independent adjudication of the cardiac events occurring in studies B-31 and N9831 determined that the incidence of symptomatic heart failure events was 2.0% in trastuzumab-treated patients compared with 0.45% in the chemotherapy-alone arm, and that and the majority (86%) of these patients recovered with appropriate treatment.[56]

The long-term incidence of cardiac AEs in patients with eBC who were treated with trastuzumab IV for 1 year after completion of neoadjuvant or adjuvant chemotherapy was also evaluated in the HERA trial. Of the 1,698 patients randomly assigned to observation and 1,703 randomly assigned to 1 year of trastuzumab treatment, 94% had been treated with anthracyclines. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% vs. 0.0%, respectively; confirmed significant LVEF decreases, 3.6% vs. 0.6%, respectively). In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery.[57]

1.2.3.2 Post-marketing Safety Summary of Trastuzumab IV

It is estimated that over one million patients have been treated with trastuzumab IV as of October 2011 (Roche, Data on file).

The most common (occurring in ≥1 out of 10 treated patients) adverse reactions are infusion-associated symptoms such as fever and chills, usually following the first infusion of trastuzumab IV. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab IV infusions in up to 40% of patients. Other very common (≥1/10 patients) adverse reactions include febrile neutropenia, tremor, dizziness, headache, blood pressure changes (increase or decrease), irregular heartbeat, palpitation, cardiac flutter, decreased ejection fraction, dyspnea, wheezing, diarrhea, vomiting, nausea, lip swelling, abdominal pain, erythema, rash, swelling of the face, arthralgia, muscle tightness, myalgia, asthenia, chest pain, fatigue, influenza-like symptoms, infusion-related reaction, and pain.

Some adverse reactions to trastuzumab IV infusion can be serious and include dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. In the post-marketing setting, very rare (<1/10,000) occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of trastuzumab IV.

Severe pulmonary events leading to death have been reported with the use of trastuzumab IV in the post-marketing setting (4 out of 10,000 treated patients). Signs, symptoms, and clinical findings included interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and pulmonary insufficiency. These events may or may not occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. Other risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine and radiation therapy.

In addition, severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab IV (the exact incidence of these events is unknown). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. Symptom onset generally occurred during an infusion, but onset after the completion of an infusion has also been reported. Reactions were most commonly reported in association with the initial infusion.

The immunogenicity of trastuzumab IV has been investigated in clinical studies that included 903 MBC patients. Human anti–human antibodies to trastuzumab were detected in one patient, who had no allergic manifestations.

More detailed information on the full safety profile of trastuzumab IV is found in the Herceptin (Ro 45-2317, Trastuzumab) IB.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The human epidermal growth factor 2 (HER2) receptors are an example of tyrosine kinase receptors that, when overexpressed through gene amplification, facilitate malignant tumorigenesis.[19,20,58] Overexpression of HER2 is observed in approximately one-fifth of tumors taken from patients with breast cancer. Therefore, a strategy to antagonize the abnormal function of overexpressed HER2 was developed to improve the course of patients with HER2 overexpressing cancer.

Trastuzumab, a humanized monoclonal antibody against HER2 receptors indicated for the treatment of patients with HER2-positive MBC (first approved in 1998) and EBC (approved in 2005). Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive breast cancer and is widely used for its approved indications in both the adjuvant and metastatic settings.[15,59,33]

In India, based on BCIRG 006 trial, trastuzumab is approved for adjuvant treatment of HER2 over-expressing node positive or high risk node negative breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel or with docetaxel and carboplatin. The current study is postmarketing requirement study to gain understanding of safety of trastuzumab in Indian patients. The efficacy and safety of intravenous (IV) trastuzumab have been well characterized. The benefit to risk ratio of adjuvant trastuzumab in the current study is therefore expected to be favourable.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective for this study is as follows:

- To evaluate the safety of Trastuzumab for the treatment of HER2-positive node positive or high risk node negative breast cancer patients with regimen consisting of doxorubicin and cyclophosphamide followed by either paclitaxel or docetaxel (AC→TH) or a regimen consisting of docetaxel and carboplatin (TCH) in Indian population.

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To determine the disease free survival (DFS).
- To determine the overall survival (OS).

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a prospective, phase IV, multi-center, single arm, open-label, interventional study in patients with HER2-positive node positive or high risk node negative breast cancer. A total of approximately 109 patients will be enrolled at approximately 10 sites across India. Patients eligible as per the inclusion and exclusion criteria will be treated with either AC→TH or TCH treatment regimens.

The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigator's discretion referring the local prescribing document of Trastuzumab.

AC→TH regimen:

- Every 3 weeks for 4 cycles, patients in the AC→TH regimen will be receiving 60 mg/m2 doxorubicin as a 5 to15 minute I.V. bolus injection followed by 600 mg/m2 cyclophosphamide as a 5 to 60 minute I.V. bolus injection.

- On Day 1 of Cycle 5, 4-mg/kg Trastuzumab loading dose will be administered as a 90 minute I.V. infusion as a weekly regimen OR 8-mg/kg Trastuzumab loading dose will be administered as a 90-minute I.V. infusion as a 3 weekly regimen at Investigator's discretion.

- If weekly regimen of Trastuzumab is selected, on Day 8 of Cycle 5, 2 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion and 2mg/ kg every week as a weekly regimen will be given OR beginning on Day 1 of Cycle 6, Trastuzumab 6 mg/kg will be administered as a 30-minute I.V. infusion every 3 weeks as a 3 weekly regimen for four cycles.

- Docetaxel 100 mg/m2 or Paclitaxel 175 mg/m2 (at investigator's discretion) will be administered as a 1 hour I.V. infusion every 3 weeks for four cycles, beginning on Day 1 of Cycle 5 and continued for up to Cycle 8.

- Three weeks after the last treatment with docetaxel/paclitaxel (i.e., on Day 1 of Cycle 9), 6 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion every 3 weeks. Trastuzumab treatment will be continued up to cycle 22 (completing a total 52 week trastuzumab therapy).

TCH regimen:

- Trastuzumab will be given intravenously at a dose of 4 mg/kg loading dose administered as a 90 minute I.V. infusion followed by 2 mg/kg administered as a 30 minute I.V. infusion weekly as a weekly regimen or 8-mg/kg Trastuzumab loading dose administered as a 90 minute I.V. infusion followed by 6 mg/kg administered as a 30 minute I.V. infusion 3 weekly as a 3 weekly regimen during chemotherapy from cycle 1 to 6 at Investigator's discretion.

- Every 3 weeks for six cycles, patients in the TCH regimen will be receiving 75 mg/m2 docetaxel as a 60-minute I.V. bolus injection followed by AUC 6 x (GFR + 25) carboplatin as a 30 to 60 minute I.V. bolus injection.

- After completion of chemotherapy, Trastuzumab will be administered at a dose of 6 mg/kg every 3 weeks up to cycle 18 (completing total 52 week trastuzumab therapy)

  Patients will be followed up for duration of 12 months from the date of last dose of Trastuzumab. All adverse events occurring during treatment and this follow up period will be captured.

3.2 PROCEDURES (SUMMARY)

3.2.1 <u>During screening and baseline phase following assessments will be carried to evaluate the subject eligibility:</u>

Informed consent, allocation of subject number, demographics, physical examination, vital signs, inclusion and exclusion criteria, relevant medical history, previous and concomitant medication details, conformation of early breast cancer disease by histology, radiography (mammogram) (tumor size < 5 cm and < 4 positive lymph nodes), CT/MRI, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), measurement of LVEF by echocardiography, haematology and biochemistry assessment.

HER2-positive status on fixed tissue blocks from the primary tumor assessed by IHC (immuno histochemistry) and/or FISH (fluorescence insitu hybridisation) according to institutional criteria will be performed at central laboratory.

3.2.2 Administration of treatment regimen:

The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigators' discretion.

Order of administration in **AC→TH protocol**: Post AC therapy, Trastuzumab first followed by docetaxel/paclitaxel.

Drug	Dose	Administration Guideline
Cycles* 1-4		
Doxorubicin	60 mg/m^2	Administered as I.V. bolus over 5 to15 min.
Cyclophosphamide	600 mg/m^2	Administered I.V. over 5 to 60 min. (use non-PVC equipment).
Cycles 5-8		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week or 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 weeks	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 90 minutes post infusion. • Maintenance dose: I.V. in 250 mL NS over 30 min on all the doses, observe for 30 minutes post infusion
Taxane	Docetaxel (100 mg/m^2) or Paclitaxel (175 mg/m^2)	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Cycles 9 to 22		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 week	I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

<u>Order of administration in TCH protocol:</u> Trastuzumab first, docetaxel second, carboplatin third.

Drug	Dose	Administration Guideline
Cycle* 1-6		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week OR 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 week	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 1 hour post-infusion • Maintenance dose: I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion
Docetaxel	75 mg/m^2	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Carboplatin	Dose = AUC 6 x (GFR + 25)	Administered I.V. in 500 mL D5W over 30 to 60 min
Cycle 7 to 18		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 weeks	I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

As per institutional practice or American Society of Clinical Oncology (ASCO) adjuvant follow-up guidelines 2006, Breast cancer assessments for DFS and OS are to be reported for every 6 months.

American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

- History/physical examination - every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually.
- Mammography - first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.
- Pelvic examination - regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI), tumor marker assessments (CA 15-3, CA 27.29, and CEA).

However, bone scan, liver imaging, and brain CT scan will be performed if clinically indicated.

3.2.3 During treatment period

- Safety parameters will be assessed for every cycle.
- Vital signs, physical examination and treatment compliance will be performed for every cycle and subject safety will be evaluated.
- LVEF and ECG will be assessed for every 3 months (4 cycles) to evaluate cardiac safety of the patients.
- ECOG will be assessed for every 3 months (4 cycles) to evaluate performance status of the patients.
- Hematology and biochemistry assessments will also be performed during the study if clinically indicated.
- Routine breast cancer follow up is done at cycle 9 and 17. History/physical examination, mammography and pelvic examination will be carried out.

3.2.4 Follow-up Phase

During follow up period of one year, Cardiac assessments at 6 and 12 months following treatment cessation. Survival follow-up can be performed by telephonic calls and/or clinic visits every 6 months.

3.3 END OF STUDY

The study is estimated to last approximately 4 years, based on an expected 18-month recruitment, 12 months of study treatment and 12 months of follow-up after the treatment.

End of study is defined as the last patient last visit in the follow-up period.

The study will end when all patients have been followed for at least 12 months after their last study treatment, or if withdrawal from the study, loss to follow up or death. The final analysis of OS and DFS will be conducted and updated safety parameters will be summarized at this stage.

3.4 RATIONALE FOR STUDY DESIGN

Four pivotal randomized controlled trials demonstrated significantly improved DFS, and three (HERA, B31 and BCIRG-006) demonstrated significantly improved OS. NCCTG 9831 study compared the concurrent and sequential use of trastuzumab in treatment of HER2+ ve early breast cancer. This study identified a strong trend for a 25% reduction in the risk of an outcome event when trastuzumab is started concurrently as compared to sequentially after paclitaxel.[45] Therefore, based on a positive risk/benefit ratio, the authors recommended that trastuzumab be incorporated in a concurrent fashion when administered with paclitaxel,[45] which also resulted in the approval of the concurrent use of trastuzumab with chemotherapy. Further, BCIRG-006 study supported the concurrent use of trastuzumab and additionally explored efficacy and safety of non-anthracycline based regimen of trastuzumab. In India, based on BCIRG 006, trastuzumab is approved for adjuvant treatment of HER2 over-expressing node positive or high risk node negative breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel (anthracycline based regimen) or with docetaxel and carboplatin(non-anthracycline based regimen). In current phase IV study, use of anthracycline or non-anthracycline regimen of trastuzumab or choice of taxane will be at the discretion of the investigator. It is designed to get safety of concurrent use of trastuzumab in the adjuvant setting in Indian HER2+ve breast cancer patients.

3.4.1 Rationale for Test Product Dosage

BCIRG006, NSABP B31, NCCTG N9831 studies support the therapeutic efficacy and safety of Trastuzumab in the treatment of early stage breast cancer. The study defined and approved dosage regiment will be used. Either weekly or 3 weekly dosing of trastuzumab will be used at the discretion of the investigator. In weekly regimen, 4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week or in 3 weekly regimen 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) trastuzumab will be given every 3 week.

3.4.2 Rationale for Patient Population

Similar to the pivotal studies of trastuzumab in adjuvant setting, in this study, adult patients with histologically confirmed early invasive HER2 positive, node positive or high risk node negative breast cancer with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage I to IIIA that is eligible for adjuvant treatment with Trastuzumab will be enrolled. The performance status of these patients on Eastern Cooperative Oncology Group (ECOG) should be from 0 to 2 and HER2 over-expression/amplification for these patients should be defined as either IHC3+, or IHC2+ and FISH-positive as determined in a central laboratory. Screening left ventricular ejection fraction (LVEF) should be $\geq$ 55%.

As Bazell summarises: "No company had ever tested a breast-cancer drug in the newly diagnosed population because doctors did not want to use an unproved therapy on patients in the early, more treatable stages of disease" (1998: 137).[60]

3.5 OUTCOME MEASURES

3.5.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Disease free survival rate (DFS) and Overall Survival rate (OS).

As per institutional practice or American Society of Clinical Oncology (ASCO) adjuvant follow-up guidelines 2006, Breast cancer assessments for DFS and OS are to be reported for every 6 months.

3.5.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All Adverse Event (AE) and Serious Adverse Event (SAE) as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

- Cardiac function will be evaluated by measuring LVEF by echocardiography.

- Symptomatic left ventricular dysfunction (congestive heart failure [CHF]) will be graded according to the New York Heart Association functional classification.

- AEs and SAEs related to Trastuzumab will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or greater.

- Patients will undergo a Safety Follow-up, 4 weeks after their last dose of study treatment.

- AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all adverse events and adverse events related to study drug.

- Adverse events will also be summarized by toxicity grade, outcome, seriousness and action taken to the study medication.

4. MATERIALS AND METHODS

4.1 PATIENTS

Adult female patients with early invasive HER2 positive, node positive or high risk node negative breast cancer.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to give written informed consent and comply with the requirements of the study protocol.
- Adult female patients, ≥18 years of age
- Histologically confirmed early invasive HER2 positive, node positive or high risk node negative breast cancer with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage I to IIIA that is eligible for adjuvant treatment with Trastuzumab
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- HER2 over-expression/amplification defined as either IHC3+, or IHC2+ and FISH-positive as determined in a central laboratory
- At time of starting Trastuzumab therapy, Left ventricular ejection fraction (LVEF) measured by echocardiography
- Screening left ventricular ejection fraction (LVEF) ≥ 55%
- Adequate bone marrow, renal, and hepatic function
- Agreement to use an adequate, non-hormonal means of contraception by women of childbearing potential

4.1.2 Exclusion Criteria

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

- Any contraindication to Trastuzumab
- Previous adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
- History of other malignancy, except for curatively treated carcinoma in situ of the cervix or basal cell carcinoma and patients with other curatively treated malignancies who have been disease-free for at least 5 years

- Past history of ductal carcinoma in situ and/or lobular carcinoma that has been treated with any systemic therapy or with radiation therapy to the ipsilateral breast where the invasive cancer subsequently develops

- Locally advanced (stage IIIB and IIIC) and Metastatic disease (stage IV)

- Clinically relevant cardiovascular disorder or disease

- Uncontrolled hypertension, or history of hypertensive crisis or hypertensive encephalopathy

- History of severe allergic or immunological reactions, e.g. difficult to control asthma

- Pregnant or lactating women

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients eligible as per the inclusion and exclusion criteria will be treated with either AC→TH or TCH treatment regimens.
The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigators' discretion referring the local prescribing document of Trastuzumab.

AC→TH regimen:

- Every 3 weeks for 4 cycles, patients in the AC→TH regimen will be receiving 60 mg/m2 doxorubicin as a 5 to15 minute I.V. bolus injection followed by 600 mg/m2 cyclophosphamide as a 5 to 60 minute I.V. bolus injection.

- On Day 1 of Cycle 5, 4-mg/kg Trastuzumab loading dose will be administered as a 90 minute I.V. infusion as a weekly regimen OR 8-mg/kg Trastuzumab loading dose will be administered as a 90-minute I.V. infusion as a 3 weekly regimen at Investigator's discretion.

- If weekly regimen of Trastuzumab is selected, on Day 8 of Cycle 5, 2 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion and 2mg/ kg every week as a weekly regimen will be given OR beginning on Day 1 of Cycle 6, Trastuzumab 6 mg/kg will be administered as a 30-minute I.V. infusion every 3 weeks as a 3 weekly regimen for four cycles.

- Docetaxel 100 mg/m2 or Paclitaxel 175 mg/m2 (at investigator's discretion) will be administered as a 1 hour I.V. infusion every 3 weeks for four cycles, beginning on Day 1 of Cycle 5 and continued for up to Cycle 8.

- Three weeks after the last treatment with docetaxel/paclitaxel (i.e., on Day 1 of Cycle 9), 6 mg/kg Trastuzumab will be administered as a 30-minute I.V. infusion every 3 weeks. Trastuzumab treatment will be continued up to cycle 22 (completing a total 52 week trastuzumab therapy).

TCH regimen:

- Trastuzumab will be given intravenously at a dose of 4 mg/kg loading dose administered as a 90 minute I.V. infusion followed by 2 mg/kg administered as a 30 minute I.V. infusion weekly as a weekly regimen or 8-mg/kg Trastuzumab loading dose administered as a 90 minute I.V. infusion followed by 6 mg/kg administered as a 30 minute I.V. infusion 3 weekly as a 3 weekly regimen during chemotherapy from cycle 1 to 6 at Investigator's discretion.

- Every 3 weeks for six cycles, patients in the TCH regimen will be receiving 75 mg/m^2 docetaxel as a 60-minute I.V. bolus injection followed by AUC 6 x (GFR + 25) carboplatin as a 30 to 60 minute I.V. bolus injection.

- After completion of chemotherapy, Trastuzumab will be administered at a dose of 6 mg/kg every 3 weeks up to cycle 18 (completing total 52 week trastuzumab therapy)

The patient will be followed up for duration of 12 months from the last dose of Trastuzumab. All adverse events occurring during treatment and this follow up period will be captured.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Trastuzumab

Trastuzumab is produced by a genetically engineered Chinese hamster ovary (CHO) cell line grown in large scale, which secretes Trastuzumab into the culture medium. The antibody is then purified extensively using standard chromatographic and filtration methods.

Trastuzumab for intravenous (IV) administration is supplied commercially as a lyophilized preparation in multi-dose (440 mg) vials. It is formulated in histidine/histidine-HCl, α,α-trehalose dihydrate, and polysorbate 20. Following reconstitution in either sterile water for injection (SWFI) or bacteriostatic water for injection (BWFI), it is further diluted in 250 mL 0.9% sodium chloride solution for administration.

Vials of trastuzumab are shipped with cool packs at a temperature ranging from 2°C to 8°C (36°F to 46°F), and must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. Do not use beyond the expiry date stamped on the vial. DO NOT FREEZE. Trastuzumab may be sensitive to shear-induced stress (e.g. agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of trastuzumab results in aggregation of the protein and may create cloudy solutions.

4.3.2 Dosage, Administration, and Compliance

HER2 testing is mandatory prior to initiation of Trastuzumab therapy.

Trastuzumab should be administrated as intravenous infusion.

Should not be administered as an intravenous push or bolus.

Weekly schedule:

AC→TH regimen:

Patients in the AC→TH regimen will be receiving 60 mg/m^2 doxorubicin as a 5 to 15 minute I.V. bolus injection followed by 600 mg/m2 cyclophosphamide as a 5 to 60 minute I.V. bolus injection, every 3 weeks for 4 cycles. Docetaxel 100 mg/m2 or Paclitaxel 175 mg/m2 (at investigator's discretion) will be administered as a 1-hour I.V. infusion every 3 weeks for four cycles, beginning on Day 1 of Cycle 5 and continued for up to Cycle 8.

TCH regimen:

Patients in the TCH regimen will be receiving 75 mg/m2 docetaxel as a 60-minute I.V. bolus injection followed by AUC 6 x (GFR + 25) carboplatin as a 30 to 60 minute I.V. bolus injection, every 3 weeks for six cycles.

Loading dose: The recommended initial loading dose is 4 mg/kg body weight. Trastuzumab administered as a 90 minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms. Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of Trastuzumab is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30 minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms.

Alternative 3-weekly schedule:

AC→TH regimen:

Patients in the AC→TH regimen will be receiving 60 mg/m2 doxorubicin as a 5 to 15 minute I.V. bolus injection followed by 600 mg/m2 cyclophosphamide as a 5 to 60 minute I.V. bolus injection, every 3 weeks for 4 cycles. Docetaxel 100 mg/m2 or Paclitaxel 175 mg/m2 (at investigators discretion) will be administered as a 1-hour I.V. infusion every 3 weeks for four cycles, beginning on Day 1 of Cycle 5 and continued for up to Cycle 8.

TCH regimen:

Patients in the TCH regimen will be receiving 75 mg/m2 docetaxel as a 60 minute I.V. bolus injection followed by AUC 6 x (GFR + 25) carboplatin as a 30 to 60 minute I.V. bolus injection, every 3 weeks for six cycles.

Initial loading dose of 8 mg/kg body weight administered as infusions over approximately 90 minutes, followed by 6 mg/kg body weight 3 weeks later as infusions over 30 minutes and then 6 mg/kg repeated at three weekly intervals as infusions over 30 minutes. If the prior dose was well tolerated, the dose can be administered as a 30 minute infusion.

Patients with early breast cancer should be treated with Trastuzumab for a total of 52 week, but not exceeding 52 week.

Dose reduction/ modification for toxicities

There are no dose adjustments of trastuzumab foreseen for toxicity. If a patient cannot tolerate trastuzumab infusions, trastuzumab treatment will be stopped completely. Trastuzumab treatment need not be delayed for some toxicities that necessitate a delay in chemotherapy.

Patients may continue trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during this time.

If the patient misses a dose of Trastuzumab by one week or less, then the usual maintenance dose of Trastuzumab (6 mg/kg in 3weekly regimen or 2 mg/kg in weekly regimen) should be given as soon as possible (do not wait until the next planned cycle). Carry on the maintenance doses according to the original schedule.

If the patient misses a dose of trastuzumab by more than one week, treatment should be restarted as if she were a new patient. The treatment should be re-started as soon as possible (don't wait until the next planned cycle) with a

loading dose of 8 mg/kg in 3weekly regimen or 4mg/kg in weekly regimen. Subsequent maintenance trastuzumab doses of trastuzumab should be given 6 mg/kg every 3 weekly or 2 mg/kg weekly from that point as per the selected schedule of administration.

To keep trastuzumab in synchrony with concurrent chemotherapy, and to maintain trastuzumab dose intensity, the maintenance trastuzumab dose 6mg/kg should be given at the scheduled time, even though the chemotherapy dose is delayed. When the chemotherapy is next given (after resolution of toxicity), trastuzumab maintenance 6mg/kg dose should also be given. Subsequent trastuzumab doses are given in synchrony with concurrent chemotherapy, every 3 weeks. Note that this means that trastuzumab doses of 6 mg/kg may occasionally be given only one week after the previous trastuzumab dose.

The specific instructions to reduce or hold the dose of chemotherapy should be followed. For instructions refer to the manufacturer's prescribing information or follow the routine center/institution practice.

Carboplatin

Intermittent courses of Carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.[61]

Doxorubicin

When possible, to reduce the risk of developing cardiotoxicity in patients receiving Doxorubicin after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, Doxorubicin-based therapy should be delayed until the other agents have cleared from the circulation. On intravenous administration of Doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. × 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation are recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m2 as a single intravenous injection administered at 21 day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and, if this occurs, the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.[62]

Cyclophosphamide

Dosages must be adjusted in accord with evidence of antitumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm^3 (following short courses) or more persistent reduction to 3000 cells/mm^3 (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia.[63]

Paclitaxel

All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to Paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before Paclitaxel.

For patients with solid tumors (ovary, breast and NSCLC), courses of Paclitaxel should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during Paclitaxel Injection, USP therapy should have dosage reduced by 20% for subsequent courses of Paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with dose.[64]

Docetaxel

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during Docetaxel Injection therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during Docetaxel Injection therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination Therapy with Docetaxel Injection in the Adjuvant Treatment of Breast Cancer Docetaxel Injection in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel Injection dose reduced to 60 mg/ m^2. Patients who experience grade 3 or 4 stomatitis should have their Docetaxel Injection dose decreased to 60 mg/ m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel Injection therapy should have their dosage of Docetaxel Injection reduced from 75 to 60 mg/ m^2. If the patient continues to experience these reactions at 60 mg/ m^2, treatment should be discontinued.[65]

Administration

Trastuzumab

Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial. Use appropriate aseptic technique when performing the following reconstitution steps: Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake. Swirl the vial gently to aid reconstitution. DO NOT SHAKE. Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow. Use of other reconstitution solvents is not allowed. The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 mL of 0.9% Sodium Chloride Injection. The product is not intended to be stored after reconstitution and dilution unless this has taken place under aseptic conditions. Once the infusion is prepared it should be administered immediately. Reconstituted solutions made with solvent (bacteriostatic water for injection) for the 440 mg vial of trastuzumab is stable for 28 days when stored refrigerated at 2°C-8°C. Any remaining reconstituted solution should be discarded after 28 days. Do not freeze the reconstituted solution. The reconstituted solution contains preservative and is therefore suitable for multiple use. Trastuzumab should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial.
Determine the volume of the solution required based on a dose (mg trastuzumab/kg body weight,)

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (mg/kg)}}{\text{21 (mg/mL, concentration of reconstituted solution)}}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.9% sodium chloride solution. Do not use with glucose-containing solutions since it causes aggregation of the protein. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. The product is not to be stored after dilution unless this has taken place under aseptic conditions. Once the infusion is prepared it should be administered immediately. If diluted aseptically the infusion may be stored for a maximum of 24 hours (at 2-8 °C). No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed. Trastuzumab can be administered in an outpatient setting. It should not be administered as an i.v. push or bolus. Patients should be observed for at least six hours after the start of the first dose of trastuzumab (i.e. 4.5 hours from the end of the infusion). The observation period may be shortened to 2 hours after the start of the infusion (i.e. 1.5 hours from the end of the infusion) based on investigators discretion. Emergency equipment must be available. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the trastuzumab infusion.

Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Chemotherapy

For chemotherapy drugs refer to the manufacturer's prescribing information or follow the routine center/institution practice, at discretion of Investigator.

Order of administration in AC→TH protocol: Post AC therapy, Trastuzumab first followed by docetaxel/paclitaxel

Drug	Dose
Cycles* 1-4	
Doxorubicin	60 mg/m^2
Cyclophosphamide	600 mg/m^2
Cycles 5-8	
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week OR 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 week
Taxane	Docetaxel (100 mg/m^2) or Paclitaxel (175 mg/m^2)
Cycles 9 to 22	
Trastuzumab	6 mg/kg (Maintenance dose) every 3 week

***Cycle: 21 days**

Order of administration in TCH protocol: Trastuzumab first, docetaxel second, carboplatin third.

Drug	Dose
Cycle* 1-6	
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week OR 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 week
Docetaxel	75 mg/m^2
Carboplatin	Dose = AUC 6 x (GFR + 25)
Cycle 7 to 18	
Trastuzumab	6 mg/kg (Maintenance dose)

***Cycle: 21 days**

Compliance:

Accountability and patient compliance will be assessed by measuring duration of drug administration as well as maintaining adequate drug dispensing records. Investigator is required to maintain adequate records of the disposition of the study medications, including dates, the quantity of drug received and to whom it was dispensed (patient -by- patient accounting), and accounts of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each patient and should contain the identification of each patient and the date and quantity of drug dispensed.

All records regarding disposition of the test product will be available for inspection by the clinical trial monitor. All supplies, including partially used or empty containers and the dispensing logs, must be returned to the Roche Monitor or designee at the end of the study.

4.3.3 Investigational Medicinal Product Accountability

The test product Trastuzumab will be provided by the sponsor and the non-investigational medicinal products required for completion of this study, purchased by the patients will be reimbursed by the sponsor as per the bills.

The test product 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 test product destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any test product is destroyed, and test product destruction must be documented on the appropriate form.

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

4.3.4 Post-Trial Access to Trastuzumab

Not Applicable.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to screening to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded in the Concomitant medications section of the eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Doxorubicin taken along with Trastuzumab causes cardiotoxicity, hence it should not be administered along with Trastuzumab.

Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Trastuzumab.

Trastuzumab is contraindicated in patients with known hypersensitivity to Trastuzumab or to any other component of the product. No formal drug interaction studies have been performed with Trastuzumab in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

The study comprises of three phases, screening phase, treatment phase and follow-up phase.

Screening phase:

During screening and baseline phase patients will undergo an evaluation to determine eligibility to participate in this study. The screening evaluation will include subject eligibility, demographic data, physical examination, vital signs, inclusion and exclusion criteria, relevant medical history, previous and concomitant medication details, conformation of early breast cancer disease by histology, radiography (mammogram) ((tumor size < 5 cm and < 4 positive lymph

nodes), CT/MRI, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), measurement of LVEF by echocardiography, haematology and biochemistry assessment.

HER2-positive status on fixed tissue blocks from the primary tumor assessed by IHC (immuno histochemistry) and/or FISH (fluorescence insitu hybridization). Sample for this test will be sent to the central laboratory for analysis.

Choice of treatment regimen:

The choice of the Trastuzumab treatment regimen (either AC→TH or TCH) will be based on investigators' discretion.
Order of administration in AC→TH protocol : Post AC therapy, Trastuzumab first followed by docetaxel/paclitaxel.

Drug	Dose	Administration Guideline
Cycles* 1-4		
Doxorubicin	60 mg/m^2	Administered as I.V. bolus over 5 to 15 min.
Cyclophosphamide	600 mg/m^2	Administered I.V. over 5 to 60 min. (use non-PVC equipment).
Cycles 5-8		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week or 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 weeks	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 90 minutes post infusion. • Maintenance dose: I.V. in 250 mL NS over 30 min on all the doses, observe for 30 minutes post infusion
Taxane	Docetaxel (100 mg/m^2) or Paclitaxel (175 mg/m^2)	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Cycles 9 to 22		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 week	I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

<u>Order of administration in TCH protocol:</u> Trastuzumab first, docetaxel second, carboplatin third.

Drug	Dose	Administration Guideline
Cycle* 1-6		
Trastuzumab	4 mg/kg (Loading dose) followed by 2 mg/kg (Maintenance dose) every week OR 8 mg/kg (Loading dose), followed by 6 mg/kg (Maintenance dose) every 3 week	• Loading dose: I.V. in 250 mL NS over 90 min. Observe for 1 hour post-infusion • Maintenance dose: I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion
Docetaxel	75 mg/m^2	Administered I.V. in 250 mL NS over 1 hour (use non-PVC equipment).
Carboplatin	Dose = AUC 6 x (GFR + 25)	Administered I.V. in 500 mL D5W over 30 to 60 min
Cycle 7 to 18		
Trastuzumab	6 mg/kg (Maintenance dose) every 3 weeks	I.V. in 250 mL NS over 30 min on the all doses, observe for 30 minutes post infusion.

***Cycle: 21 days**

As per institutional practice or American Society of Clinical Oncology (ASCO) adjuvant follow-up guidelines 2006, Breast cancer assessments for DFS and OS are to be reported for every 6 months.

American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

- History/physical examination - every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually.
- Mammography - first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.

- Pelvic examination - regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI), tumor marker assessments (CA 15-3, CA 27.29, and CEA).

However, bone scan, liver imaging, and brain CT scan will be performed if clinically indicated.

During treatment period

- Safety parameters will be assessed for every cycle.
- Vital signs, physical examination and treatment compliance will be performed for every cycle and subject safety will be evaluated.
- LVEF and ECG will be assessed for every 3 months (4 cycles) to evaluate cardiac safety of the patients.
- ECOG will be assessed for every 3 months (4 cycles) to evaluate performance status of the patients.
- Hematology and biochemistry assessments will also be performed during the study if clinically indicated.

Follow-up Phase:

Thereafter during follow up period of one year, Cardiac assessments at 6 and 12 months following treatment cessation. Survival follow-up can be performed by regular telephonic calls and/or clinic visits every 6 months.

4.5.1.1 Medical History and Demographic Data

A complete medical history including 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 2 weeks prior to screening will be recorded on the eCRF. Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.1.2 Physical Examinations

A complete physical examination will be performed at each visit on relevant body systems and data will be recorded in the eCRF. Any abnormality identified at baseline should be recorded in the eCRF.

At subsequent visits, changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events.

4.5.1.3 Vital Signs

As per routine clinical practice, available vital signs including measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature will be measured before and after trastuzumab infusion, and recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event Form.

4.5.1.4 Tumor and Response Evaluations

Available data on tumor and treatment outcome from the medical records and patient interviews on medical history and disease characteristics (which are routinely performed in accordance with current guidelines and local standard of care) will be documented in the eCRF. The data available according to the response assessment will be captured in the eCRF.

The investigator will continue to assess patients according to routine clinical practice at their discretion. Additional treatment outcome data may be collected for patients who continue to visit the doctor as per local standard of care till the end of study.

4.5.1.5 Laboratory Assessments

The laboratory assessments including hematology and biochemistry will be performed at screening visit from all the enrolled patients. Samples for these tests will be sent to the study site's local laboratory for analysis:

Hematology and Biochemistry need not be repeated at baseline if not clinically indicated.
The laboratory tests to be performed are listed below:

- Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, absolute differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

- Biochemistry (sodium, potassium, chloride, bicarbonate, fasting glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, magnesium, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, creatine phosphokinase, uric acid, LDH).

HER2-positive status on fixed tissue blocks from the primary tumor assessed by IHC (immuno histochemistry) and/or FISH (fluorescence insitu hybridisation) according to institutional criteria will be performed at central laboratory. Please see Appendix 4 for algorithm on HER2 testing.

Laboratory test results will be recorded on the laboratory results pages of the Case Report Form. Laboratory test value abnormalities as such should not be reported on the AE page of the eCRF as adverse events, unless there is an associated clinical condition for which the patient is given treatment or concomitant treatment altered, it is considered to be a serious adverse event, leads to a change in study medication (e.g. dose modification/ interruption) or the patient is permanently discontinued from study drug because of the abnormal test value.

4.5.1.6 12 Lead ECG

ECGs will be performed at baseline, cycle 5, cycle 9, cycle 13, cycle 17, cycle 21(only for AC-TH Regimen), termination visit and during follow-up.

ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e. g: television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

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.

Screening tests and evaluations will be performed within 2 weeks prior to cycle 1, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 2 weeks prior to cycle 1 may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. 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.

Pretreatment tests and evaluations will be performed within 2 weeks prior to cycle 1after confirmation of other eligibility criteria, unless otherwise specified.

Please see Appendix 1 and 2 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1 and 2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.
All the enrolled patients will be required to visit the study site during week -2 to -1(baseline), study cycles 1 to 22 (1 cycle=21 days) for AC→TH regimen and cycles 1 to 18 for TCH regimen. Unscheduled clinical evaluations may occur at anytime if deemed appropriate by the Investigator.

- Safety parameters will be assessed for every cycle.
- Vital signs before and after study drug administration, physical examination and treatment compliance will be performed for every cycle and subject safety will be evaluated.
- LVEF and ECG will be assessed for every 3 months (4 cycles) to evaluate cardiac safety of the patients.
- ECOG will be assessed for every 3 months (4 cycles) to evaluate performance status of the patients.
- Hematology and biochemistry assessments will also be performed during the study if clinically indicated.

Please see Appendix 1 and 2 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Study Completion/Early Termination Visit

Patients who complete the study or discontinue from the study early will be asked to return to the clinic 4 weeks after the last dose of study drug. The visit at which response assessment shows recurrent disease may be used as the study completion/early termination visit.

Please see Appendix 1 and 2 for the schedule of assessments performed at the study completion/early termination visit.

4.5.2.4 Follow-up Assessments

During follow up period of one year, Cardiac (LVEF and ECG) assessments at 6 and 12 months following treatment cessation are done. Survival follow-up can be performed by regular telephonic calls and/or clinic visits every 6 months.

Please see Appendix 1 and 2 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

Please see Appendix 1 and 2 for assessments that are required to be performed in case of an unplanned visit.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

4.6.1.1 Discontinuation from Study Drug

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

- Pregnancy (unless the potential benefit for the mother outweighs the potential risk to the fetus).

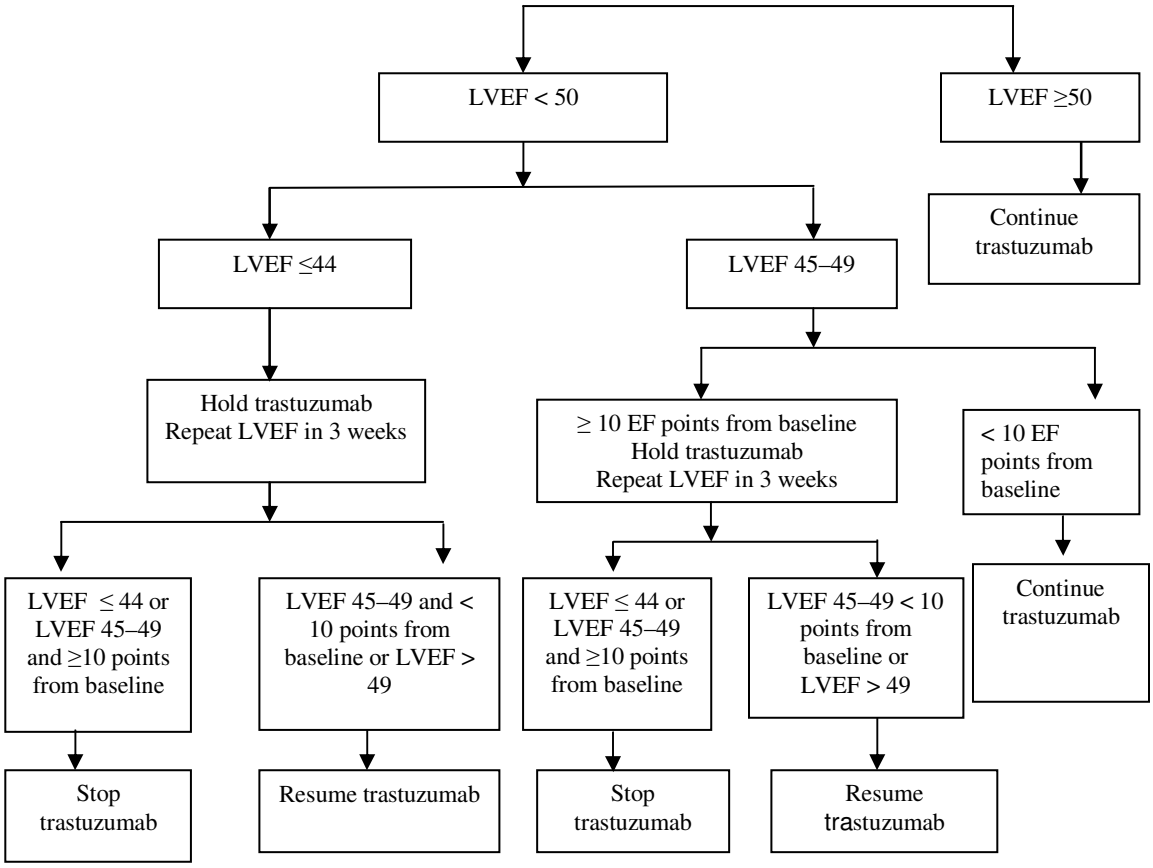
- If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Trastuzumab therapy has been seen.

- If LVEF has not improved, or declined further, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

- Discontinuation of Trastuzumab therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit and may undergo follow-up assessments. The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

Algorithm for knowing how to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy using trastuzumab based on the changes in LVEF[66]



4.6.1.2 Withdrawal from Study

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. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 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, unsatisfactory patient enrollment.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The Sponsor has the right to replace a site at any time. Reasons for replacing 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 GCP guidelines and regulations

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Trastuzumab therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

The council of International organizations of Medical sciences (CIOMS) working group has recommended as the use of the development core safety information (DCSI) as the summary of identified safety issues for an investigational product or drug.[66] The Developmental Core Safety Information (DCSI) provides a concise summary of any contraindications, warnings and precautions, provisional adverse drug reactions (ADRs) and other significant safety information regarding the use of Trastuzumab.

1) Infusion Reactions

Serious adverse reactions to Trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. The Trastuzumab infusion should be discontinued and the patient monitored until resolution of any observed symptoms. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome.
Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or comorbidities may be at increased risk of a fatal

infusion reaction. Therefore, these patients should be treated with extreme caution and the risk versus the benefit considered for each patient.

2) Pulmonary Adverse Events

Severe pulmonary events have been reported rarely with the use of Trastuzumab in the post-marketing setting. These rare events have occasionally resulted in fatal outcome. In addition, rare cases of pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory insufficiency have been reported. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnoea at rest, may be at greater risk of severe reactions.

3) Cardiovascular Adverse Events

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving Trastuzumab therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death.

Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension, or documented coronary artery disease. Candidates for treatment with Trastuzumab, especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG and echocardiogram. A careful risk-benefit assessment should be made before deciding to treat with Trastuzumab.
In Early Breast Cancer, the following patients were excluded from the HERA trial, therefore there are no data about the benefit : risk balance, and consequently treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a

continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Trastuzumab therapy has been seen.

If LVEF drops 10 ejection points from baseline and to below 50%, Trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

If symptomatic cardiac failure develops during Trastuzumab therapy, it should be treated with the standard medications for this purpose. Discontinuation of Trastuzumab therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Trastuzumab in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment. This included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Trastuzumab treatment continued on weekly therapy with Trastuzumab without additional clinical cardiac events.

4) Interstitial lung disease

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy.

5) Benzyl Alcohol Sensitivity

Benzyl alcohol, used as a preservative in bacteriostatic water for injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Trastuzumab to a patient with a known sensitivity to benzyl alcohol, Trastuzumab should be reconstituted with water for injection, and only one dose per Trastuzumab vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vial, does not contain benzyl alcohol.

6) Pregnancy/Nursing Mothers

Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. In the post-marketing setting, some associated with fatal pulmonary hypoplasia of the fetus, cases of oligohydramnios have been reported in pregnant women receiving Trastuzumab.

Women of childbearing potential should be advised to use effective contraception during treatment with Trastuzumab and for at least 6 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Trastuzumab, close monitoring by a multidisciplinary team is desirable. It is not known whether Trastuzumab can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the fetus.

7) Potential for Drug-Drug Interactions

There has been no formal drug interaction studies performed with Trastuzumab in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed.

5.1.1 Management of Specific Adverse Events

Table - 1 Guidelines for Managing Specific Adverse Events

Event	Action to Be Taken
Infusion Reactions	• During the first infusion with Trastuzumab, chills and/or fever are observed commonly in patients. • Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, asthenia, and hypertension. • These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Trastuzumab infusions. • These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

All the Adverse Event (AE) and Serious Adverse Events (SAEs) will be captured appropriately.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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).

- 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).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death).
- This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.

- 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 adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); 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 adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

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

Immediate reporting to the Sponsor is already well defined for serious adverse events. Non-serious adverse events of special interest also require immediate reporting to the Sponsor for real-time monitoring. Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours) Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice.

Investigators must report as an adverse event the occurrence of either of the follow:

- Suspected transmission of an infectious agent by the study drug.
- Cardiac failure congestive.

5.2.4 Selected Adverse Events

Selected adverse events do not require immediate reporting and should not be confused with non-serious adverse events of special interest which require reporting to the Sponsor immediately (i.e., no more than 24 hours) after learning of an event.

Additional data will be collected for the following selected adverse events in guided questionnaire :

- Cardiac AEs
- Hemolytic Anemia
- Infusion related reactions
- Interstitial Lung Disease
- Thyroid dysfunction

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor.
For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, 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.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events, regardless of relationship to study drug will be reported after the last dose of study drug. After the end of the follow-up period and after study closure, all SAEs and non-serious AESIs (regardless of causality) occurring to a subject should be reported to the sponsor if the investigator becomes aware of them. The investigator is not required to actively monitor patients after the study has ended.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. 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?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table below will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 - Adverse Event Severity Grading Scale

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 adverse event [d]

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

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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 one's self, 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 serious adverse event.

[d] Grade 4 and 5 events must be reported as serious adverse events

5.3.4 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 adverse event 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 (where 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

5.3.5 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 adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF 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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

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

Recurrence of breast cancer should not be reported as an AE since this is clearly consistent with progression/relapse of the underlying disease. Hospitalization due solely to the relapse of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of relapse may be reported as AEs if the symptom cannot be determined as exclusively due to the relapse of the underlying malignancy, or does not fit the expected pattern of relapse for the disease under study. If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- 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.
- Clinically significant in the investigator's judgment.

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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 adverse event. 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- 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.
- 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 adverse event.
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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN) 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. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN.
- Treatment-emergent ALT or AST $> 3 \times$ ULN 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 and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest.

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression of Early Breast Cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

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 only be used 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 of 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.

During post-study survival follow-up, deaths attributed to progression of Early Breast Cancer should be recorded only on the Survival eCRF or Study Completion/Early Discontinuation eCRF.

5.3.5.8 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 adverse event 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").

5.3.5.9 Lack of Efficacy or Worsening of Early Breast Cancer

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., 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 suffered an adverse event.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 **hours after learning of the event).**

5.4 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 after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events.
- Non-serious adverse events of special interest.
- Pregnancies.

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 serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information:

Primary Contact

Medical Monitor: Dr. [redacted]
Telephone No.: +91-22-24941414
Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted]
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

To ensure the safety of study patients, details will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF. A paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest eCRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 105-140 days 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). 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 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.

A Ppregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3.2 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1.1 Investigator Follow-Up

The investigator should follow each adverse event 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 serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.1.2 Sponsor Follow-Up

For serious adverse events, 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.

5.6 POST-STUDY ADVERSE EVENTS

At the safety follow-up visit, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events.

After study closure, the Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, or other adverse event of special interest occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug. The investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

During post-study survival follow-up, deaths attributed to progression of early breast cancer should be recorded only on the Survival eCRF or Study Completion/Early Discontinuation eCRF.

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

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events 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 adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Local prescribing information for Trastuzumab
- Trastuzumab Core Data Sheet

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 109 subjects will be required to conduct a phase IV study to evaluate safety and efficacy of Trastuzumab in HER2 positive node positive or high risk node negative breast cancer by assuming level of significance 5%, incidence of adverse event 65.9%, precision 10% and dropout rate 20%.

Incidence of adverse event in AC-TH group with Grade 3 or 4 hematologic events such as neutropenia, leucopenia, febrile neutropenia, neutropenic infection, anemia, thrombocytopenia, leukemia were 71.5%, 60.3 %, 10.9%, 11.9%, 3.1%, 2.1% and 0.1% respectively. In TCH group incidence of adverse event with Grade 3 or 4 hematologic events such as neutropenia, leucopenia, febrile neutropenia, neutropenic infection, anemia, thrombocytopenia, leukemia were 65.9%, 48.2 %, 9.6 %, 11.2%, 5.8%, 6.1% and 0.1% respectively.

While considering the 71.5%, the highest incidence of adverse event in AC-TH group, sample of size 99 patients will be required. Similarly, by considering the highest incidence of adverse event 65.9% in TCH group, sample of size 109 patients will be required. Also considered the incidence of 68.7% (i.e. mean of 71.5% and 65.9%), 104 patients will be required. The above three calculations, assumed a 5% level of significance, 10% precision and 20% dropout rate. Considering all the above calculation, it is suggested that approximately 109 patients will be required for the proposed study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The demographic characteristics will be summarized for all the patients enrolled into the study. All baseline & demographic data and general medical history will be summarized at screening visit. Descriptive statistics such as number of non-missing observations (n), mean, median, Standard Deviation (SD), 1st Quartile (Q1), 3rd Quartile (Q3), minimum and maximum will be estimated for continuous variables (e.g. Age, Height .etc) and frequency counts and percentages will be employed for categorical variables (e.g. Gender, Race.etc). All statistical tests will be done at 5 % significance level and $p \leq 0.05$ indicate the significance. Two – sided 95% confidence interval (CI) will be constructed, wherever appropriate.

6.3 EFFICACY ANALYSES

The secondary objectives include Disease free survival and Overall survival. DFS is defined as time from the date of first study treatment to the date of local, regional or distant recurrence, contra-lateral breast cancer or death due to any cause. OS is defined as time from the date of first study treatment until date of death, regardless of the cause of death.

The median Disease free survival time and median overall survival time with 95% confidence interval will be estimated using Kaplan Meier method and KM plots will also be provided. Log rank test will be used to compare the median survival time between subjects with ECOG PS 0 and ECOG PS 1-2 at baseline for DFS and OS.

6.4 SAFETY ANALYSES

Safety measurements include adverse events, laboratory tests (hematology and biochemistry), vital signs, electrocardiograms, physical examinations, and toxicity evaluations. Toxicities will be evaluated at each course of therapy using the NCI-CTCAE version 4.0 or a non-CTC grading scale for toxicities that are not covered by the NCI CTC.

Adverse Events (AEs) and Serious Adverse Events (SAEs) related to Trastuzumab will be summarized by using number and percentage (Incidence of AEs and SAEs). AEs and SAEs related to Trastuzumab will be coded using MedDRA, version 15.1 or greater. AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all adverse events and adverse events related to study drug. Adverse events will also be summarized by toxicity grade, outcome, seriousness and action taken to the study medication.

All the Laboratory evaluations (hematology & biochemistry) will be considered at baseline and completion/early termination visits. Descriptive statistics such as n, mean, median, standard deviation (SD), Q1,Q3, minimum (Min), and maximum (Max) will be provided for all. Change from Baseline will be calculated for all the available hematology and biochemistry parameters as specified in the eCRF pages. Mean change from baseline will be compared using paired t test or Wilcoxon signed-rank test based on normality assumption.

ECOG performance status will be collected at baseline and every 4 Cycles during treatment period. Counts and percentages will be reported in the results. Generalized McNemar's test will be used to compare the ECOG PS between baseline and follow-up visits.

Patient data will be analyzed for evidence of cumulative toxicity with repeated courses of therapy. Summary of ECG status will be evaluated at all visits. Counts and percentages will be reported in the results.

HER-2 testing will be collected at Baseline/Screening. This will be summarized using number and percentage.

LVEF will be collected for every 3 months or and percentage change from baseline will be reported for every 3 months. Mean change from baseline will be compared using paired t test or Wilcoxon signed-rank test based on normality assumption. All statistical tests will be done at 5 % significance level and $p \leq 0.05$ indicate the significance.

6.5 INTERIM ANALYSES

No Interim Analysis Planned for this study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

a) Data collection

Source data entered manually will be collected via mEDC using eCRFs. Sites will be responsible for data entry into the mEDC system. In the event of discrepant data, the clarification from the sites will be requested, which the sites will resolve electronically in the mEDC system. If a subject withdraws from the study, the reason must be noted on the eCRF. All missing data should also be accounted for in the eCRF. The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor. A comprehensive validation check program will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator.

b) Data management

Data cleaning activity will be performed by the data management team. For any missing/incorrect/ uncertain data in the eCRF, the data management team will raise a query. The investigator is requested to provide the necessary justification.

c) Assignment of preferred terms

For classification purposes, preferred terms will be assigned by the sponsor to the original terms entered on the eCRF, using the current version of MedDRA (Medical dictionary for regulatory activities) for AEs and diseases.

7.2 ELECTRONIC CASE REPORT FORMS

Sites will receive training and will have access to eCRF filling instructions. eCRFs will be submitted electronically to the CRO and should be handled in accordance with instructions from the Sponsor/CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs 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.

7.3 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.

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 investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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.

7.5 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.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" and or with the laws and regulations of India (Schedule-Y), whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If 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 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 case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to 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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

It is the responsibility of the Ethics Committee/ Institutional Review Board to have the EC/ IRB registered duly with the DCGI (vide gazette G. S. R. 72(E) before granting the approvals.

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 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events 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.

8.4 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 only be disclosed to third parties 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 U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 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.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 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, which includes an audit trail containing a complete record of all changes to data.

9.2 MONITORING

On-site monitoring will be performed before, during, and after the study. The monitor will ensure that the study is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements. The monitor will check the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The investigator will provide direct access to source data/documents for study-related monitoring.

The monitor will follow written SOPs as well as procedures that are specified by Sponsor for monitoring of this study.

9.3 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.

9.4 ADMINISTRATIVE STRUCTURE

The study will be conducted by the sponsor. Data Management and Statistical services will be provided by a contract research organization (CRO). Assessment of laboratory test results will be performed locally.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. 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.

9.6 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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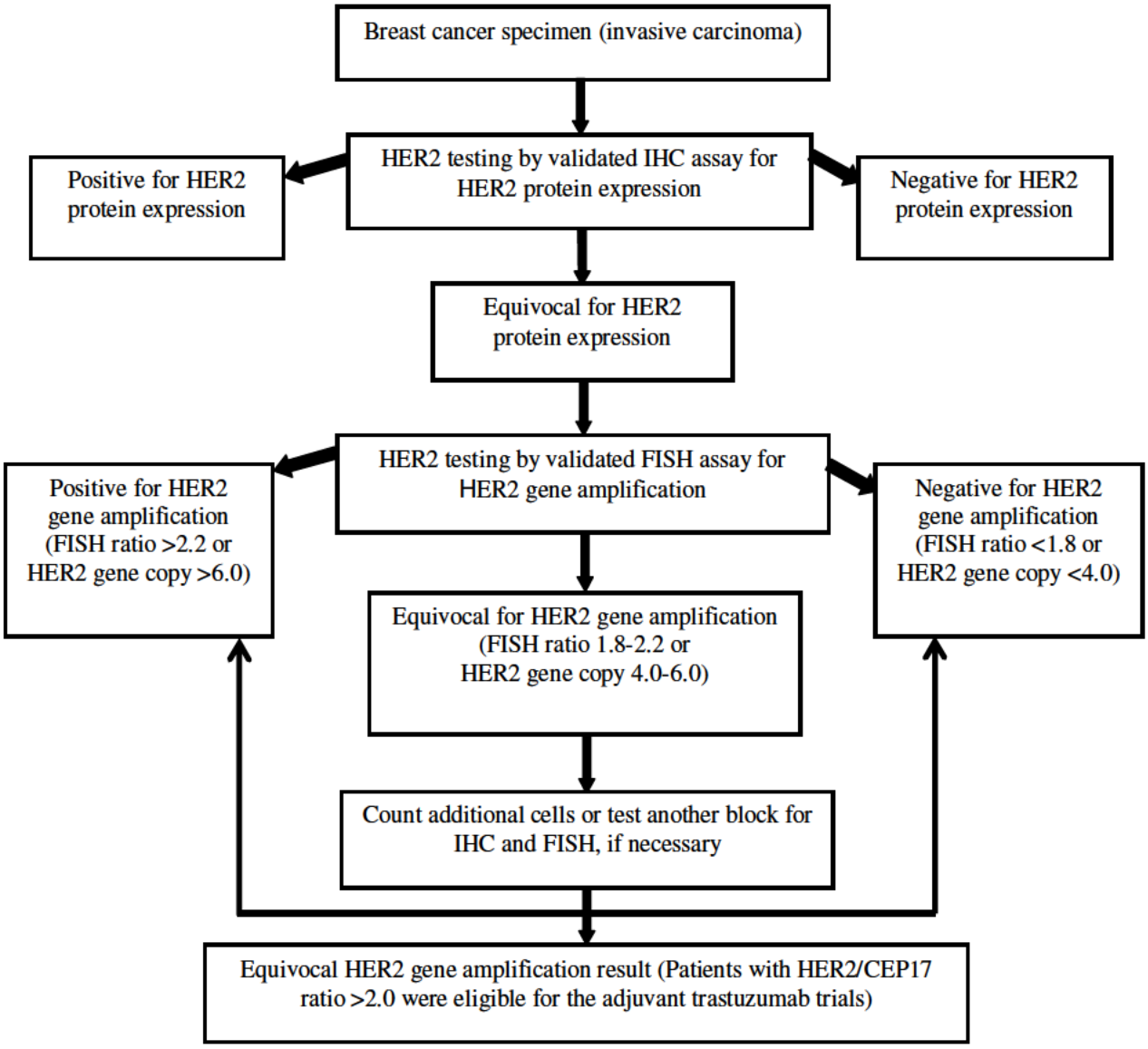
Appendix 3 - ECOG Performance Status*

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T.,Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 4 - HER2 testing and algorithm in breast cancer

Test at diagnosis starting with IHC and then reflex to FISH according to the diagram below.



Source: Wolff A, Hammond M, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. J Clin Oncol, 2007; 23(1):1-28.

Appendix 5 - Salient features from Breast cancer assessment ASCO adjuvant follow up guidelines 2006

Mode of Surveillance	Summary of Recommendations
Recommended breast cancer surveillance	
History/physical examination	Every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, abdominal pain, dyspnea or persistent headaches; helpful websites for patient education include www.plwc.org and www.cancer.org
Referral for genetic counseling	Criteria include: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative
Breast self-examination	All women should be counseled to perform monthly breast self-examination
Mammography	First post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis but no earlier than 6 months after definitive radiation therapy; subsequent mammograms should be obtained as indicated for surveillance of abnormalities
Coordination of care	Continuity of care for breast cancer patients is encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormonal therapy for the particular patient; this may necessitate rereferral for oncology assessment at an interval consistent with guidelines for adjuvant hormonal therapy
Pelvic examination	Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians
Breast cancer surveillance testing: not recommended	
Routine blood tests	CBCs and liver function tests are not recommended

Imaging studies	Chest x-ray, bone scans, liver ultrasound, computed tomography scans, FDG-PET scans, and breast MRI are not recommended
Tumor markers	CA 15-3, CA 27.29, and carcinoembryonic antigen are not recommended
FDG-PET	FDG-PET scanning is not recommended for routine breast cancer surveillance
Breast MRI	Breast MRI is not recommended for routine breast cancer surveillance

Abbreviations; PCP, primary care physician; FDG-PET, _18F_fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging.

Source: Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.