A Phase 3, Randomized, Open-Label, Two-Arm Study of Neratinib Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel as First-Line Treatment for ErbB-2-Positive Locally Recurrent or Metastatic Breast Cancer

Date of Original Protocol: 21 May 2009

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1.0 DISCLOSURE STATEMENT

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21 May 2009

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21 May 2009

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Protocol 3144A2-3005-WW
21 May 2009

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My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Global Medical Monitor or Physician Designee Signature

Date of Signature (DD Mmm YYYY)

Global Medical Monitor or Physician Designee Name (print)
4.0 INVESTIGATOR SIGNATURE

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature ____________________________ Date of Signature ____________________________

(DD Mmm YYYY)

Investigator Name and Title (print)
### 5.0 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tbody>
<tr>
<td>ADCC</td>
<td>antibody-dependent cell-mediated cytotoxicity</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>AUCss</td>
<td>area under the curve at steady state</td>
</tr>
<tr>
<td>β-HCG</td>
<td>beta-human chorionic gonadotropin</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CBR</td>
<td>clinical benefit rate</td>
</tr>
<tr>
<td>CFR</td>
<td>code of federal regulations</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CISH</td>
<td>chromogenic in situ hybridization</td>
</tr>
<tr>
<td>Cmax</td>
<td>maximum concentration</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran Mantel-Haenszel</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
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<tr>
<td>CSA</td>
<td>clinical study agreement</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTC</td>
<td>common terminology criteria</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome</td>
</tr>
<tr>
<td>DLT</td>
<td>dose-limiting toxicity</td>
</tr>
<tr>
<td>DOR</td>
<td>duration of response</td>
</tr>
<tr>
<td>ECD</td>
<td>extracellular domain</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECHO</td>
<td>echocardiogram</td>
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<tr>
<td>Abbreviation</td>
<td>Term</td>
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<td>--------------</td>
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</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol 5-Dimension Questionnaire</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptors</td>
</tr>
<tr>
<td>erbB</td>
<td>erythroblastic leukemia viral oncogene homolog</td>
</tr>
<tr>
<td>FACT-B</td>
<td>Functional Assessment of Cancer Therapy for Breast Cancer</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>granulocyte macrophage colony stimulating factor</td>
</tr>
<tr>
<td>HbsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HER2</td>
<td>human epidermal growth factor receptor 2; also termed erbB-2</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HOA</td>
<td>health outcomes assessment</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>ICF</td>
<td>informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IDMC</td>
<td>independent data monitoring committee</td>
</tr>
<tr>
<td>IEC</td>
<td>independent ethics committee</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVRS</td>
<td>interactive voice response system</td>
</tr>
<tr>
<td>IWRS</td>
<td>interactive web response system</td>
</tr>
<tr>
<td>LD</td>
<td>longest diameter</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MBC</td>
<td>metastatic breast cancer</td>
</tr>
<tr>
<td>MED</td>
<td>minimum efficacious dose</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>MHLW</td>
<td>Ministry of Health, Labour and Welfare</td>
</tr>
<tr>
<td>MMRM</td>
<td>mixed model repeated measures</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
</tr>
<tr>
<td>MUGA</td>
<td>multiple gated acquisition</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>NSCLC</td>
<td>non-small cell lung cancer</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>ORR</td>
<td>objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free-survival</td>
</tr>
<tr>
<td>PgR</td>
<td>progesterone receptors</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetics</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceuticals and Medicinal Devices Agency</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>RTK</td>
<td>receptor tyrosine kinases</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SLD</td>
<td>sum of the longest diameter</td>
</tr>
<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SUSAR</td>
<td>suspected unexpected serious drug reactions</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>TdP</td>
<td>torsade de pointes</td>
</tr>
<tr>
<td>t½</td>
<td>terminal half life</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time to maximum plasma concentration</td>
</tr>
<tr>
<td>TKI</td>
<td>tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>TTP</td>
<td>time to tumor progression</td>
</tr>
<tr>
<td>Vss/F</td>
<td>steady state volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
</tbody>
</table>
### 6.0 Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>A measurement that is linked to normal health, disease, or response to drug treatment.</td>
</tr>
<tr>
<td>Genotype</td>
<td>A specific combination of alleles for a given gene that can be used to predict the function of the gene’s encoded protein.</td>
</tr>
<tr>
<td>Investigational product</td>
<td>Pharmaceutical form of an active ingredient or placebo, comparator, nutritional product, dietary supplement, herbal product, vaccine, biologic product, or device being tested or used as a reference in a clinical trial, including a product with a marketing authorization, when used or assembled in a way different from the approved form, or for an unapproved indication, or used to gain further information about an approved use.</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td>The science of using qualitative assessments of DNA sequence only (ie, genotyping) to study the differences in disease mechanism and/or drug response due to variation in the sequences of individual genes. Because DNA is stable, only a single DNA sample is required from a subject during a study in order to perform a pharmacogenetic analysis.</td>
</tr>
<tr>
<td>Protein</td>
<td>Large molecules consisting of long sequences of amino acids. Proteins are 75% of the dry weight of most cell matter and are the building blocks of all cells.</td>
</tr>
<tr>
<td>Regulation</td>
<td>The term regulation refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations (United States); the European Clinical Trials Directive; the Good Clinical Practice: Consolidated Guideline (Canada); the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice; the Pharmaceutical Affairs Law and Good Clinical Practice (Japan); the Therapeutic Goods Administration Annotated International Conference on Harmonisation (ICH) Guidelines (Australia); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Regulatory agency</td>
<td>The term <em>regulatory agency</em> refers to all health and regulatory agencies with oversight responsibility for the study. These may be international, national, or local and may include but are not limited to the Australian Therapeutic Goods Administration (TGA); the Canadian Health Products and Food Branch (HPFB); the European Medicines Agency (EMEA); the Japanese Ministry of Health, Labour and Welfare (MHLW); the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); the US Food and Drug Administration (FDA).</td>
</tr>
<tr>
<td>Screen Failure</td>
<td>Only a subject who has signed an informed consent form, does not meet eligibility criteria and is not randomized will be designated a screen failure. Subjects who meet all eligibility criteria but discontinue from the study for other reasons (e.g., Subject Request) are not screen failures, and their reason for conclusion of subject participation will be recorded on the Conclusion of Patient Participation CRF.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>The term <em>sponsor</em> refers but is not limited to the <em>sponsor</em> listed in the front of this document.</td>
</tr>
<tr>
<td>Subject</td>
<td>A participant in a clinical study. A subject may be healthy or have a disease. For obtaining informed consent, this term also includes legally acceptable representative where applicable.</td>
</tr>
</tbody>
</table>
7.0 SYNOPSIS

This is a synopsis. The body of the protocol must be referenced for the complete study information.

Study Title: A Phase 3, Randomized, Open-Label, Two-Arm Study of Neratinib Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel as First-Line Treatment for ErbB-2-Positive Locally Recurrent or Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Phase</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>3144A2-3005-WW</td>
<td>3</td>
<td>Interventional</td>
</tr>
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</table>

Condition/Disease: Locally Recurrent or Metastatic Breast Cancer.

Approximate

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Duration of Subject Participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200</td>
<td>~31 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Study Centers</th>
<th>Duration of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>~350</td>
<td>~54 months (includes 23.5 months enrollment, 12 months treatment, 18 months survival follow-up for last subject enrolled)</td>
</tr>
</tbody>
</table>

Rationale:

Breast cancer is the most frequently diagnosed malignancy and 1 of the top 2 causes of cancer-related deaths in women in the world. Among women with primary breast cancer, 40% to 50% will develop metastatic disease despite active cytotoxic chemotherapy and newer biologic agents. The erythroblastic leukemia viral oncogene homolog (erbB) family of receptor tyrosine kinases (RTKs) consists of 4 members: erbB-1 (epidermal growth factor receptor [EGFR], human erythrocyte growth factor 1 [HER1]), erbB-2 (HER2, neu), erbB-3 (HER3) and erbB-4 (HER4). The erbB family of receptors is involved in cell proliferation, tumorigenesis, and metastasis and is abnormally expressed in multiple tumor types. The oncogenic role of erbB-2 has been most extensively documented in breast cancer, where it is overexpressed (as measured by fluorescence in situ hybridization [FISH]) + or immunohistochemistry [IHC] 3+) in 25% to 30% of breast cancers. ErbB-2-overexpressing breast cancers are associated with more aggressive disease, higher recurrence and metastatic rates, and worse survival.

Trastuzumab is a humanized monoclonal antibody that acts extracellularly on the erbB-2 receptor. Paclitaxel is among the most active agents in the treatment of metastatic breast cancer. The combination of paclitaxel plus trastuzumab has been shown to be more effective than paclitaxel alone in the treatment of erbB-2-positive breast cancer, increasing both response rate and overall survival. Among preferred treatment regimens for subjects with breast cancer, paclitaxel plus trastuzumab has emerged as a widely accepted standard of care for erbB-2-positive disease.

Neratinib is a small molecule, irreversible pan-erbB receptor inhibitor that blocks signaling through the erbB-2 pathway by acting intracellularly as a tyrosine kinase inhibitor, a mechanism of action that is different from trastuzumab. Its clinical activity in erbB-2 positive breast cancer has been shown in phase 1 and phase 2 trials. In a phase 1 study of neratinib monotherapy, a 32% objective response rate (ORR) was observed among subjects with trastuzumab refractory erbB-2 overexpressing disease (specifically 8 of 25 subjects had partial response). These phase 1 results were confirmed in a phase 2 study of neratinib monotherapy. An interim data snapshot
from 30 October 2008 showed that the ORR was 57% (95% CI; 43, 68) and median progression free survival was 40 weeks (95% CI; 32, 55) in trastuzumab naive subjects who received prior chemotherapy treatment in the metastatic setting. Preliminary results from an ongoing phase 2 trial of neratinib in combination with paclitaxel indicate that the combination was well tolerated with adverse events (AEs) similar to those seen with neratinib or paclitaxel when administered alone. As of 25 March 2009, 102 subjects have been enrolled in the maximum tolerated dose confirmation portion of the study. Twenty (20) of these subjects were treated in first line setting and considered evaluable for efficacy. Among this evaluable population, 12 subjects had either confirmed complete or partial responses [ORR 60%, (95% CI, 36%; 81%)]. Thus, the combination of neratinib with paclitaxel may have additional beneficial effects in the treatment of subjects whose tumors are erbB-2-positive.

Objectives:
Primary:
To compare the independently assessed progression free survival (PFS) following treatment with neratinib in combination with paclitaxel versus trastuzumab plus paclitaxel in subjects who have not received previous treatment for erbB-2-positive locally recurrent or metastatic breast cancer.

Secondary:
• To compare independently assessed clinical activity between treatment arms by measuring: overall survival (OS), ORR, and duration of response (DOR) and clinical benefit rate (CBR; CR + PR + stable disease [SD] ≥ 24 weeks).
• To compare safety (AEs; serious adverse events [SAEs]) between treatment arms.
• To compare patient reported breast specific quality of life between treatment arms.
• To compare the frequency of and time to symptomatic or progressive central nervous system (CNS) lesions between treatment arms.

Exploratory:
• To compare health care utilization including hospitalization and physician visits between treatment arms.
• To identify biomarkers predictive of neratinib response/resistance (apart from erbB-2).

Design:
This is a multicenter phase 3, randomized, open-label, parallel-group study. The study will include the following 2 treatment arms:
• Paclitaxel weekly + neratinib daily (experimental arm)
• Paclitaxel weekly + trastuzumab weekly (control arm)

One thousand two hundred (1200) subjects will be randomized in a 1:1 fashion (600 in each arm) to receive treatment with either: paclitaxel in combination with neratinib (experimental arm); or paclitaxel and trastuzumab (control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent. Subjects will be stratified by prior adjuvant trastuzumab exposure (yes/no), prior lapatinib exposure (yes/no), estrogen receptors (ER)/progesterone receptors (PgR) status (ER and/or PgR positive, ER and PgR negative), and region (1=United States; 2=Western Europe, Australia, South Africa, and Canada; 3=Asia Pacific, India, Eastern Europe, Africa, and South America).

Subjects discontinuing from the active treatment phase will enter the follow-up phase during which survival and new anticancer therapy information will be collected. The follow-up phase will continue until a total of approximately 631 deaths have been observed.
Main Inclusion Criteria:
1. Female subjects aged 18 years or older.
2. Histologically and/or cytologically confirmed diagnosis of breast cancer.
3. Locally recurrent or metastatic breast cancer that is not amenable to curative surgery and/or radiation.
4. Documentation of erbB-2 gene amplification by FISH (as defined by a ratio >2.2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer’s kit instruction) or documentation of erbB-2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory or initial diagnostic results utilizing 1 of the sponsor-approved assays. If erbB-2 status is unavailable or was determined using a test other than a sponsor-approved assay and cannot be assessed using 1 of these assays prior to randomization, testing and study eligibility must be obtained from the sponsor-identified central laboratory prior to randomization.
5. All subjects must have tumor tissue (ie, most recent archived formalin fixed-embedded tissue [block or unstained slides]) available for central review of erbB-2 expression levels by FISH testing performed by the sponsor-identified central laboratory.
6. Documentation of ER/PgR status (positive or negative) based on local laboratory or initial diagnostic results must be available before study entry. If results are unavailable, tumor tissue may be sent to the sponsor-identified central vendor for assessment prior to study entry as per investigator’s discretion.
7. At least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.
8. Eastern Cooperative Oncology Group (ECOG) status of 0 to 2 (not declining within 2 weeks prior to signing informed consent).
9. Left ventricular ejection fraction (LVEF) within institutional range of normal as measured by multiple-gated acquisition (MUGA) or echocardiogram (ECHO).
10. Screening laboratory values within the following parameters:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/mm^3)
   - Platelet count ≥ 100 x 10^9/L (100,000/mm^3)
   - Hemoglobin ≥ 9.0 g/dL (90 g/L)
   - Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
   - Total bilirubin ≤ 1.5 x ULN (< 3 ULN if Gilbert’s disease)
   - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases are present)
11. Recovery (to grade 1 or baseline) from all clinically significant acute adverse effects of prior therapies (excluding alopecia).
12. All subjects who are not surgically sterile or postmenopausal must agree and commit to the use of a reliable method of birth control starting 2 weeks prior to the administration of the first dose of investigational product until 28 days after the last dose of investigational product. A woman of childbearing potential is one who is biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives.

Main Exclusion Criteria:
1. Prior systemic anticancer therapy (including cytotoxic chemotherapy, signal transduction inhibitors [eg, lapatinib], biologic [eg, trastuzumab], or other investigational anticancer therapy) for locally recurrent or metastatic disease. Prior endocrine therapy in any setting is allowed.
2. Prior treatment with an erbB-2 inhibitor, other than trastuzumab, lapatinib, or the combination of the two, in the neoadjuvant or adjuvant setting.
3. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of >400 mg/m^2, epirubicin dose >800 mg/m^2, or the equivalent dose for other anthracyclines or derivatives
Neratinib (HKI-272)
Protocol 3144A2-3005-WW
21 May 2009

(eg, 72 mg/m² of mitoxantrone).

4. Subjects with recurrence or progression of disease within 12 months after completion of adjuvant or neoadjuvant systemic anticancer therapy (including cytotoxic chemotherapy, signal transduction inhibitors [eg, lapatinib], biologic [eg, trastuzumab], or other investigational anticancer therapy), other than endocrine therapy, for early breast cancer.

5. Subjects with bone or skin as the only site of measurable disease. Subjects with skin lesions measurable by computed tomography (CT) scans or magnetic resonance imaging (MRI) as only site of measurable disease are allowed.

6. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other cancer therapy within 2 weeks before the administration of the first dose of investigational product.

7. Active uncontrolled or symptomatic CNS metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Subjects with a history of CNS metastases or cord compression are eligible if they have been definitively treated and are off anticonvulsants and steroids for at least 4 weeks before first dose of investigational product.

8. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association [NYHA] functional classification of ≥3), unstable angina, and myocardial infarction (within 12 months of study entry).

9. Inadequately controlled hypertension (ie, systolic blood pressure [BP] > 180 mm Hg or diastolic BP > 100 mm Hg).

10. Family history of congenital long or short QT syndrome, Brugada syndrome or QT/QTc interval > 0.45 second or known history of QT/QTc prolongation or torsade de pointe (TdP).

11. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn’s disease, malabsorption, or grade ≥2 diarrhea of any etiology at baseline).

12. Preexisting grade 2 or greater motor or sensory neuropathy.

13. History of life-threatening hypersensitivity reaction to taxanes or trastuzumab.

14. Clinical contraindication to steroids preventing their use as part of paclitaxel premedication.

15. Women who are pregnant, breast-feeding, or women of childbearing potential who are not using effective contraception during participation in the study and do not agree to do so for at least 28 days after final dose of investigational product.

16. Inability or unwillingness to swallow oral medications.

17. Immunocompromised subjects, including known seropositivity for human immunodeficiency virus (HIV), or current or chronic hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen [HbsAg] or antibody to hepatitis C virus [anti HCV] with confirmatory testing). (Note: testing is not mandatory to be eligible for the study. However if a subject is at risk for having undiagnosed HCV [due to history of injection drug use or due to geographic location for example], testing at screening should be considered.)

18. Any other cancer, including contralateral breast cancer, within 5 years prior to screening with the exception of adequately treated ductal carcinoma in situ, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin.

19. Evidence of significant medical illness or abnormal laboratory finding that, in the investigator’s judgment, will substantially increase the risk associated with the subject’s participation in, and completion of, the study, or could preclude the evaluation of the subject’s response. Examples include, but are not limited to, serious active infection (ie, requiring intravenous [IV] antibiotic or antiviral agent), uncontrolled major seizure disorder, significant pulmonary disorder (eg, interstitial pneumonitis, pulmonary hypertension), or psychiatric disorder that would interfere with the subject safety or informed consent.
**Concomitant Treatment:**

**Prohibited:**
- Any concurrent chemotherapy, radiotherapy, surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents and hormonal agents.

**Permitted:**
- Standard therapies for preexisting medical conditions, medical and/or surgical complications, and palliation. All medications should be recorded.
- Antidiarrheal medications. Subjects should be instructed to treat diarrhea at its earliest occurrence. If significant diarrhea recurs, prophylactic loperamide or other anti-diarrhea medications should be recommended.
- Bisphosphonates, regardless of indication, provided subjects have been on stable doses for at least 2 weeks prior to randomization. Stable dose should be maintained during the investigational product treatment period. Subjects requiring initiation of bisphosphonate treatment, during the course of the study, should be discontinued due to progressive disease unless disease progression can be completely ruled out and clearly documented in the subject’s source documentation.
- Secondary prophylactic use of growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]) may be implemented per the American Society of Clinical Oncology (ASCO) guidelines at the investigator’s discretion if significant neutropenia or febrile neutropenia/infection is observed.

**Other:**
- Subjects should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (eg, ketoconazole) for the duration of the active phase of the study. Subjects should also avoid grapefruit and herbal remedies, including St John's Wort.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as premedication for paclitaxel, as antiemetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- Subjects using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECGs) at the investigator’s discretion.

**Investigational product(s) and Administration:**
- Neratinib (240 mg) orally once daily.
- Paclitaxel 80 mg/m² IV weekly (administered on days 1, 8, and 15 of a 28-day cycle).
- Trastuzumab (4 mg/kg IV x 1 initial followed by 2 mg/kg IV weekly) on days 1, 8, 15, and 22 of a 28-day cycle.

**Safety Evaluation:**
All safety assessments are outlined in the study flowchart. Safety will be assessed based on medical history, vital sign measurements, physical examination findings, ECG results, MUGA or ECHO, and laboratory assessments (ie, serum chemistry, complete blood count [CBC] with differential, coagulation panel, beta-human chorionic gonadotropin [β-HCG]). AEs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC), version 3. SAEs will be reported until 28 days after the last dose of investigational product(s) and will be followed until resolution. Any SAEs beyond 28 days after the last dose of investigational product(s) considered related to investigational product(s) will also be reported. An Independent Data Monitoring Committee will meet approximately every 6 months to monitor safety and efficacy data.
### Efficacy Evaluation:

Clinical activity will be assessed using RECIST criteria by performing tumor assessments for all subjects at screening, and then after every 8 weeks of treatment. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death.

Follow-up after subject discontinuation of investigational product will be conducted approximately every 12 weeks to assess for survival until subject death.

To be considered evaluable for efficacy, subjects must have completed at least one follow-up radiological tumor assessment approximately 8 weeks after first dose of investigational product, received at least 7 doses of neratinib or 2 doses of trastuzumab and at least 2 doses of paclitaxel and have no major protocol violations (as defined in the protocol).

Tumor response based efficacy endpoints (ie, ORR, PFS, DOR, and CBR) analyses will be based on assessments performed by investigators, and by an independent radiology vendor. The interim and primary analyses will be based on the independent vendor’s assessments.

### Health Outcomes Assessment:

The following questionnaires will be used to collect patient-reported quality of life data:

1. Breast cancer specific quality of life - Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B)
2. Generic quality of life using the EuroQual 5 Dimension questionnaire (EQ-5D)

Patient-reported outcomes assessments will be performed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6…), and at the time of treatment discontinuation.

Data on underlying disease related and non-disease related physician visits, emergency visits, nurse visits, and hospitalizations related to breast cancer diagnosis and treatment will be collected to assess impact on health care resource utilization.

Reasons for missing data will be documented and incorporated into the analysis as necessary.

### Pharmacogenetic:

HER-2/neu status will be confirmed by FISH using a central vendor.

Original tumor biopsy sample will be studied for: *PIK3CA* mutations in hotspots (ie, exons 9,20 via gene sequencing), *PIK3CA* amplification (q-PCR or FISH), PTEN loss and erbB family members (erbB-1, erbB-3, and erbB-4) (IHC), c-Myc amplification (q-PCR or FISH). Blood samples will be taken at baseline; cycle 1, day 15; and cycle 2, day 1 for assessment of serum HER2/ECD.

### Statistical Considerations:

The primary endpoint is PFS, defined as time from date of randomization to date of progressive disease (PD) or death if no progression. The secondary endpoints include OS, ORR, CBR, DOR, breast cancer specific quality of life, safety, CNS criteria, and biomarkers.

**Sample Size:** This is a group sequential design with 1 interim analysis intended for stopping for futility. The power family (delta=0.3) beta spending function is employed for futility analysis. The Lan-Demets
O’Brien-Flemming (OF) alpha spending function is used for controlling the type 1 error rather than early stopping for efficacy on PFS.

The assumptions for sample size calculations are the following. Median PFS of the trastuzumab plus paclitaxel arm is 9 months and median PFS of neratinib + paclitaxel arm is 11.7 months (30% improvement in median PFS, hazard ratio [HR]=0.77). Enrollment rate is expected to be about 60 per month. The design is based on 1-sided log-rank test with alpha=0.025, power=90% (adjusted per Carroll 2007), and an interim analysis when 40% of required PFS events are observed. The 2-year dropout rate is assumed to be 15%. Taking into account the power loss due to time lapse between tumor assessments, a total of 749 PFS events will be needed. With 1200 subjects enrolled in 23.5 months, the final PFS analysis will be about 30.5 months (2.5 years) from the date of first subject randomization.

**Power for OS Analysis:** Assume median OS of 24 months for the trastuzumab plus paclitaxel arm and 30 months for neratinib plus paclitaxel arm (25% improvement on median OS, HR=0.8). With 1200 subjects enrolled in about 23.5 months, there will be about 631 observed OS events in about 44 months from the date of first subject randomization. This provides 80% power for a one-sided log-rank test with alpha=0.025. One (1) interim analysis for OS will be performed at the time of final PFS analysis. Type I error will be controlled through a power family (delta=-0.5) alpha spending function.

**Statistical Analysis:** The primary analyses of the efficacy endpoints will be based on the intent-to-treat (ITT) population. The ITT population is defined as all subjects randomized to the study.

For the primary efficacy analysis, PFS, OS, and DOR will be compared using the stratified log-rank test with prior exposure to erbB-2 inhibitors (prior adjuvant trastuzumab or prior lapatinib exposure, Yes/No) and ER/PgR (positive/negative) as stratification variables. The hazard ratio and corresponding 95% 2-sided confidence interval using stratified Cox proportional hazard regression will be presented. The median time-to-event will be estimated using the Kaplan-Meier method and will be reported with two-sided 95% confidence intervals for each arm. Sensitivity analyses of the primary endpoint will be described in the statistical analysis plan (SAP).

ORR and CBR will be compared between the 2 treatment arms using the generalized Cochran-Mantel-Haenszel (CMH) test adjusted for prior exposure to erbB-2 inhibitors (prior adjuvant trastuzumab or prior lapatinib exposure, Yes/No) and ER/PgR (positive/negative). For each treatment arm, the rates along with the exact 95% confidence intervals will be computed.

AEs and SAEs will be summarized by arm. The incidence of grade 3 or higher diarrhea and cardiac failure events will be compared between the 2 treatment arms using the Fisher’s exact test.

Presence or absence of symptomatic or progressive CNS lesions will be assessed at tumor progression for each patient. Frequency of symptomatic or progressive CNS lesions at the time of tumor progression will be summarized by arm and compared between the 2 treatment arms using the generalized CMH test. The median time to symptomatic or progressive CNS lesions will be estimated for each arm using the Kaplan-Meier method and compared between the 2 treatment arms using the stratified log-rank test.

Breast cancer specific quality of life scores and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for prespecified covariates.
Discontinuation from the study and dose reduction due to AEs and therapies implemented to treat some specific AEs will be compared between the treatment groups to assess the impact of AEs on treatment compliance. Physician visits, emergency visits, nurse visits, and hospitalizations related to breast cancer diagnosis and treatment will be compared between the 2 treatment groups as exploratory analysis.

Subjects will be stratified by prior adjuvant trastuzumab exposure (yes/no), prior lapatinib exposure (yes/no), ER/PgR status (ER and/or PgR positive, ER and PgR negative) and by region (1=United States; 2=Western Europe, Australia, and Canada; 3=Asia-Pacific, India, Eastern Europe, Africa, South America).

**Interim Analysis:**
Two (2) interim analyses will be performed. One (1) is for PFS and the other 1 is for OS. The interim analysis for PFS will occur when 40% PFS events (300 PFS events) have been observed. The interim analysis will occur at about 17.7 months from first randomization. Boundaries will be calculated based on the actual numbers of events observed. If the interim analysis is conducted as planned and p-value > 0.4207, then the trial may be stopped for futility based on PFS. The trial will not be stopped for efficacy at the interim PFS analysis. The stopping probability is 58% under the null hypothesis and 2% under the alternative hypothesis for interim PFS analysis. The interim analysis for OS will be performed at the time of final PFS analysis. The efficacy on OS might be claimed if p-value< 0.0012.

The interim analysis will be conducted by an independent statistician outside of Wyeth and the results of the data analysis will be sent to the independent data monitoring committee (IDMC) for review. The summary data analyses will not be shared with the study team so that the trial may remain blinded.

**Final Analysis:**
Final PFS analysis will be conducted when approximately 749 PFS events have been observed. If the interim and final analyses occur as planned, a p-value < 0.0249, will demonstrate the superiority of neratinib in combination with paclitaxel.

A follow-up analysis of overall survival will be conducted when approximately 631 OS events have been observed. If the interim and follow-up analyses for OS occur as planned, a p-value < 0.0249, will demonstrate the superiority of neratinib in combination with paclitaxel for OS.

**Ethical Considerations:**
This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the IRB/IEC-approved ICF.
# STUDY FLOWCHART (S)

## 8.1 Study Flowchart for Subjects Receiving Neratinib + Paclitaxel

<table>
<thead>
<tr>
<th>Study week</th>
<th>Screening</th>
<th>Treatment period</th>
<th>Survival follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cycle 2 and higher&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cycle day</td>
<td></td>
<td>Week</td>
<td>Week</td>
</tr>
<tr>
<td></td>
<td>1 8 15 22</td>
<td>1 2 3 4 1 2 3 4</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>Study week</td>
<td></td>
<td>-28 ± 2</td>
<td>± 2 ± 2 ± 4 ± 2 ± 2</td>
</tr>
<tr>
<td>Cycle Visit Window in days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical/cancer history/demography</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>β-HCG for women of child bearing potential</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Complete blood count with differential&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistry panel&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Coagulation panel&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacogenetic blood draw&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
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<td>Stool culture&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Digital ECG&lt;sup&gt;1&lt;/sup&gt; (12 lead)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IGCA or ECHO&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor assessment&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Neratinib administration&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications/Non-pharmacologic treatments, and Adverse Events&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health Outcomes Assessments&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health Care Resource Utilization Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>1</sup> Continuous daily dosing

<sup>2</sup> As clinically indicated

<sup>3</sup> Monitored continuously
Footnotes:

a. One (1) cycle = 28 days.
b. End of treatment visit will be performed as soon as possible, but no later than 4 weeks after last dose of investigational product and prior to the start of any new anticancer therapy.
c. **For subjects who discontinue the active treatment phase due to radiographic disease progression:** 1) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 2) New anticancer treatment administered after the subject discontinues study drug will be collected and documented.

d. **For subjects who discontinue the active treatment phase for reasons other than radiographic disease progression:** 1) Tumor assessments will continue to be performed approximately every 8 weeks (± 4 days) until documented disease progression, initiation of new anticancer therapy or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up), whichever occurs first 2) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 3) New anticancer treatments administered after the subject discontinues study drug will be collected and documented.

d. Informed consent may be obtained greater than 28 days from day 1; however, must be obtained prior to any protocol required assessments that are not considered standard of care, being performed. Radiographic assessments and/or LVEF testing performed as routine procedures before the signing of informed consent form do not need to be repeated and may be used as screening assessments, if performed within the protocol-allowed screening window (if applicable) and if per the protocol-defined method(s) for this procedure. Appropriate documentation indicating that these radiographic tumor and/or LVEF assessments were performed as standard of care must be available in the subject’s source notes.

e. Documentation of locally assessed erbB-2 status by FISH, IHC or CISH using one of the sponsor-approved assay should be retrieved. Tumor tissue (ie, most recent archived formalin fixed-embedded tissue [block or unstained slides]) should also be collected and sent for central FISH testing (will not be used for eligibility unless prior documentation does not already exist).

f. A complete physical examination including a full neurological exam, which may be performed by a physician, registered nurse or other qualified health care provider is only required at screening. Symptom directed physical and neurological examinations will be performed at subsequent visits. All neurological events must be followed until resolution (to baseline or grade 1 level).

g. To be performed only at cycle 2. Starting with cycle 3, symptom directed physical examination will only be performed on day 1 of every cycle.

h. Does not need to be repeated if performed within 14 days before cycle 1, day 1.

i. The sample can be serum or urine.

j. Complete blood count (CBC) to include WBC with 3-5 part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count (ANC).

k. Lab values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. CBC may be performed up to 3 days prior to paclitaxel infusions.
1. Serum chemistry includes sodium, potassium, calcium, chloride, bicarbonate or carbon dioxide, albumin, BUN or urea, glucose, total protein, serum creatinine, ALT, AST, alkaline phosphatase, total bilirubin, and magnesium. Serum chemistry will be monitored every 4 weeks and whenever clinically indicated. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

m. Coagulation panel to include prothrombin time (PT; expressed in seconds) or international normalized ratio (INR), and partial thromboplastin time (PTT). Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

n. Blood samples will be taken at baseline (screening), cycle 1, day 15 and cycle 2, day 1 for assessment of serum HER2/ECD. Baseline sample may be drawn at anytime from the time of informed consent signing up to the administration of the first dose of investigational product.

o. If stool culture was performed to exclude infectious causes of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia) results should be reported on the appropriate eCRF.

p. If ECHO or MUGA was performed as part of the routine care within 6 weeks of first dose, this result will be accepted for screening purposes. At the end of treatment visit, testing does not need to be repeated if done within 8 weeks prior to the visit. It is strongly recommended to use the same method of measurement for the same subject throughout the duration of the study. During the treatment period, ECHO/MUGA will be performed every 12 weeks starting with cycle 4, day 1. If deterioration of LVEF is observed then ECHO/MUGA should be performed every 4 weeks and test-article dose adjustments should be performed.

q. Tumor assessments will be performed approximately every 8 weeks, regardless of dose delays and/or interruptions. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death. Tumor assessment images will be sent to a central independent vendor for review. Please refer to Study Reference Manual for guidelines.

r. Neratinib will be taken daily with food, preferably in the morning. Subjects will continue neratinib treatment until progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

s. Paclitaxel will be administered on a weekly basis on days 1, 8, and 15 of a 28-day cycle. Subjects will continue paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator’s discretion. Treatment should be stopped in case of disease progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

t. Concomitant medications and non-pharmacologic treatments/therapies are recorded from 14 days prior to signing the ICF until the end of treatment visit. AEs and SAEs are monitored continuously and recorded in the source documents, from the signing of consent form until 28 days after the last dose of investigational products. SAEs will be reported and followed until resolution. Any SAEs beyond 28 days after the last dose of investigational products considered related to investigational products will be reported. Documentation of AE and concomitant treatment (medications and non-pharmacologic) data on the eCRF will be done. Data will be done on an ongoing basis.

u. FACT-B and EQ-5D will be assessed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6, etc), at the time of treatment discontinuation. Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. On the day of study drug discontinuation, it is acceptable for the questionnaires to be administered after study procedures are completed.
v. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (ie, 12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (eg, death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or interim data analyses.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECHO = echocardiogram; CISH = chromogenic in situ hybridization; ECG = electrocardiogram; EQ-5D = EuroQual 5 Dimension questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; INR = international normalized ratio; MUGA = multiple-gated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time.
## 8.2 Study Flowchart for Subjects Receiving Trastuzumab + Paclitaxel

<table>
<thead>
<tr>
<th>Study week</th>
<th>Screening</th>
<th>Treatment period</th>
<th>Survival follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cycle 2 and higher&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week</td>
<td>Week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cycle day</td>
<td></td>
<td>±2</td>
<td>±2</td>
</tr>
<tr>
<td>Study Visit Window in days</td>
<td>-28 to 1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Informed Consent&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor tissue for FISH/IHC/CISH testing&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical/cancer history/demography</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examinations&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>Vitals signs&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>β-HCG for women of child bearing potential&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Complete blood count with differential&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum chemistry panel&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>Coagulation panel&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic blood draw&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td>Stool Culture&lt;sup&gt;k&lt;/sup&gt;</td>
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<tr>
<td>Digital ECG (12 lead)&lt;sup&gt;l&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>MUGA or ECHO&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Tumor assessment&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>X</td>
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<tr>
<td>Trastuzumab administration&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Paclitaxel administration&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>X</td>
<td>X&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>Health Outcomes Assessments&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Health Care Resource Utilization Assessment</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- <sup>a</sup> Cycle 1 and Cycle 2 and higher for all patients
- <sup>b</sup> Week 1-4 for Cycle 2 and higher
- <sup>c</sup> Visit 1
- <sup>d</sup> Data collected during cycle 1
- <sup>e</sup> Data collected for all cycles
- <sup>f</sup> Data collected during cycle 1 and cycle 2
- <sup>g</sup> Data collected for all cycles
- <sup>h</sup> Data collected for all cycles
- <sup>i</sup> Data collected for women of child bearing potential
- <sup>j</sup> Data collected for all cycles
- <sup>k</sup> Data collected for all cycles
- <sup>l</sup> Data collected for all cycles
- <sup>m</sup> Data collected for all cycles
- <sup>n</sup> Data collected for all cycles

*As clinically indicated*
Footnotes:
a. One (1) cycle = 28 days.
b. End of treatment visit will be performed as soon as possible, but no later than 4 weeks after last dose of investigational product and prior to the start of any new anticancer therapy.
c. For subjects who discontinue the active treatment phase due to radiographic disease progression: 1) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 2) New anticancer treatment administered after the subject discontinues study drug will be collected and documented.

d. Informed consent may be obtained greater than 28 days from day 1, however must be obtained prior to any protocol required assessments that are not considered standard of care, being performed. Radiographic assessments and/or LVEF testing performed as routine procedures before the signing of informed consent form do not need to be repeated and may be used as screening assessments, if performed within the protocol-allowed screening window (if applicable) and if per the protocol-defined method(s) for this procedure. Appropriate documentation indicating that these radiographic tumor and/or LVEF assessments were performed as standard of care must be available in the subject’s source notes.

e. Documentation of locally assessed erbB-2 status by FISH, IHC or CISH using one of the sponsor-approved assay should be retrieved. Tumor tissue (ie, most recent archived formalin-fixed-embedded tissue [block or unstained slides]) should also be collected and sent for central FISH testing (will not be used for eligibility unless prior documentation does not already exist).

f. A complete physical examination, including a full neurological exam, which may be performed by a physician, registered nurse or other qualified health care provider, is only required at screening. Symptom directed physical and neurological examinations will be performed at subsequent visits. All neurological events must be followed until resolution (to baseline or grade 1 level).

g. To be performed at cycle 2 only. Starting with cycle 3, symptom directed physical examination will only be performed on day 1 of every cycle.

h. Does not need to be repeated if performed within 14 days before cycle 1, day 1.

i. The sample can be serum or urine.

j. Complete blood count (CBC) to include WBC with 3-5 part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count (ANC).

k. Lab values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. CBC may be performed up to 3 days prior to paclitaxel / trastuzumab infusions.
1. Serum chemistry includes sodium, potassium, calcium, chloride, bicarbonate or carbon dioxide, albumin, BUN or urea, glucose, total protein, serum creatinine, ALT, AST, alkaline phosphatase, total bilirubin and magnesium. Serum chemistry will be monitored every 4 weeks and whenever clinically indicated. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

m. Coagulation panel to include prothrombin time (PT; expressed in seconds) or international normalized ratio (INR), and partial thromboplastin time (PTT). Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

n. Blood samples will be taken at baseline (screening), cycle 1, day 15 and cycle 2, day 1 for assessment of serum HER2/ECD. Baseline sample may be drawn at anytime from the time of informed consent signing up to the administration of the first dose of investigational product.

o. If stool culture was performed to exclude infectious causes of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia) results should be reported on the appropriate eCRF.

p. If ECHO or MUGA was performed as part of the routine care within 6 weeks of first dose, this result will be accepted for screening purposes. At the end of treatment visit, testing does not need to be repeated if done within 8 weeks prior to the visit. It is strongly recommended to use the same method of measurement for the same subject throughout the duration of the study. During the treatment period, ECHO/MUGA will be performed every 12 weeks starting with cycle 4, day 1. If deterioration of LVEF is observed then ECHO/MUGA should be performed every 4 weeks and test-article dose adjustments should be performed.

q. Tumor assessments will be performed approximately every 8 weeks, regardless of dose delays and/or interruptions. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death. Tumor assessment images will be sent to a central independent vendor for review. Please refer to Study Reference Manual for guidelines.

r. Trastuzumab will be administered on a weekly basis. Subjects will continue trastuzumab treatment until progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

s. Paclitaxel will be administered on a weekly basis on days 1, 8 and 15 of a 28-day cycle. Subjects will continue paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator’s discretion. Treatment should be stopped in case of disease progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

t. Concomitant medications and non-pharmacologic treatments/therapies are recorded from 14 days prior to signing the ICF until the end of treatment visit. AEs and SAEs are monitored continuously and recorded in the source documents, from the signing of consent form until 28 days after the last dose of investigational products. SAEs will be reported and followed until resolution. Any SAEs beyond 28 days after the last dose of investigational products considered related to investigational products will be reported. Documentation of AE and concomitant treatment (medications and non-pharmacologic) data on the eCRF will be done within an ongoing basis.

u. FACT-B and EQ-5D will be assessed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6, etc), and at the time of treatment discontinuation. Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. On the day of study drug discontinuation, it is acceptable for the questionnaires to be administered after study procedures are completed.
v. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (ie, 12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (eg, death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or interim data analyses.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CISH = chromogenic in situ hybridization; ECHO = echocardiogram; ECG = electrocardiogram; EQ-5D = EuroQual 5 Dimension questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; FISH = fluorescence in situ hybridization; IHC = immunochemistry; INR = international normalized ratio; MUGA = multiple-gated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time.
# Study Flowchart for Subjects Who Discontinue Paclitaxel and Continue on Neratinib Monotherapy

<table>
<thead>
<tr>
<th>Study week</th>
<th>Treatment period</th>
<th>Survival follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cycle 2 and higher&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Week 1 2 3 4</td>
<td>Week 1 2 3 4</td>
</tr>
<tr>
<td>Cycle day</td>
<td>1 8 15 22 1 8 15 22</td>
<td></td>
</tr>
<tr>
<td>Study Visit Window in days</td>
<td>0 ±2 ±2 ±4 ±2 ±2 ±2 ±2</td>
<td></td>
</tr>
<tr>
<td>Symptom directed physical examination</td>
<td>X X X X X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>β-HCG for women of child bearing potential</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Complete blood count with differential&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistry panel&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation panel&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacogenetic blood draw&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stool culture&lt;sup&gt;h&lt;/sup&gt;</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Digital ECG (12 lead)</td>
<td>Refer to Electrocardiogram Flowchart</td>
<td></td>
</tr>
<tr>
<td>MUGA or ECHO&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor assessment&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neratinib administration&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Continuous daily dosing</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications/Non-pharmacologic treatments, and Adverse Events&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Monitored continuously</td>
<td></td>
</tr>
<tr>
<td>Health Outcomes Assessments&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health Care Resource Utilization Assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Cycle 1 and Cycle 2 and higher are different periods for the treatment cycle.  
<sup>b</sup> End of treatment Visit is the last visit before the end of the treatment period.  
<sup>c</sup> Survival follow-up includes the period after the last treatment.  
<sup>d</sup> Complete blood count with differential includes hemoglobin, leukocyte count, differential, platelet count, and red cell indices.  
<sup>e</sup> Serum chemistry panel includes liver function tests, renal function tests, electrolyte panel, and other metabolic panels.  
<sup>f</sup> Coagulation panel includes PT/INR, aPTT, fibrinogen, and D-dimer.  
<sup>g</sup> Pharmacogenetic blood draw is performed to identify patients who are sensitive to Neratinib.  
<sup>h</sup> Stool culture is performed to detect any gastrointestinal infection.  
<sup>i</sup> Digital ECG (12 lead) is performed as part of the electrocardiogram (ECG) flowchart.  
<sup>j</sup> MUGA or ECHO is performed to assess myocardial function.  
<sup>k</sup> Tumor assessment includes imaging studies to evaluate the tumor burden.  
<sup>l</sup> Concomitant Medications/Non-pharmacologic treatments, and Adverse Events are monitored continuously throughout the study.  
<sup>m</sup> Health Outcomes Assessments include quality of life assessments.  
<sup>n</sup> Health Care Resource Utilization Assessment evaluates the healthcare resources used by the patients.  
<sup>o</sup> Overall Survival is determined at the end of the study period.
Footnotes:

a. One (1) cycle = 28 days.

b. End of treatment visit will be performed as soon as possible, but no later than 4 weeks after last dose of investigational product and prior to the start of any new anticancer therapy.

c. For subjects who discontinue the active treatment phase due to radiographic disease progression: 1) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 2) New anticancer treatment administered after the subject discontinues study drug will be collected and documented.

d. Subjects need to have received at least one dose of paclitaxel before continuing on neratinib monotherapy. Refer to the neratinib + paclitaxel flowchart for details on procedures to be performed at cycle 1, day 1. Continuation on neratinib monotherapy following discontinuation of paclitaxel for intolerable toxicity or treatment completion per institution/investigator standards will be at the investigator’s discretion.

e. To be performed at cycle 2 only. Starting with cycle 3, symptom directed physical examination will only be performed on day 1 of every cycle.

f. The sample can be serum or urine.

g. Complete blood count (CBC) to include WBC with 3-5 part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count (ANC).

h. Lab values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. CBC may be performed up to 3 days prior to day 1 of each cycle.

i. Serum chemistry includes sodium, potassium, calcium, chloride, bicarbonate or carbon dioxide, albumin, BUN or urea, glucose, total protein, serum creatinine, ALT, AST, alkaline phosphatase, total bilirubin and magnesium. Serum chemistry will be monitored every 4 weeks and whenever clinically indicated. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

j. Coagulation panel to include prothrombin time (PT; expressed in seconds) or international normalized ratio (INR), and partial thromboplastin time (PTT). Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

k. Blood samples will be taken at baseline (screening); cycle 1, day 15; and cycle 2, day 1 for assessment of serum HER2/ECD.
1. If stool culture was performed to exclude infectious causes of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia) results should be reported on the appropriate eCRF.

m. During the treatment period, ECHO/MUGA will be performed every 12 weeks starting with cycle 4, day 1. If deterioration of LVEF is observed then ECHO/MUGA should be performed every 4 weeks and test-article dose adjustments should be performed. At the end of treatment visit, testing does not need to be repeated if done within 8 weeks prior to the visit.

n. Tumor assessments will be performed approximately every 8 weeks, regardless of dose delays and/or interruptions. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death. Tumor assessment images will be sent to a central independent vendor for review. Please refer to Study Reference Manual for guidelines.

o. Neratinib will be taken daily with food, preferably in the morning. Subjects will continue neratinib treatment until progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (e.g., death, subject’s request, lost to follow-up).

p. Concomitant medications and non-pharmacologic treatments/therapies are recorded from 14 days prior to signing the ICF until the end of treatment visit. AEs and SAEs are monitored continuously and recorded in the source documents, from the signing of consent form until 28 days after the last dose of investigational products. SAEs will be reported and followed until resolution. Any SAEs beyond 28 days after the last dose of investigational products considered related to investigational products will be reported. Documentation of AE and concomitant treatment (medications and non-pharmacologic) data on the eCRF will be done on an ongoing basis.

q. FACT-B and EQ-5D will be assessed at screening, day 1 of every other cycle (i.e., cycle 2, 4, 6, etc.), and at the time of treatment discontinuation. Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. On the day of study drug discontinuation, it is acceptable for the questionnaires to be administered after study procedures are completed.

r. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (i.e., 12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (e.g., death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or interim data analyses.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECHO = echocardiogram; ECG = electrocardiogram; EQ-5D = EuroQual 5 Dimension questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; INR = international normalized ratio; MUGA = multiple-gated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time.
### 8.4 Study Flowchart for Subjects Who Discontinue Paclitaxel and Continue on Trastuzumab Monotherapy

<table>
<thead>
<tr>
<th>Study week</th>
<th>Treatment period</th>
<th>End of treatment Visit</th>
<th>Survival follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1 Week</td>
<td>Cycle 2 and higher Week</td>
<td>Visi</td>
</tr>
<tr>
<td></td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
<td>1</td>
</tr>
<tr>
<td>Cycle day</td>
<td>1 8 15 22</td>
<td>1 8 15 22</td>
<td></td>
</tr>
<tr>
<td>Study Visit Window in days</td>
<td>0 ±2 ±2 ±2 ±4 ±2 ±2 ±2 ±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom directed physical examination</td>
<td>X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>β-HCG for women of child bearing potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count with differential</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum chemistry panel</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Coagulation panel</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic blood draw</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Stool Culture</td>
<td>As clinically indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital ECG (12 lead)</td>
<td>Refer to Electrocardiogram Flowchart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUGA or ECHO</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Trastuzumab administration</td>
<td>X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications/Non-pharmacologic treatments, and Adverse Events</td>
<td></td>
<td></td>
<td>Monitored continuously</td>
</tr>
<tr>
<td>Health Outcomes Assessments</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Resource Utilization Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Footnotes:

a. One (1) cycle = 28 days.

b. End of treatment visit will be performed as soon as possible, but no later than 4 weeks after last dose of investigational product and prior to the start of any new anticancer therapy.

c. For subjects who discontinue the active treatment phase due to radiographic disease progression: 1) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 2) New anticancer treatment administered after the subject discontinues study drug will be collected and documented.

For subjects who discontinue the active treatment phase for reasons other than radiographic disease progression: 1) Tumor assessments will continue to be performed approximately every 8 weeks (± 4 days) until documented disease progression, initiation of new anticancer therapy or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up), whichever occurs first 2) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 3) New anticancer treatments administered after the subject discontinues study drug will be collected and documented.

d. Subjects need to have received at least one dose of paclitaxel before continuing on trastuzumab monotherapy. Refer to the trastuzumab + paclitaxel flowchart for details on procedures to be performed at cycle 1, day 1. Continuation on trastuzumab monotherapy following discontinuation of paclitaxel for intolerable toxicity or treatment completion per institution/investigator standards will be at the investigator’s discretion.

e. To be performed at cycle 2 only. Starting with cycle 3, symptom directed physical examination will only be performed on day 1 of every cycle.

f. The sample can be serum or urine.

g. Complete blood count (CBC) to include WBC with 3-5 part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count (ANC).

h. Lab values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. CBC may be performed up to 3 days prior to day 1 of each cycle.

i. Serum chemistry includes sodium, potassium, calcium, chloride, bicarbonate or carbon dioxide, albumin, BUN or urea, glucose, total protein, serum creatinine, ALT, AST, alkaline phosphatase, total bilirubin and magnesium. Serum chemistry will be monitored every 4 weeks and whenever clinically indicated. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

j. Coagulation panel to include prothrombin time (PT; expressed in seconds) or international normalized ratio (INR), and partial thromboplastin time (PTT). Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

k. Blood samples will be taken at baseline (screening), cycle 1, day 15 and cycle 2, day 1 for assessment of serum HER2/ECD.
1. If stool culture was performed to exclude infectious causes of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia) results should be reported on the appropriate eCRF.

m. During the treatment period, ECHO/MUGA will be performed every 12 weeks starting with cycle 4, day 1. If deterioration of LVEF is observed then ECHO/MUGA should be performed every 4 weeks and test-article dose adjustments should be performed. At the end of treatment visit, testing does not need to be repeated if done within 8 weeks prior to the visit.

n. Tumor assessments will be performed approximately every 8 weeks, regardless of dose delays and/or interruptions. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death. Tumor assessment images will be sent to a central independent vendor for review. Please refer to Study Reference Manual for guidelines.

o. Trastuzumab will be administered on a weekly basis. Subjects will continue trastuzumab treatment until progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

p. Concomitant medications and non-pharmacologic treatments/therapies are recorded from 14 days prior to signing the ICF until the end of treatment visit. AEs and SAEs are monitored continuously and recorded in the source documents, from the signing of consent form until 28 days after the last dose of investigational products. SAEs will be reported and followed until resolution. Any SAEs beyond 28 days after the last dose of investigational products considered related to investigational products will be reported. Documentation of AE and concomitant treatment (medications and non-pharmacologic) data on the eCRF will be done will be done on an ongoing basis.

q. FACT-B and EQ-5D will be assessed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6, etc), and at the time of treatment discontinuation. Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. On the day of study drug discontinuation, it is acceptable for the questionnaires to be administered after study procedures are completed.

r. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (ie, 12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (eg, death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or interim data analyses.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECHO = echocardiogram; ECG = electrocardiogram; EQ-5D = EuroQual 5 Dimension questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; INR = international normalized ratio; MUGA = multiple-gated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time.
### Study Flowchart for Subjects Who Discontinue Neratinib or Trastuzumab and Continue on Paclitaxel Monotherapy

<table>
<thead>
<tr>
<th>Study week</th>
<th>Cycle 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cycle 2 and higher&lt;sup&gt;b&lt;/sup&gt;</th>
<th>End of treatment Visit&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Survival follow-up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle day</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; 8 15 22</td>
<td>1 8 15 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Visit Window in days</td>
<td>0 ±2 ±2 ±4 ±2 ±2 ±2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom directed physical examination</td>
<td>X X X X X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>β-HCG for women of child bearing potential&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Complete blood count with differential&lt;sup&gt;g,h&lt;/sup&gt;</td>
<td>X X X X X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serum chemistry panel&lt;sup&gt;h,i&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Coagulation panel&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic blood draw&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Stool Culture&lt;sup&gt;l&lt;/sup&gt;</td>
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<td>X</td>
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</tr>
<tr>
<td>Digital ECG (12 lead)</td>
<td></td>
<td></td>
<td></td>
<td>Refer to Electrocardiogram Flowchart</td>
</tr>
<tr>
<td>MUGA or ECHO</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Paclitaxel administration&lt;sup&gt;s&lt;/sup&gt;</td>
<td>X X X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications/Non-pharmacologic treatments, and Adverse Events&lt;sup&gt;s&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Monitored continuously</td>
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<td>Health Outcomes Assessments&lt;sup&gt;t&lt;/sup&gt;</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Health Care Resource Utilization Assessment</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Footnotes:

a. One (1) cycle = 28 days.

b. End of treatment visit will be performed as soon as possible, but no later than 4 weeks after last dose of investigational product and prior to the start of any new anticancer therapy.

c. **For subjects who discontinue the active treatment phase due to radiographic disease progression:** 1) Survival information will be collected approximately every 12 weeks from the last day of investigational product administration until death or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. 2) New anticancer treatment administered after the subject discontinues study drug will be collected and documented.

d. Subjects need to have received at least one dose of neratinib or trastuzumab before continuing on paclitaxel monotherapy treatment. Refer to the neratinib + paclitaxel or trastuzumab + paclitaxel flowcharts, as applicable, for details on procedures to be performed at cycle 1, day 1. Continuation on paclitaxel monotherapy following discontinuation of neratinib or trastuzumab for intolerable toxicity or treatment completion per institution/investigator standards, as applicable, will be at the investigator’s discretion.

e. To be performed at cycle 2 only. Starting with cycle 3, symptom directed physical examination will only be performed on day 1 of every cycle.

f. The sample can be serum or urine.

g. Complete blood count (CBC) to include WBC with 3-5 part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count (ANC).

h. Lab values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. CBC may be performed up to 3 days prior to paclitaxel infusions.

i. Serum chemistry includes sodium, potassium, calcium, chloride, bicarbonate or carbon dioxide, albumin, BUN or urea, glucose, total protein, serum creatinine, ALT, AST, alkaline phosphatase, total bilirubin and magnesium. Serum chemistry will be monitored every 4 weeks and whenever clinically indicated. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

j. Coagulation panel to include prothrombin time (PT; expressed in seconds) or international normalized ratio (INR), and partial thromboplastin time (PTT). Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

k. Blood samples will be taken at baseline (screening), cycle 1, day 15 and cycle 2, day 1 for assessment of serum HER2/ECD.
1. If stool culture was performed to exclude infectious causes of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia) results should be reported on the appropriate eCRF.

m. Once neratinib or trastuzumab treatment is discontinued, LVEF monitoring should be performed as clinically indicated. At the end of treatment visit, testing does not need to be repeated if done within 8 weeks prior to the visit.

n. Tumor assessments will be performed approximately every 8 weeks, regardless of dose delays and/or interruptions. Missed tumor assessments must be performed as soon as possible. Subjects who discontinue from study treatment for a reason other than objective disease progression will have radiological tumor assessments performed until documented objective disease progression, initiation of new anticancer therapy or death. Tumor assessment images will be sent to a central independent vendor for review. Please refer to Study Reference Manual for guidelines.

o. Paclitaxel will be administered on a weekly basis on days 1, 8, and 15 of a 28-day cycle. Subjects will continue paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator’s discretion. Treatment should be stopped in case of disease progression, symptomatic deterioration, study termination because of intolerable toxicity or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up).

p. Concomitant medications and non-pharmacologic treatments/therapies are recorded from 14 days prior to signing the ICF until the end of treatment visit. AEs and SAEs are monitored continuously and recorded in the source documents, from the signing of consent form until 28 days after the last dose of investigational products. SAEs will be reported and followed until resolution. Any SAEs beyond 28 days after the last dose of investigational products considered related to investigational products will be reported. Documentation of AE and concomitant treatment (medications and non-pharmacologic) data on the eCRF will be done on an ongoing basis.

q. FACT-B and EQ-5D will be assessed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6, etc), and at the time of treatment discontinuation. Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. On the day of study drug discontinuation, it is acceptable for the questionnaires to be administered after study procedures are completed.

r. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (eg, death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or interim data analyses.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECHO = echocardiogram; ECG = electrocardiogram; EQ-5D = EuroQual 5 Dimension questionnaire; FACT-B = Functional Assessment of Cancer Therapy-Breast; INR = international normalized ratio; MUGA = multiple-gated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time.
### 8.6 Tumor Assessment Requirements Flowchart

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Treatment Period</th>
<th>Response Confirmation</th>
<th>End of Treatment Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT or MRI of chest, abdomen, and liver</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>CT or MRI of any other site of disease, as clinically indicated</td>
<td>Required</td>
<td>Required for sites of disease identified at screening</td>
<td>Required for sites of disease identified at screening</td>
<td>Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere</td>
</tr>
<tr>
<td>Bone scan</td>
<td>Required</td>
<td>Required only if disease present or clinically indicated</td>
<td>Required for sites of disease identified at screening</td>
<td>Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere</td>
</tr>
<tr>
<td>CT or MRI of brain</td>
<td>Required</td>
<td>Required only if disease present or clinically indicated</td>
<td>Required for sites of disease identified at screening</td>
<td>Required only if disease present or clinically indicated, unless disease progression has been confirmed elsewhere</td>
</tr>
</tbody>
</table>
a. Screening scans must occur within 28 days prior to cycle 1, day 1. Radiographic assessments obtained per the subject’s standard of care prior to randomization into the study are acceptable to use as screening evaluations, if obtained within 28 days before randomization and if the method used meet protocol requirements so that the same technique can be used throughout the study.
b. Scans must be done every 8 weeks, on day 28 of the cycle ± 4 days during the treatment period, regardless of treatment delays/interruptions.
c. Listed are scans that are required at the next 8-week time point, if the tumor assessment at the previous time point documented a response (ie, CR or PR). Per RECIST, tumor measurements to confirm response must be repeated no less than 4 weeks after the criteria for response are first met.
d. Subjects who have already demonstrated objective disease progression do not need to have scans repeated at the end of treatment visit or during long-term follow-up. For subjects who do not have documented objective disease progression at time of treatment discontinuation, scans will continue to be performed at the end of treatment/long-term follow-up visits every 8 weeks (± 4 days) following discontinuation of investigational product until disease progression, initiation of new anticancer treatment, or death.
e. Contrast should be used for CT scans unless contraindicated in the subject. In case of contrast sensitivity, enhanced CT scan without contrast should be performed for the chest and MRI for all other locations.
f. CT/MRI/X-ray films may be performed at the investigator’s discretion to confirm sites of tumor involvement identified at screening or for confirmation of response. Per RECIST, bone lesions are never considered measurable and always reported as non-target lesions.
g. Clinically indicated if subject describes bone pain, or has elevated alkaline phosphatase level, or other signs and symptoms of new/progressing bony metastases.

**Notes:**
Radiographic tumor assessments can be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST, subjects are expected to discontinue study therapy and to begin the follow-up phase of the trial.
8.7 Electrocardiogram Flowchart

<table>
<thead>
<tr>
<th>Cycle / Cycle Day</th>
<th>Screening</th>
<th>Cycle 1 Day 1</th>
<th>Every other cycle starting with cycle 3, Day 1</th>
<th>End of Treatment Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Day</td>
<td>-28 to 1</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Digital ECG (12-lead) Frequency</td>
<td>Single ECG</td>
<td>Single ECG</td>
<td>Single ECG</td>
<td>Single ECG</td>
</tr>
<tr>
<td>Sampling time (hour)</td>
<td>Any</td>
<td>0 (Pre-dose) (^a)</td>
<td>0 (Pre-dose) (^b)</td>
<td>Any (^a)^(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Pretreatment checking Ca, Mg, and K on the same day. Laboratory assessment should be performed prior to investigational product administration on Day 1.

\(^b\) If during the treatment period, a subject experiences grade 3 or greater QTc prolongation (>0.5 sec), investigational product should be held, pending further evaluation and the ECG should be repeated within 2 weeks after the last dose of investigational product. Further evaluation may include review and adjustment of concomitant medications for contribution to QTc prolongation as well as cardiology consultation.
9.0 BACKGROUND INFORMATION AND RATIONALE

Breast cancer is the most frequently diagnosed malignancy in women and one of the top 2 causes of cancer-related deaths in women worldwide.1 The incidence of breast cancer in the world is increasing, and it is estimated that the disease will affect 5 million women in the next decade. Treatments allow for control of symptoms, prolongation of survival, and maintenance of quality of life. But in approximately 40% to 50% of all subjects treated with curative intent, incurable metastatic disease will develop2. Metastatic breast cancer (MBC) is considered not curable, with a median survival of 2 to 4 years for women with MBC at diagnosis. Therefore, current therapeutic goals for MBC are palliative, with the aim of improving quality of life, inhibiting disease progression, and improving survival time.

Both erythroblastic leukemia viral oncogene homolog (erbB)1- and erbB-2-targeted agents have shown clinical activity in subjects with cancer. The oncogenic role of erbB-2 has been most extensively documented in breast cancer, where the receptor is overexpressed, as determined by immunohistochemistry +3 (IHC +3) or the erbB gene is amplified as determined by fluorescence in situ hybridization (FISH), or both, in 25% to 30% of breast cancers. Breast cancers associated with erbB-2 overexpression are more aggressive, and result in higher rates of local recurrence and metastases rates and poorer overall survival (OS) in affected subjects, compared with breast tumors that do not overexpress erbB-2.3 ErbB-2 has also been validated as a target in erbB-2-overexpressing metastatic breast cancer, given the clinical tumor responses observed with the anti-erbB-2 antibody, trastuzumab. The mechanism of action of trastuzumab is only partially understood, but part of its activity is likely mediated through the inhibition of signal transduction. However, primary and secondary clinical resistance has been observed in subjects with breast cancer, which results in treatment failure and disease recurrence. Additional clinical benefit may be derived from agents such as neratinib that concurrently inhibit more than 1 erbB receptor.

The purpose of this study is to investigate the benefit of combining a new tyrosine kinase inhibitor, neratinib, with a cytotoxic agent, paclitaxel over the registered combination of trastuzumab and paclitaxel in first line treatment of erbB-2-positive metastatic breast cancer.
9.1 Background on Trastuzumab

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2/erbB-2). Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress erbB-2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on erbB-2 overexpressing cancer cells compared with cancer cells that do not overexpress erbB-2. Among preferred treatment regimens for subjects with breast cancer, trastuzumab in combination with paclitaxel has emerged as a widely accepted standard of care for erbB-2-positive disease.

Paclitaxel is an antineoplastic agent belonging to the taxoid family, which stabilizes microtubules resulting in the inhibition of the normal dynamic reorganization of the microtubule network essential for interphase and mitotic cellular function. Paclitaxel alone or in combination with other agents (including erbB-2 targeted agents) has been approved for a variety of cancers including breast, ovarian, non-small cell lung cancer (NSCLC), and acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma. Paclitaxel has received health authority approval in both the US and EU for advanced or metastatic breast cancer.4

Before reviewing the results of the pivotal trial combining trastuzumab and paclitaxel, it is important to highlight the results from the phase II randomized trial evaluating the safety and efficacy of trastuzumab monotherapy as first line treatment in erbB-2+ (IHC2+ or 3+) metastatic breast cancer subjects5 as these will provide a good element of comparison when reviewing the neratinib monotherapy phase 2 results. In this 2-arm study, 114 subjects were randomized between trastuzumab administered at the recommended dose (4 mg/kg loading dose, then 2 mg/kg weekly) or trastuzumab given at a higher dose (8 mg/kg loading dose, then 4 mg/kg weekly). Amongst the 58 subjects evaluable for efficacy, treated with the recommended dose of trastuzumab, 14 objective responses were observed (response rate: 24%, 95% CI: 13.1-35.2) and the median time to tumor progression was 3.5 months (95% CI: 3.3-5.1).
In the metastatic setting, the combination of trastuzumab with every three weeks paclitaxel has been approved as first line treatment of erbB-2+ breast cancer based on the results of a randomized phase 3 that enrolled 469 subjects. Subjects with progressive metastatic breast cancer overexpressing erbB-2 (IHC 2+ or 3+) who had not previously received chemotherapy for metastatic disease were eligible and randomized to receive either chemotherapy alone or the same chemotherapy plus trastuzumab. Chemotherapy consisted of the combination of an anthracycline plus cyclophosphamide in subjects who had never received an anthracycline or paclitaxel for those who had received adjuvant anthracycline. Among the 469 subjects enrolled, 96 received paclitaxel alone and 92 received paclitaxel in combination with trastuzumab. Overall, results showed that the median time to tumor progression (TTP) was significantly longer in subjects receiving chemotherapy plus trastuzumab compared to subjects treated with chemotherapy alone: 7.4 months versus 4.6 months (p<0.0001, RR [95% CI]: 0.51 [0.41 – 0.63]). Similarly, objective response rates, duration of response, time to treatment failure were longer in the trastuzumab-containing arm as compared to the chemotherapy alone arm. Lastly, median survival was also significantly longer in the trastuzumab arm (25.1 versus 20.3 months; p=0.046, RR [95% CI]: 0.8 [0.64-1.00]). In the paclitaxel subgroup, similar improvements were observed with a median TTP of 6.9 months versus 3.0 months in the paclitaxel alone arm (p<0.001; RR, 95% CI: 0.38 [0.27 – 0.53]) and survival of 22.1 versus 18.4 months (p=0.17; 95% CI=0.8 [0.56-1.11]).

More recently paclitaxel was administered weekly alone or in combination with trastuzumab. Dose-dense paclitaxel (eg, paclitaxel administered on a weekly schedule) has been shown to be a safe and effective treatment of metastatic breast cancer, inducing tumor responses ranging between 22 and 53% in subjects with metastatic breast cancer. The Cancer and Leukemia Group B 9840 study enrolled 580 subjects; approximately 80% of subjects had not received prior chemotherapy. Subjects received either paclitaxel weekly (80 mg/m²) or every 3 weeks (175 mg/m²), with some subjects in both treatment groups also receiving concomitant trastuzumab. Among the 577 subjects who were evaluable for efficacy, subject treated with weekly paclitaxel has a significantly longer median TTP (9 months vs 5 months), median survival (24 months vs 12 months) and better objective response rate (42% vs 29%) than subjects
receiving paclitaxel every 3 weeks. No data are available for the subgroups of erbB-2+ patients who received trastuzumab in addition to paclitaxel in both arms.

Overall, there is no phase 3 data currently available comparing paclitaxel given every 3 weeks in combination with trastuzumab to paclitaxel given weekly with trastuzumab. However, a recent review of the literature of weekly administration of paclitaxel in metastatic or advanced breast cancer came to the conclusion that, in a broader experience, weekly paclitaxel combined with trastuzumab in various lines setting produced objective response rates in the range of 56% - 74% of patients, with a median time to progression of 8.6 – 9.8 months. Moreover, the toxicity of this regimen was mild and consisted mainly of neutropenia and neuropathy.\textsuperscript{10} More specifically, results from phase 2 trials investigating the efficacy of weekly paclitaxel (90 or 80 mg/m\textsuperscript{2}) in combination with trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly) as first line treatment in subjects with erbB-2-overexpressing advanced breast cancer produced objective response rates in the range of 62% - 75% of treated subjects with a median time to tumor progression of 9-9.8 months.\textsuperscript{11,12}

Consequently, the combination of trastuzumab plus paclitaxel at the dose of 80 mg/m\textsuperscript{2} weekly is considered to be the reference arm for our study.

9.2 Background on Neratinib

Neratinib is a potent orally available pan-erythroblastic leukemia viral oncogene homolog tyrosine kinase inhibitor that blocks signal transduction through 3 receptors, erbB-1, erbB-2, and erbB-4 by irreversible covalent binding to their respective intracellular tyrosine kinase domains.

9.2.1 Pre-clinical Data

Neratinib is highly active in vitro against cell lines overexpressing erbB-2 or erbB-1: neratinib blocks erbB receptor autophosphorylation in cells at doses consistent with inhibition of cell proliferation. Neratinib most likely inhibits kinase activity through irreversible binding at a targeted cysteine residue in the adenosine triphosphate (ATP) binding pocket of the receptor. In
agreement with the predicted effects of erbB-2 inactivation, neratinib treatment of cells results in inhibition of downstream signal transduction events and cell cycle regulatory pathways. This leads to arrest at the G1/S (Gap 1/DNA synthesis) phase transition of the cell division cycle, ultimately resulting in decreased cell proliferation.

Like other EGFR/erbB-2 inhibitors, neratinib potentiates the preclinical activity taxanes. At least additive in vitro growth inhibition was detected in 3 breast cancer cell lines when neratinib was combined with paclitaxel. (Wyeth data on file)

In vivo, neratinib is active in erbB-2 and erbB-1 dependent tumor xenograft models, when administered orally on once-a-day schedule. Overall, neratinib is less potent against erbB-1 dependent tumors than erbB-2 dependent tumors in vivo, even though it has equivalent activity against the 2 kinases in vitro.

Refer to the most recent version of the investigator’s brochure for a summary of findings from nonclinical studies that potentially have clinical relevance.

9.2.2 Neratinib Phase 1 and Pharmacokinetic (PK) Data

9.2.2.1 First-in-Human Study

Protocol 3144A1-102-US was a first-in-human, phase 1, open-label, dose escalation study of neratinib. Neratinib was administered once daily to 72 patients, median age of 57 years (range, 34 to 90 years), at doses of ranging from 40 to 400 mg. Diarrhea was the primary dose-limiting toxicity (DLT). The maximum tolerated dose (MTD) was determined to be 320 mg. The neratinib 320-mg dose cohort was expanded to include 39 additional subjects to confirm the safety and tolerability of neratinib at this dose. Most of the toxicities were grade 1-2. Diarrhea (32% of subjects), dyspnea (10%), fatigue (8%), and vomiting (7%) were the most commonly reported grade 3 or higher adverse events (AEs). Most were considered drug related. No grade 4 or grade 5 diarrhea was reported in this study. There were no related grade 4 or 5 AEs, or any symptomatic congestive heart failure (CHF) events of any grade. This phase 1 data suggests that monotherapy with neratinib has an acceptable safety profile.
After administration of single oral doses of neratinib 40 mg to 400 mg with food, absorption of neratinib was relatively slow, with a median time to maximum plasma concentration ($t_{\text{max}}$) of approximately 3 to 6.5 hours. Mean maximum concentration ($C_{\text{max}}$) on day 1 after a single dose ranged from 5.0 ng/mL (coefficient of variation [CV]=44%; 40-mg dose) to 76.5 ng/mL (CV=52%; 400-mg dose). For the same respective doses, steady-state mean $C_{\text{max}}$ on day 21 ranged from 5.8 ng/mL (CV=8%) to 105 ng/mL (CV=43%). After a single oral dose of neratinib on day 1, mean area under the curve (AUC) ranged from 54.2 ng•h/mL (CV=37%; 40-mg dose) to 1833 ng•h/mL (CV=42%; 400-mg dose). On day 21, for the same respective doses, the area under curve at steady state ($AUC_{\text{ss}}$) ranged from 76.0 ng•h/mL to 1704 ng•h/mL (CV=20%). Multiple-dose exposures were 1.17- to 2.66-fold higher than single-dose exposures (mean accumulation ratio, $AUC_{\text{ss}}$/area under the concentration-time curve from 0 to 24 hours [$AUC_{0-24\text{h}}$]) at the doses ranging from 40 to 400 mg. The mean accumulation ratio was 1.18 after administration of neratinib 240 mg and 1.52 after administration of neratinib 320 mg, indicating no major accumulation of neratinib after repeated daily oral administration in subjects with cancer.

Trough concentrations of neratinib measured through cycle 6 did not show any significant changes with protracted treatment. The apparent steady-state volume of distribution ($V_{\text{ss/F}}$) was large, with values ranging from 33 to 155 L/kg (CV=9% to 128%). Mean $CL_T$ ranged from 2.5 to 8 L/h/kg (CV=8% to 67%). Mean $t_{\frac{1}{2}}$ after a single dose on day 1 ranged from 8 to 17 hours, with a CV of 8% to 65%.

After a single dose or multiple doses, neratinib $C_{\text{max}}$ and AUC appeared to increase with increasing dose. However, statistical lack-of-fit tests for $C_{\text{max}}$ and AUC versus dose indicated that the relationships between $C_{\text{max}}$ and AUC versus dose were not linear. The assessment of the effect of age and sex on pharmacokinetic (PK) exposure showed that neither had an effect on the PK profile of neratinib.
9.2.2.2 Thorough QTc Study

Study 3144A1-105-US was a randomized, single-dose, double-blind with respect to neratinib, crossover, placebo- and open-label, moxifloxacin-controlled study of the effects of neratinib on cardiac repolarization in healthy adult subjects. The study consisted of 2 parts with subjects randomly assigned to treatment in each part, utilizing a crossover design. A minimum 14-day washout period was instituted between neratinib doses.

The study is clinically complete. Preliminary safety data presented below are for 60 enrolled subjects; 59 subjects were included in the primary analysis of neratinib 240 mg compared with placebo (the therapeutic dose comparison) and 54 subjects were included in the analysis of neratinib 240 mg in combination with ketoconazole compared with placebo in combination with ketoconazole (the supratherapeutic dose comparison). Rationale for the selection of the 240 mg neratinib dose is provided in section 9.2.3.

For both the therapeutic dose comparison and the supratherapeutic dose comparison, the upper bounds of the 90% CIs for the baseline-adjusted population QTc were <10 ms at all time points postdose. In addition, the overall sensitivity of the study conditions was demonstrated with a statistically significant prolongation of the QTc, with a mean increase of 6.5 ms at the moxifloxacin median \( t_{\text{max}} \) after moxifloxacin administration compared with placebo. After single doses of neratinib 240 mg given alone with food, the mean \( C_{\text{max}} \) was 68 ng/mL with a CV of 40% and mean AUC was 1236 ng•h/mL with a CV of 39%. These results were consistent with data previously reported for both healthy subjects and subjects with cancer. Under conditions of ketoconazole inhibition of neratinib metabolism, mean \( C_{\text{max}} \) (CV) of 163 ng/mL (46%) and mean AUC of 3801 ng•h/mL (49%) were 2.4- and 3-fold, respectively, greater than those under conditions of a single dose of neratinib alone. These boosted neratinib exposures represent a 2.2- and 4-fold increase from mean exposures at steady state observed in subjects with cancer after daily oral doses of neratinib 240 mg with food \( (C_{\text{max}}, 73 \text{ ng/mL and AUC}_{\text{ss}}, 939 \text{ ng•h/mL}) \). Moreover, 13 subjects in this study had \( C_{\text{max}}, >219 \text{ ng/mL during the supratherapeutic dose comparison, a 3-fold increase from the mean } C_{\text{max}} \text{ observed in subjects in study 3144A1-102-US. The highest } C_{\text{max}} \text{ achieved in an individual subject in the supratherapeutic dose comparison} \)
sequence was 327 ng/mL. By comparison, the highest neratinib plasma concentration observed to date in any individual subject with cancer has been 247 ng/mL. The results are from an assessment of plasma concentration data for a total of 241 subjects who received neratinib in studies 3144A1-102-US, 3144A1-200-WW, and 3144A1-201-WW. On the basis of these comparisons, the neratinib plus ketoconazole treatment utilized in this study is representative of supratherapeutic neratinib exposures under clinical conditions.

These results showed that neratinib does not prolong QTc interval in humans at the dose of neratinib 240 mg daily with food and under conditions of supratherapeutic exposures.

9.2.3 Neratinib Phase II Data

9.2.3.1 Neratinib Monotherapy Data

9.2.3.1.1 Selection of Neratinib 240 mg/Day as the Recommended Dose in Monotherapy

Neratinib 320 mg was initially selected as the starting dose for phase 2 studies, on the basis of the results from the first-in-human, phase 1, dose-escalating study, 3144A1-102-US and of the safety, tolerability, PK, and pharmacodynamic profiles of neratinib administered orally with food to subjects with erbB-2- or erbB-1-positive solid tumors.

Thus, neratinib 320 mg, taken as a continual oral dose with food was the starting dose selected for study 3144A1-200-WW, a phase 2 study in subjects with advanced NSCLC. The first subjects enrolled in this study experienced a high frequency of diarrhea, which was considered drug-related, and often required a dose reduction. Based on these results, it was decided to set the recommended starting dose to neratinib 240 mg, and the protocol was amended accordingly. The frequency of grade 3 or grade 4 diarrhea was reduced from 44% to 23% among subjects who received the reduced starting dose, compared with those who received neratinib 320 mg. On the basis of these results, neratinib 240 mg became the recommended starting dose used in all subsequent monotherapy studies.

PK data from study 3144A1-102-US also support the neratinib 240 mg continual oral once-daily dosage. The prolonged half-life in subjects allows for systemic exposures to be sustained with
once-daily dose administration. Oral administration of neratinib with food resulted in a 2-fold increase in neratinib exposure; it is therefore recommended that neratinib 240 mg be administered with a standard meal to achieve optimal exposure for efficacy. Mean AUC of 939 ng•h/mL (CV=34%) for neratinib 240 mg once daily with food exceeds exposures at the minimum efficacious dose (MED) of 431 ng•h/mL in the preclinical efficacy model (BT474). All 8 subjects with metastatic breast cancer who had a partial response (PR) had systemic exposures greater than the preclinical MED. The AUC values ranged from 532 to 2752 ng•h/mL for the 6 subjects who received neratinib 320 mg; AUC was 946 ng•h/mL for the subject who received neratinib 180 mg and 713 ng•h/mL for the subject who received neratinib 120 mg.

9.2.3.1.2 Antitumor Activity in Subjects With ErbB-2-Positive Breast Cancer

The clinical and antitumor activity of neratinib in subjects with erbB-2-positive breast cancer is primarily supported by the results from the completed phase 1 study, 3144A1-102-US and preliminary results, as of 30 October 2008, from the ongoing phase 2 study, 3144A1-201-WW, of neratinib in women with erbB-2-positive locally recurrent or metastatic breast cancer.

Breast cancer was the primary cancer diagnosis for 29 of the 72 subjects (40%) enrolled in the study 3144A1-102-US. Twenty-five (25) subjects with breast cancer were considered evaluable for efficacy. Eight (8) of the 25 evaluable subjects with metastatic breast cancer had a PR corresponding to an objective response rate (ORR) of 32% (95% CI, 14.9%, 53.5%). Seven (7) of the 8 subjects who had a PR overexpressed erbB-2 and all had progressed after prior trastuzumab therapy. In addition, all responders had received between 2 and 8 prior chemotherapy regimens prior to entry into the trial. Moreover, 2 of these PRs were at neratinib doses of 120 or 180 mg per day, below the current recommended monotherapy dosage.

The antitumor activity of neratinib monotherapy in subjects with metastatic breast cancer after treatment with standard therapies was further confirmed in the ongoing phase 2 study 3144A1-201-WW, whose preliminary results have been presented at the 2008 San Antonio Breast Cancer Symposium. In this phase 2, multicenter, open-label, 2-group study, neratinib was given at the dose of 240 mg in women, 18 years or older, with ErbB-2-overexpressing
advanced or metastatic breast cancer. Subjects were divided into 2 treatment groups at enrollment, on the basis of their baseline disease characteristics and prior anticancer therapies. Treatment group A consisted of subjects with advanced breast cancer and confirmed erbB-2 gene amplification whose disease progressed during or after trastuzumab-based adjuvant therapy or after at least 6 weeks of standard doses of trastuzumab in the metastatic or locally advanced setting. Treatment group B consisted of subjects with advanced breast cancer and confirmed erbB-2 gene amplification who had received no prior trastuzumab or erbB-2-targeted treatment.

As of 30 October 2008, enrollment has been completed and preliminary data were available for 136 subjects. The median age of enrolled women was 50 years (range, 31 to 83 years). Sixty eight (68) subjects (50%), 34 in each of the 2 treatment groups, had received between 2 and 3 prior cytotoxic regimens; and 40 subjects (29%), 24 (36%) in treatment group A and 16 (23%) in treatment group B, had received >3 prior cytotoxic regimens. Eighty-nine percent (89%) of the subjects in treatment group A had received 1 to 3 trastuzumab-based regimens in the metastatic setting; 26% of these subjects had received trastuzumab in the neoadjuvant or adjuvant settings. Efficacy analyses were performed on the basis of tumor assessments from an independent radiology review and the investigator. The efficacy-evaluable population for the independent assessment consisted of 127 subjects. On the basis of the independent assessment of tumor response, the ORR was 26.2% (95% CI, 15.8%, 39.1%) for subjects in treatment group A and 56.9% (95% CI, 43.3%, 68.3%) for subjects in treatment group B. A PR was reported for 53 evaluable subjects. The 16-week progression-free survival (PFS) rate was 60.0% (95% CI, 45.6%, 71.7%) and 77.0% (95% CI, 64.2%, 85.7%) and median PFS was 23.1 weeks (95% CI, 15.9, 39.0 weeks) with data censored for 23 subjects, and 40.0 weeks (95% CI, 31.7, 55.4 weeks) with data censored for 32 subjects for subjects in treatment group A and B, respectively.

Diarrhea (90% of subjects), which was reversible and generally manageable by medication, temporary discontinuation of treatment, or dose reduction regardless of toxicity grade, was the most commonly reported drug-related AE, regardless of toxicity. Other drug-related AEs reported for ≥10% of subjects were nausea (29% of subjects), vomiting (21%), fatigue and rash (16%), anorexia (15%), and abdominal pain (13%).
These data show that daily oral doses of 240 mg of neratinib are generally well tolerated, and neratinib has significant antitumor activity in patients with ErbB-2-positive advanced breast cancer. These results compare favorably to those of the phase 2 randomized trial evaluating the safety and efficacy of trastuzumab monotherapy as first line treatment in erbB-2+ (IHC2+ or 3+) metastatic breast cancer subjects\(^5\) mentioned earlier.

**9.2.3.2 Neratinib in Combination With Paclitaxel**

The antitumor activity of neratinib in combination with paclitaxel is under investigation in study 3144A1-203-WW. The objectives of this phase 1/2 study is (1) to determine the MTD of neratinib when administered in combination with paclitaxel in subjects with advanced solid tumors (part 1) and (2) to assess the clinical activity of the combination in subjects with erbB-2-positive breast cancer receiving a daily oral dose of neratinib at the MTD in combination with paclitaxel 80 mg/m\(^2\) intravenously (IV) administered on days 1, 8, and 15 of a 28-day cycle (part 2). Subjects enrolled in the expanded MTD cohort were divided into 2 groups: treatment group A (subjects who received no more than 1 prior cytotoxic chemotherapeutic regimens for metastatic disease) and treatment group B (subjects who received no more than 3 prior cytotoxic chemotherapeutic regimens for metastatic disease). Preliminary results are shown below.

As of 25 March 2009, 110 subjects (105 women and 5 men) have been enrolled in the study. Eight (8) subjects were enrolled in the dose-escalation phase of the study and 102 subjects in the expanded MTD cohort.

Among the 8 subjects participating in the dose-escalation phase of the study, 3 subjects received neratinib 160 mg and 5 subjects received neratinib 240 mg in combination with paclitaxel 80 mg/m\(^2\) on days 1, 8, and 15 of a 28-day cycle. No DLTs were reported, and the neratinib MTD was determined to be 240 mg. An additional 102 subjects with erbB-2-positive breast cancer were enrolled in the expanded MTD cohort and received neratinib 240 mg, administered in combination with paclitaxel 80 mg/m\(^2\), which are the recommended doses for the proposed trial.
The median age of women enrolled in the expanded MTD was 50.5 years (range, 20 to 76 years); 73 subjects (71.6%) were Asian and 27 subjects (26.5%) were white. Approximately equal proportions of subjects in the expanded MTD cohort had an ECOG performance status of 0 (52%) or 1 (48%). Thirty-one (31) subjects (30.4%) had received 1 prior cytotoxic regimen; 15 subjects (14.7%) had received 2 such prior regimens; and 5 subjects (4.9%) had received 3 such regimens in the metastatic setting. Most subjects (72; 70.6%) in the expanded MTD cohort had received no trastuzumab prior to enrollment. Twenty-two (22) subjects (21.6%) had received 1 prior trastuzumab-based therapy; 6 subjects (5.9%) had received 2 trastuzumab-based regimens.

At the time of the cut-off, the median treatment duration for subjects treated in the expanded MTD cohort was 16 weeks for neratinib and 19 weeks for paclitaxel.

At least 1 TEAE was reported for 100 subjects (98.0%) in the expanded MTD cohort. The TEAEs reported for ≥20% of subjects were diarrhea (89.2% of subjects); alopecia (43.1%); decreased white blood cell (WBC) count /leucopenia (41.2%); neutrophil count decreased/neutropenia (40.2%); nausea and rash (25.5% each).

At least 1 grade 3 or higher TEAE was reported for 51 subjects (50.0%) in the expanded MTD cohort. Grade 3 diarrhea (25 subjects; 24.5%) was the most commonly reported grade 3 or higher TEAE. No grade 4 or grade 5 diarrhea was reported. Grade 3 or higher decreased WBC count/leukopenia was reported for 17 subjects (16.7%); grade 3 or higher neutrophil count decreased/neutropenia for 16 subjects (15.7%). Grade 4 neutrophil count decreased/neutropenia and WBC count decreased/leucopenia was reported for 5 subjects each. Grade 4 antineutrophil cytoplasmic antibody decreased was reported for 2 subjects. Grade 4 anemia, grade 4 febrile neutropenia, grade 4 infection, and grade 4 hypoglycemia were reported for 1 subject each.

Fifteen (15) subjects (14.7%) in the expanded MTD cohort had at least 1 TEAE that was reported as an SAE. Diarrhea was reported as an SAE for 5 subjects and dyspnea for 2 subjects. Other SAEs were reported for 1 subject each. At least 1 drug-related SAE was reported for
8 subjects (7.8%). Diarrhea was considered drug related; dyspnea was considered to be not drug related. No adverse event was reported that led to the discontinuation of study treatment.

Twenty-eight (28) subjects (27.5%) in the expanded MTD cohort had at least 1 TEAE that led to a dose reduction. Diarrhea led to a dose reduction for 10 subjects; neutrophil count decreased/neutropenia and decreased WBC count/leucopenia for 5 subjects each; decreased weight for 3 subjects; and vomiting, increased ALT, increased AST, and peripheral neuropathy for 2 subjects each.

Efficacy analyses were performed on the basis of tumor assessments from the investigator. Radiologic assessment of disease status was used to determine preliminary antitumor activity, according to RECIST guidelines, modified by Wyeth as appropriate for the study. Subjects in the expanded MTD cohort were considered evaluable for response if they received at least 2 weeks of a continual oral daily dose of neratinib and at least 2 doses of paclitaxel, and underwent at least 1 postbaseline tumor assessment. A subject who died before the first scheduled postbaseline tumor assessment was also to be included in the efficacy-evaluable population. Data were censored for subjects for whom disease progression or death was not observed at the date of their last tumor assessment. The results presented are from the analyses performed on the preliminary, incomplete data in the clinical database as of 25 March 2009.

At the date of cut-off, 82 subjects with erbB-2-positive breast cancer treated at the MTD dose level (ie, neratinib 240 mg + paclitaxel 80 mg/m²) were considered evaluable for efficacy, of which 20 were treated in the first line setting. Twelve (12) of the 20 subjects had either a confirmed CR or PR. The overall response rate for this subset of subjects was 60% (95% CI, 36%;81%). The 16-week PFS rate for the subject was 85% (95% CI, 62%;97%). At the time of analysis, data were immature and only 3 progressive disease events were reported. Data analysis is ongoing.

These results indicate that the combination of neratinib with paclitaxel has antitumor activity and is well tolerated with AEs similar to those seen with neratinib or paclitaxel when administered alone.
9.3  Rationale for Comparing Neratinib and Paclitaxel to Trastuzumab and Paclitaxel in 1st Line Treatment of erbB-2-Overexpressing Metastatic Breast Cancer Subjects

In the first line setting, among the preferred chemotherapy regimens for the treatment of subjects with advanced or metastatic erbB-2-positive breast cancer the combinations of trastuzumab with paclitaxel has become one of the most widely used treatment regimen. However, with the increasing use of trastuzumab in earlier setting (neoadjuvant and adjuvant), there is a greater risk of increasing acquired resistance to trastuzumab. As neratinib binds irreversibly to the intracellular domain of erbB receptors and leads to a sustained inhibition of erbB-2 signal transduction, neratinib could provide a treatment alternative for subjects who have primary or secondary trastuzumab resistance. Preliminary results seem to indicate that the combination of neratinib with paclitaxel is feasible and there is preclinical evidence that the addition of EGFR/erbB-2 inhibitor, including neratinib, to a taxane will intensify the antitumor activity. In addition, neratinib has already demonstrated significant clinical antitumor activity in erbB-2+ breast cancer subjects not previously treated with trastuzumab, as well as in subjects who received prior trastuzumab.

This study provides the opportunity to demonstrate the clinical benefit of the use of a small-molecule pan erbB irreversible kinase inhibitor, such as neratinib, in conjunction with paclitaxel. The study is designed to compare the PFS following treatment with neratinib (240 mg) in combination with paclitaxel (80 mg/m²) versus trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly thereafter) plus with paclitaxel (80 mg/m²) in erbB-2-overexpressing locally recurrent or metastatic breast cancer subjects. Refer to the Investigational product and Administration section for further information on the route and schedule of administration.

Refer to the most recent version of the investigator’s brochure for a summary of findings from nonclinical studies that potentially have clinical significance and from clinical studies that are relevant to the study. Also, refer to the most recent version of the investigator’s brochure for a summary of the known and potential risks and benefits, if any, to human subjects.
9.4  **Rationale for the Pharmacogenetic Portion of the Study**

Breast cancer cells may become resistant to trastuzumab on the basis of extracellular domain (ECD) truncated erbB-2 receptor, that can no longer be recognized by the antibody, surface p95 expression\(^1\)\(^6\), or because of alternate survival signaling pathways being activated such as coactivation of erbB-1 (EGFR) signaling or downstream activation of phosphatidyl-inositol-3-kinase (PI3K) signaling.\(^17\),\(^18\),\(^19\) Because neratinib acts on the intracellular tyrosine kinase domain, such cells are likely to be persistently sensitive to neratinib.\(^20\)

The pharmacogenetic portion of the study will evaluate possible correlations between baseline tumor phenotypes and genotypes and clinical response in subjects with HER-2/neu overexpressed/amplified breast cancer after administration of neratinib. The overall goal of these exploratory endpoints is to use biomarkers to define the patient population that will have benefit from the addition of neratinib in the first line setting. Three (3) sets of assays are planned.

First, the tumor samples obtained at the initial diagnosis will be studied for evidence of phosphatidyl-inositol-3-kinase (PI3K) signaling pathway activation (PIK3CA mutation analysis at hotspots in exons 9, 20), PIK3CA amplification by FISH and PTEN loss and erB2 family members via immunohistochemistry.

Second, the presence of coamplification of c-MYC and erbB-2 (via FISH) will be also be assessed with the goal to use biomarkers to identify those patients’ tumors that might be predicted to be sensitive to trastuzumab based first line therapy.

Finally, the quantitative levels of soluble HER2/ECD will also be measured during the active treatment phase of the trial. This biomarker can serve two purposes. First, baseline levels of soluble HER2/ECD have shown some correlation with tumor expression of truncated HER2/p95, and second, responses of soluble HER2/ECD levels have correlated with response to therapy. Kinetics of serum HER2/ECD decline with trastuzumab therapy indicate that the earliest time point to detect a drop in ECD levels is day 8, however optimal indication of drug response is day
15-22. Based on these results and other reports investigating serum ECD as an indicator of early clinical efficacy, serum HER2/ECD levels will be assessed at two time points, day 15 (cycle 1, day 15) and day 28-30 (cycle 2, day 1).

**10.0 OBJECTIVES**

**10.1 Primary**

The primary objective of this study is to compare the independently assessed progression-free survival (PFS) following treatment with neratinib in combination with paclitaxel versus trastuzumab plus paclitaxel in subjects who have not received previous treatment for erbB-2-positive locally recurrent or metastatic breast cancer.

**10.2 Secondary**

The secondary objectives of this study are:

- To compare independently assessed clinical activity between treatment arms by measuring: OS, ORR, duration of response (DOR), and clinical benefit rate (CBR; CR + PR + stable disease [SD] ≥ 24 weeks).
- To compare safety (AEs; serious adverse events [SAEs]) between treatment arms.
- To compare patient reported breast specific quality of life between treatment arms.
- To compare the frequency of and time to symptomatic or progressive central nervous system (CNS) lesions in both treatment arms.

**10.3 Exploratory**

The exploratory objectives of this study are:

- To compare health care utilization including hospitalization and physician visits between treatment arms.
- To identify biomarkers predictive of neratinib response/resistance (apart from erbB-2).
11.0 STUDY DESIGN

11.1 Description
This is a multicenter phase 3, randomized, open-label, parallel-group study of neratinib in combination with paclitaxel versus trastuzumab plus paclitaxel.

Approximately 1200 subjects with erbB-2-positive locally recurrent or metastatic breast cancer will be randomized in a 1:1 fashion (600 in each arm) to receive treatment with either: paclitaxel in combination with neratinib (arm A: experimental arm); or paclitaxel and trastuzumab (arm B: control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent. Subjects will be stratified by prior adjuvant trastuzumab exposure (yes/no), prior lapatinib exposure (yes/no), estrogen receptors (ER)/progesterone receptors (PgR) status (ER and/or PgR positive / ER and PgR negative) and by region (1=United States; 2=Western Europe, Australia, South Africa, and Canada; 3=Asia Pacific, India, Eastern Europe, Africa, and South America).

Subjects discontinuing the active treatment phase will enter the follow-up phase during which survival and new anticancer therapy information will be collected. The follow-up phase will continue until a total of approximately 631 deaths have been observed.

11.2 Approximate Duration of Subject Participation
Subjects will participate in the study for approximately 31 months. This includes 1 month of screening, 12 months of treatment (treatment will be given for as long as tolerated and there is no disease progression), and approximately 18 months follow-up for survival.

11.3 Approximate Duration of Study
This study will be completed in approximately 54 months. This includes 23.5 months for accrual and approximately 12 months for active treatment (treatment will be given for as long as tolerated and there is no disease progression) and approximately 18 months follow-up survival for the last subject enrolled. The final PFS analysis is projected to occur after approximately
30.5 months (when 749 PFS events have occurred) and follow-up for overall survival is projected to conclude after approximately 44 months (when a total of 631 deaths have occurred). The end of the study is the last contact of the last subject.

11.4 Approximate Number of Subjects

Approximately 1200 subjects will participate in this study at approximately 350 sites. The number of subjects enrolled at each site may vary based on enrollment capabilities. Approximately 600 subjects will be enrolled in each treatment arm. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

12.0 SELECTION OF SUBJECTS

The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form before any subjects provide consent. Each subject must participate in the informed consent process and sign and date an informed consent form for this protocol before any protocol-required procedures are performed. As required, assent must be obtained. Throughout this document, the requirements for informed consent apply to assent as well.

If informed consent has not been obtained, no protocol-required procedures are to be performed on the subject and no subject data are to be transferred to the sponsor. Documentation of informed consent must be recorded in the source documents for each subject.

If a subject is not physically or mentally competent to understand and to give their informed consent to participate in the trial (eg, is blind or illiterate), their legally acceptable representative may sign the consent form on her behalf. It remains the responsibility of the principal investigator to assure that the subject is suitable for inclusion in this study and will be able to adhere to all study procedures throughout the course of the study.
Radiographic tumor assessments included in the Tumor Assessment Flowchart performed within 28 days before cycle 1 day 1 as routine procedure but before informed consent form (ICF) signature do not need to be repeated and may be used as screening assessments as long as they meet the requirements outlined in the Procedures section. Left ventricular ejection fraction (LVEF) as determined by multiple-gated acquisition (MUGA) scans or echocardiogram (ECHO) as well as bone and/or brain scans performed as routine procedures within 6 weeks before cycle 1 day 1 are accepted as baseline assessments as long as they meet the requirements outlined in the Procedures section. Eligibility will be assessed based on screening test results closest to (and including) the date of randomization.

Prospective and retrospective waivers for deviations from the eligibility criteria will not be granted.

12.1 Inclusion Criteria

Subjects must meet all of the following criteria for inclusion in the study

1. Female subjects aged 18 years or older.
2. Histologically and/or cytologically confirmed diagnosis of breast cancer.
3. Locally recurrent or metastatic breast cancer that is not amenable to curative surgery and/or radiation.
4. Documentation of erbB-2 gene amplification by FISH (as defined by a ratio >2.2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer’s kit instruction) or documentation of erbB-2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory or initial diagnostic results utilizing 1 the sponsor-approved assays. If erbB-2 status is unavailable or was determined using a test other than a sponsor-approved assay (see Attachment 1) and cannot be assessed using 1 of these assays prior to randomization, testing and study eligibility must be obtained from the sponsor-identified central laboratory prior to randomization.
5. All subjects must have tumor tissue (ie, most recent archived formalin fixed-embedded tissue [block or unstained slides]) available for central review of erbB-2 expression levels by FISH testing performed by the sponsor-identified central laboratory.

6. Documentation of ER/PgR status (positive or negative) based on local laboratory or initial diagnostic results must be available before study entry. If results are unavailable, tumor tissue may be sent to the sponsor-identified central vendor for assessment prior to study entry as per investigator’s discretion.

7. At least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (specifically, no ascites, pleural, or pericardial effusions, osteoblastic bone metastases, or carcinomatous lymphangitis of the lung as only lesion).

8. Eastern Cooperative Oncology Group (ECOG) status of 0 to 2 (not declining within 2 weeks prior to signing informed consent). (See Attachment 2)

9. LVEF within institutional range of normal as measured by MUGA or ECHO.

10. Screening laboratory values within the following parameters:
    ➢ Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9 /L (1500/mm^3)$
    ➢ Platelet count $\geq 100 \times 10^9 /L (100,000/mm^3)$
    ➢ Hemoglobin $\geq 9.0 \text{ g/dL (90 g/L)}$
    ➢ Serum creatinine $\leq 1.5 \times \text{ upper limit of normal (ULN)}$
    ➢ Total bilirubin $\leq 1.5 \times \text{ ULN (<3 ULN if Gilbert’s disease)}$
    ➢ Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 2.5 \times \text{ ULN (<5 x ULN if liver metastases are present)}$

11. Recovery (to grade 1 or baseline) from all clinically significant acute adverse effects of prior therapies (excluding alopecia).

12. All subjects who are not surgically sterile or postmenopausal must agree and commit to the use of a reliable method of birth control starting 2 weeks prior to the administration of the first dose of investigational product until 28 days after the last dose of investigational product. A woman of childbearing potential is one who is biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives.
12.2 Exclusion Criteria

1. Prior systemic anti-cancer therapy (including cytotoxic chemotherapy, signal transduction inhibitors [eg, lapatinib], biologic [eg, trastuzumab]), or other investigational anticancer therapy) for locally recurrent or metastatic disease. Prior endocrine therapy in any setting is allowed.

2. Prior treatment with an erbB-2 inhibitor, other than trastuzumab, lapatinib or the combination of the two, in the neoadjuvant or adjuvant setting.

3. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of >400 mg/m², epirubicin dose >800 mg/m², or the equivalent dose for other anthracyclines or derivatives (eg, 72 mg/m² of mitoxantrone).

4. Subjects with recurrence or progression of disease within 12 months after completion of adjuvant or neoadjuvant systemic anticancer therapy (including cytotoxic chemotherapy, signal transduction inhibitors [eg, lapatinib], biologic [eg, trastuzumab], or other investigational anticancer therapy), other than endocrine therapy, for early breast cancer.

5. Subjects with bone or skin as the only site of measurable disease. Subjects with skin lesions measurable by computed tomography (CT) scans or magnetic resonance imaging (MRI) as only site of measurable disease are allowed.

6. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other cancer therapy within 2 weeks before the administration of the first dose of investigational product.

7. Active uncontrolled or symptomatic CNS metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Subjects with a history of CNS metastases or cord compression are eligible if they have been definitively treated and are off anticonvulsants and steroids for at least 4 weeks before first dose of investigational product.

8. Active uncontrolled cardiac disease, including cardiomyopathy, CHF (New York Heart Association [NYHA] functional classification of ≥3), unstable angina, and myocardial infarction (within 12 months of study entry).

9. Inadequately controlled hypertension (ie, systolic blood pressure [BP] > 180 mm Hg or diastolic BP > 100 mm Hg).
10. Family history of congenital long or short QT syndrome, Brugada syndrome or QT/QTc interval > 0.45 second or known history of QT/QTc prolongation or torsade de pointe (TdP).

11. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn’s disease, malabsorption, or grade ≥2 diarrhea of any etiology at baseline).

12. Preexisting grade 2 or greater motor or sensory neuropathy.

13. History of life-threatening hypersensitivity reaction to taxanes or trastuzumab.

14. Clinical contraindication to steroids preventing their use as part of paclitaxel premedication.

15. Women who are pregnant, breast-feeding or women of child bearing potential who are not using effective contraception during participation in the study and do not agree to do so for at least 28 days after final dose of investigational product.

16. Inability or unwillingness to swallow oral medications.

17. Immunocompromised subjects, including known seropositivity for human immunodeficiency virus (HIV), or current or chronic hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen [HbsAg] or antibody to hepatitis C virus [anti HCV] with confirmatory testing). (Note: testing is not mandatory to be eligible for the study. However, if a subject is at risk for having undiagnosed HCV [due to history of injection drug use or due to geographic location for example], testing at screening should be considered.)

18. Any other cancer, including contralateral breast cancer, within 5 years prior to screening with the exception of adequately treated ductal carcinoma in situ, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin.

19. Evidence of significant medical illness or abnormal laboratory finding that, in the investigator’s judgment, will substantially increase the risk associated with the subject’s participation in, and completion of, the study, or could preclude the evaluation of the subject’s response. Examples include, but are not limited to, serious active infection (ie, requiring IV antibiotic or antiviral agent), uncontrolled major seizure disorder, significant pulmonary disorder (eg, interstitial pneumonitis, pulmonary hypertension), or psychiatric disorder that would interfere with the subject safety or informed consent.
13.0 PRIOR TREATMENT

All anticancer related treatments received for breast cancer before signing the informed consent form will be recorded on the eCRF regardless of when they were administered. This should include:

- Any prior anticancer medications (ie, regimen number, medication names, start and stop date of each medication, treatment reason/indication, reason for stopping each medication, best response achieved for each regimen, date of progression of disease [if known]).
- Cancer related surgical procedures (ie, name of procedure and when it was performed).
- Cancer related radiotherapy (ie, body location, total dose, unit, start and stop date, whether the radiotherapy is continuing or not, reason/indication for treatment, best response achieved and date of disease progression at the irradiated site on or after treatment), and immunotherapy if applicable.

The start date, stop date, and indication for all other relevant prior medications and nonpharmacological treatments/therapies received within 14 days before signing the informed consent form will be recorded on the case report form (CRF).

14.0 CONCOMITANT TREATMENT

The start date, stop date, and indication for concomitant treatments and/or therapies and medications given because of an AE received from the signing of the informed consent form until the end of the treatment will be recorded on the CRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed while the subject is enrolled in the study can be recorded as “unspecified anesthesia” on the concomitant treatment records; it is not necessary to list the specific
anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all subjects in this study.

### 14.1 Prohibited Concomitant Treatment During Active Phase of the Study

The following treatments are prohibited throughout the duration of the active phase of the study:

- Any concurrent chemotherapy, radiotherapy, surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents and hormonal agents.

### 14.2 Permitted Concomitant Treatment During Active Phase of the Study

The following treatments are permitted during the study:

- Standard therapies for preexisting medical conditions, medical and/or surgical complications, and palliation. All medication should be recorded.
- Antidiarrheal medications. Subjects should be instructed to treat diarrhea at its earliest occurrence. If significant diarrhea persists, prophylactic loperamide or other anti-diarrhea medications should be recommended. Refer to Attachment 3 for dietetic and pharmacologic guidelines for the treatment of cancer treatment-induced diarrhea.
- Bisphosphonates, regardless of indication, provided subjects have been on stable doses for at least 2 weeks prior to randomization. Stable dose should be maintained during the investigational product treatment period. Subjects requiring initiation of bisphosphonate treatment, during the course of the study, should be discontinued due to progressive disease unless disease progression can be completely ruled out and clearly documented in the subject’s source documentation.
- Secondary prophylactic use of growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]) may be implemented per the American Society of Clinical Oncology (ASCO) guidelines at the investigator’s discretion if significant neutropenia or febrile neutropenia/infection is observed.
14.3 Other

- Subjects should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the active phase of the study. Subjects should also avoid grapefruit and herbal remedies, including St John's Wort. Refers to Attachment 4 for a list of inhibitors and inducers of the Cytochrome P450 CYP3A4, 5, 7 isoenzymes.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as premedication for paclitaxel, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- Subjects using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECGs) at the investigator’s discretion. Refer to Attachment 5 for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing TdP.

15.0 PROCEDURES

Refer to the flowchart(s) for the procedures and their time points.

The health outcomes assessment surveys (see Attachment 6) are for the purpose of exploring the subject’s own perceptions about her quality of life. The investigator and/or site staff must not influence the subject’s assessments. Every effort should be made to maintain an unbiased assessment. Questionnaires should be administered prior to any other study procedures on the day of the study visit. On the day of treatment discontinuation, it is acceptable for questionnaires to be performed after study procedures.

15.1 Screening/Baseline Visit

The following information/assessments will be collected at screening:

- Obtain signed and dated IRB/IEC-approved ICF.
Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed; however, it may be obtained more than 28 days before cycle 1 day 1. Radiographic tumor assessments (as documented on the Tumor Assessment Requirement Flowchart) that were performed before the signing of the informed consent form as routine procedures (but within 28 days before cycle 1, day 1) do not need to be repeated and may be used as screening assessments, as long as:

- The tests were performed per the method requirements outlined in the Tumor Assessment Requirement Flowchart, the Efficacy section.
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the subject’s source notes.

LVEF as determined by MUGA scan or ECHO as well as bone and/or brain scans performed as routine procedures within 6 weeks before cycle 1 day 1 may also be accepted as baseline assessment if they meet the same requirements listed above.

- Documentation of erbB-2 gene amplification by FISH (as defined by a ratio > 2.2) or CISH (as defined by the manufacturer’s kit instruction) or documentation of erbB-2 gene overexpression by IHC (as defined by IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory or initial diagnostic results utilizing one of the Sponsor-approved assays (see Attachment 1). If FISH or CISH results using 1 of these assays are not available and cannot be assessed using 1 of these assays prior to randomization, tumor biopsy specimen (ie, most recent archived formalin fixed-embedded tissue [block or unstained slides]) must be retrieved for FISH analysis by the study central vendor to determine subject eligibility. In addition, tumor tissue must be available and adequate for all subjects for centralized FISH testing. In case of more than 1 result, the status retrieved on the most recent biopsy should be used. Whenever available metastatic tissue, rather than the original tumor tissue, should be sent to the central vendor for the confirmation of erbB-2 gene amplification or overexpression. Additional exploratory analyses in the erbB signal transduction pathway may also be performed.
- Subject demography (including date of birth, sex, race [Asian, Black or African American, White, Other]).
• Presence of chronic conditions and/or medical history of significance (include review of history of cardiac, pulmonary, gastrointestinal, and liver disease) including relevant surgical procedures.

• Collection of cancer history, including but not limited to:
  ➢ Histology, tumor stage at first diagnosis and at time of screening, date of first local relapse and/or date of first metastasis.
  ➢ Prior anticancer medications (including regimen number, medication names, start and stop date of each medication, treatment reason, reason for stopping each medication, best response achieved for each regimen, date of progression of disease [if known]).
  ➢ Cancer related surgical procedures (including name of procedure and when it was performed).
  ➢ Cancer related radiotherapy (including body location, total dose, unit, start and stop date, reason for treatment, best response achieved and date of progression at the site of irradiation on or after treatment).
  ➢ ErbB-2 status as well as tumor expression data for estrogen, and progesterone receptor status (positive or negative) should also be obtained. If results are unavailable, tumor tissue may be sent to the sponsor-identified central vendor for assessment prior to study entry as per investigator’s discretion.
  ➢ For all subjects who received trastuzumab in the adjuvant setting, LVEF pre-, and posttreatment as well as the lowest value reported during the adjuvant treatment will be recorded. This will include method of assessment, LVEF value in percentage, date of assessment and whether or not changes were assessed to be clinically significant.

• Physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes; including worsening of medical history conditions. A full neurological examination, which may be performed by a physician, registered nurse or other qualified health care provider, will be done at screening. Results must
be recorded on source documents and the Medical History or Adverse Event case report form as appropriate. All neurological events must be followed until resolution (to baseline or grade 1 level).

- Vital signs including height, weight, heart rate, blood pressure, temperature (oral, axillary or tympanic), and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (ie, highest or lowest) value must be reported.

- Assessment of ECOG Performance Status (see Attachment 2).

- Single standard 12-lead digital ECG, including heart rate, rhythm and RR, PR, QRS, and QTc intervals at screening. ECG will be read and interpreted at the investigational site for subject safety monitoring, and documentation stored with the source documents. Ensure that QTc meets eligibility (ie, subjects with QTc interval > 0.45 second or known history of QTc prolongation or TdP are not eligible). Digital data will be transmitted to an independent vendor for central assessment.

- Laboratory evaluations as described in the Laboratory Determinations section and the study flowchart.

- LVEF assessment by MUGA or ECHO. It is strongly recommended to use the same method of measurement for the same subject throughout the duration of the study.

- Health Outcomes questionnaires (see Attachment 6). Questionnaires should be performed prior to any other study procedures on the day of the visit. If questionnaires can only be completed after the study visit, they should be administered no later than 5 days from the visit. Both questionnaires need to be completed on the same day.

- Tumor assessment by radiographic evaluation as defined in the Tumor Assessment Requirement Flowchart. The same method of tumor assessment should be used, for the same subject, throughout the study.

- Review and assessment of any pretreatment AEs and prior concomitant medications. AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart(s). Concomitant medication and nonpharmacologic therapies/treatment will be collected as described in the
prior treatment section. AEs and SAEs are monitored continuously and recorded in the source documents, starting with the signing of the informed consent form. Documentation of AE and concomitant medication data on the eCRF will be done on an ongoing basis.

- If the subject is found eligible for the study, the subject should be randomized using the sponsor’s interactive voice response system (IVRS) no more than 2 business days before administration of the first dose of investigational product.

15.2 Active Treatment Phase

For the purpose of this trial, a cycle (and a month) will be defined as a 28-day period.

Refer to flowcharts 8.1 and 8.2 for the procedures and their time points to be performed for subjects receiving the combination of neratinib + paclitaxel or trastuzumab + paclitaxel respectively.

During the course of the study, subjects who discontinue one of the investigational product from the combination therapy may continue on the active treatment phase receiving the other investigational product as monotherapy at the investigator’s discretion. Procedures marked with “**” indicate procedures for which alternative schedules are used depending on the treatment the subject is receiving. Please refer to flowcharts 8.3, 8.4, and 8.5 for the procedures and their time points to be performed during neratinib, trastuzumab, or paclitaxel monotherapy, respectively.

15.2.1 Tumor Assessments

Tumor assessments (see Tumor Assessment Flowchart) will be performed and evaluated approximately every 8 weeks starting from first dose of investigational product (± 4 days). This will be done until there is radiographically confirmed objective disease progression, initiation of new anticancer therapy, or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up). The scheduling of radiographic assessments will remain unchanged regardless of treatment schedule modification (eg, dose delay and/or interruption). Missed tumor
assessments must be performed as soon as possible. The same method of measurement should be used for the same subject throughout the duration of the study.

Subjects who discontinue from study treatment for a reason other than objective disease progression will continue to have tumor assessments performed during follow-up visits every 8 weeks (± 4 days) until disease progression, initiation of new anticancer therapy or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up), whichever occurs first.

15.2.2 Cycle 1
15.2.2.1 Cycle 1, Day 1
The following information/assessments are required at cycle 1 day 1 but do not need to be repeated if obtained during screening within 14 days prior to day 1:

- Vital signs including height, weight, heart rate, blood pressure, temperature (oral, axillary, or tympanic), and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (ie, highest or lowest) value must be reported.
- Assessment of ECOG performance status.
- Laboratory evaluations as described in the Laboratory Determinations section and the Flowchart.

The following information/assessments will be collected on study day 1 of cycle 1:

- Symptom directed physical examination evaluating any new clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes; including worsening of baseline conditions. All neurological events must be followed until resolution (to baseline or grade 1 level). Results must be recorded on source documents and the Adverse Event CRF as appropriate.
- Single standard 12-lead digital ECG, including heart rate, rhythm and RR, PR, QRS, and QTc intervals to be performed prior to the first dose of investigational product. ECG will
be read and interpreted at the investigational site for subject safety monitoring, and
documentation stored with the source documents. Digital data will be transmitted to an
independent vendor for central assessment.

- Concomitant treatment and/or therapies and medications as described in the
  Concomitant Treatment section.
- AEs as described in the Adverse Event and Serious Adverse Event Recording and
  Reporting section and the flowchart.
- Dispense investigational product (ie, neratinib, paclitaxel, or trastuzumab). Laboratory
  values should be reviewed prior to each cycle and prior to dispensing investigational
  products to the subject.
- The amount of neratinib required for a 4-week cycle will be dispensed on the first day of
  each cycle.
  - Paclitaxel and trastuzumab infusions will be administered as indicated in the
    “paclitaxel administration” and “trastuzumab administration” sections.

15.2.2.2 Cycle 1, Days 8 and 15 (± 2 Days)
The following information/assessments will be collected on study day 8, and 15 of cycle 1:

- Symptom directed physical examination** evaluating any new clinically significant
  abnormalities within the following body systems: general appearance, skin, head, eyes,
ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities,
neurological, back/spinal, and lymph nodes; including worsening of baseline conditions.
All neurological events must be followed until resolution (to baseline or grade 1 level).
Results must be recorded on source documents and the Adverse Event CRF as
appropriate.
- Laboratory evaluations** as described in the Laboratory Determinations section and the
  study flowchart.
- Concomitant treatment and/or therapies and medications as described in the
  Concomitant Treatment section.
- AEs as described in the Adverse Event and Serious Adverse Event Recording and
  Reporting section and the flowchart.
• Dispense investigational product** (ie, paclitaxel, or trastuzumab). Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational products to the subject.
  ➢ Paclitaxel and trastuzumab infusions will be administered as indicated in the “paclitaxel administration” and “trastuzumab administration” sections.

15.2.2.3 Cycle 1, Day 22 (± 2 Days)
The following information/assessments will be collected on study day 22 of cycle 1:
• Concomitant treatment and/or therapies and medications as described in the Concomitant Treatment section.
• AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart.
• Dispense investigational product** (ie, trastuzumab). Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational products to the subject.
  ➢ Trastuzumab infusions will be administered as indicated in the “trastuzumab administration” sections.

15.2.3 Cycle 2 and Higher
15.2.3.1 Cycle 2 and Higher, Day 1 (± 4 Days)
The following information/assessments are required at day 1 of cycle 2 and higher:
• Health Outcomes questionnaires will be assessed at day 1 of every other cycle starting with cycle 2 (ie, cycle 2, 4, 6, etc). Health outcomes assessment should be performed prior to any other study procedures on the day they are collected. If questionnaires can only be completed after the study visit, they should be administered no later than 5 days from the visit. Both questionnaires need to be completed on the same day.
• Health care resource utilization during the previous cycle will be assessed at day 1 of every cycle.
• Symptom directed physical examination evaluating any new clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes; including worsening of baseline conditions. All neurological events must be followed until resolution (to baseline or grade 1 level). Results must be recorded on source documents and the Adverse Event CRF as appropriate.

• Vital signs including heart rate, blood pressure, temperature (oral, axillary or tympanic), and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (ie, highest or lowest) value must be reported.

• Assessment of ECOG performance status.

• Laboratory evaluations as described in the Laboratory Determinations section and the Flowchart.

• Starting with cycle 3, single standard 12-lead digital ECG, including heart rate, rhythm and RR, PR, QRS, and QTc intervals to be performed prior to investigational product administration every other cycle (ie, cycle 3, 5, 7 etc). ECG will be read and interpreted at the investigational site for subject safety monitoring, and documentation stored with the source documents. Digital data will be transmitted to an independent vendor for central assessment. If during the treatment period, a subject experiences grade 3 or greater QTc prolongation (>0.5 s) refer to the Dose Adjustments section for further instructions.

• LVEF assessment by MUGA or ECHO to be performed every 12 weeks starting with cycle 4, day 1. It is strongly recommended to use the same method of measurement for the same subject throughout the duration of the study. If deterioration of LVEF is observed then ECHO/MUGA should be performed every 4 weeks and test-article dose adjustments should be performed (See section 17.2.1 for further instructions)

• Concomitant treatment and/or therapies and medications as described in the Concomitant Treatment section.

• AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart.
 Dispense investigational product** (ie, neratinib, paclitaxel, or trastuzumab). Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational products to the subject.

- The amount of neratinib required for a 4-week cycle will be dispensed on the first day of each cycle.
- Paclitaxel and trastuzumab infusions will be administered as indicated in the “paclitaxel administration” and “trastuzumab administration” sections.

15.2.3.2 Cycle 2 and Higher, Days 8 and 15 (± 2 Days)

The following information/assessments will be collected on study day 8, and 15 of cycle 2 or higher:

- Symptom directed physical examination evaluating any new clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes; including worsening of baseline conditions will be performed on day 8 and 15 of cycle 2 only. All neurological events must be followed until resolution (to baseline or grade 1 level). Results must be recorded on source documents and the Adverse Event CRF as appropriate.
- Laboratory evaluations** as described in the Laboratory Determinations section and the study flowchart.
- Concomitant treatment and/or therapies and medications as described in the Concomitant Treatment section.
- AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart.
- Dispense investigational product** (ie, paclitaxel, or trastuzumab). Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational products to the subject.

- Paclitaxel and trastuzumab infusions will be administered as indicated in the “paclitaxel administration” and “trastuzumab administration” sections.
15.2.3.3  Cycle 2 and Higher, Day 22 (± 2 Days)

The following information/assessments will be collected on study day 22 of cycle 2 or higher:

- Concomitant treatment and/or therapies and medications as described in the Concomitant Treatment section.
- AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart.
- Dispense investigational product** (ie, trastuzumab). Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational products to the subject.
  - Trastuzumab infusions will be administered as indicated in the “trastuzumab administration” sections.

15.3  End of Treatment Visit

The end of treatment visit will be performed as soon as possible, but no later than 4 weeks after the last dose of investigational product and prior to the start of a new anticancer therapy.

The following information/assessments will be collected at the end of treatment visit:

- Health outcomes assessment. It is acceptable for the questionnaires to be administered after study procedures are completed. If questionnaires can only be completed after the study visit, they should be administered no later than 5 days from the visit. Both questionnaires need to be completed on the same day. Questionnaires do not need to be completed again if completed within 7 days prior to the end of treatment visit.
- Health care resource utilization since last assessment will be recorded.
- Symptom directed physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, breasts, abdomen, external genitalia, extremities, neurological, back/spinal, and lymph nodes; including worsening of medical history conditions. All neurological events must be followed until resolution (to baseline or grade 1 level). Results must be recorded on source documents and the Medical History or Adverse Event case report form as appropriate.
• Vital signs including heart rate, blood pressure, temperature (oral, axillary or tympanic), and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (ie, highest or lowest) value must be reported.

• Assessment of ECOG Performance Status (see Attachment 2).

• Laboratory evaluations as described in the Laboratory Determinations section and the study flowchart.

• Single standard 12-lead digital ECG, including heart rate, rhythm and RR, PR, QRS, and QTc intervals to be performed at the end of treatment visit. ECG will be read and interpreted at the investigational site for subject safety monitoring, and documentation stored with the source documents. Digital data will be transmitted to an independent vendor for central assessment. If QTc prolongation is evident (QTc > 0.5 s), then repeat ECG at least 2 weeks after the last dose of investigational product.

• LVEF assessment by MUGA or ECHO. Testing does not need to be repeated, if done within 8 weeks prior to the end of treatment visit. It is strongly recommended to use the same method of measurement for the same subject throughout the duration of the study.

• Tumor assessment by radiographic evaluation as defined in the Tumor Assessment Requirement Flowchart. The same method of tumor assessment should be used, for the same subject, throughout the study.
  ✓ Subjects who have already demonstrated objective disease progression do not need to have scans repeated at the end of treatment visit.
  ✓ For subjects who do not have documented objective disease progression at time of treatment discontinuation, tumor assessments will continue to be performed approximately every 8 weeks (± 4 days) until disease progression, initiation of new anticancer therapy or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up), whichever occurs first.

• Concomitant treatment and/or therapies and medications as described in the Concomitant Treatment section.

• AEs as described in the Adverse Event and Serious Adverse Event Recording and Reporting section and the flowchart.
15.4 Survival Follow-up

Survival data will be collected for all subjects. Survival follow-up visits (or information collected via telephone call) will be conducted approximately every 3 months (ie, 12 weeks) starting from the last day of investigational product administration until discontinuation of the subject from study (eg, death, subject’s request, lost to follow-up), or cutoff date when a total of approximately 631 deaths have been observed, whichever occurs first. These visits may be conducted by telephone interview (if applicable, as indicated below) and will include the following information:

- Subject status (eg, alive, deceased or unknown):
  - If subject is deceased, the date and cause of death must be provided (by telephone).
  - If subject status is unknown, the date of the subject was last known alive must be provided. The reason for the inability to obtain the status as well as the site personnel’s attempts to obtain the subject’s status must be well documented in the source documentation.

- Anticancer therapy (ie, medications) initiated after last dose of investigational product (by telephone). This will include the name of the therapy, the start and stop dates if available.

- Tumor assessments:
  - Subjects who discontinue study treatment for reasons other than disease progression, will continue to have tumor assessments performed during follow-up visits every 8 weeks (± 4 days) until disease progression, initiation of new anticancer therapy or discontinuation of subject from study (eg, death, subject’s request, lost to follow-up), whichever occurs first.
  - Subjects who discontinue study treatment due to documented objective disease progression do not require scans during the follow-up period.

During the conduct of the trial, the sponsor may request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, as needed for primary or
interim data analyses. These data sweeps will collect the survival status of all subjects on treatment and in the follow-up portion of the trial with the intent to capture the date each subject was last known alive. Participation and commitment to contact all subjects still on trial, either on treatment or in follow-up phase, is required to ensure successful conduct of the trial.

15.5 Total Volume of Blood Collected
The volume of blood collected from each subject will be:
- At screening and final visit: approximately 7 mL each (total 14 mL).
- At any given cycle: approximately 15 mL total.
- Subjects participating to pharmacogenetic portion of the study will have another 15 mL collected for assessment of HER2/ECD.

For example, in the case of a subject receiving 12 cycles worth of treatment (may be longer or shorter), a total of approximately 194 mL (209 mL if subject is participating in the pharmacogenetic portion of the study) blood would be collected during the course of the study.

16.0 INVESTIGATIONAL PRODUCT AND ADMINISTRATION
Subjects will be randomized to receive either neratinib (240 mg oral daily) in combination with paclitaxel (80 mg/m² IV on day 1, 8, and 15 of a 28-day cycle), or trastuzumab (4 mg/kg IV x 1 initial loading dose followed by 2 mg/kg IV weekly on days 1, 8, 15, and 22 of a 28-day cycle) in combination with paclitaxel (80 mg/m² IV on day 1, 8, and 15 of a 28-day cycle).

Investigational product is only administered to subjects who have provided informed consent. Once an investigational product has been assigned to a subject it must not be reassigned to another subject.

Subjects will continue receiving the investigational product until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.
16.1 Packaging and Labeling
Neratinib 40-mg, or 240-mg tablets will be supplied by the sponsor and will be packaged in bottles.

Paclitaxel and trastuzumab vials will be supplied by the sponsor where required.

Detailed packaging information is available in the study reference manual. Investigational product will be labeled according to regulations.

16.2 Storage and Stability
Neratinib will be stored by sites at 25°C (77°F) or below with desiccant; do not freeze. Excursions are permitted to 30°C (86°F). Neratinib should be stored in a secure location with limited access. Subjects should be instructed to store neratinib in a safe place at room temperature (25°C or below; do not freeze).

Paclitaxel and trastuzumab will be stored at the site pharmacy as described in the product package insert. After reconstitution, paclitaxel and trastuzumab will be used and stored as described in the product package insert.4,24

The investigational product must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

16.3 Investigational Product Administration
16.3.1 Neratinib Administration
The number of neratinib tablets taken will depend on the prescribed dose. Neratinib (240 mg) will be taken on a daily basis by mouth with food, preferably in the morning until disease
progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

16.3.2 Paclitaxel Administration
Paclitaxel will be administered IV (80 mg/m²) on days 1, 8, and 15 of a 28-day cycle. Subjects will receive paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator’s discretion. Treatment will be stopped in case of disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

Paclitaxel should be administered IV over 1 hour. All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reaction. Premedications will be supplied by the site. Such premedication may consist of corticosteroids (eg, dexamethasone), diphenhydramine and H₂ antagonist. Please refer to package insert for additional information.⁴

16.3.3 Trastuzumab Administration
Trastuzumab will be administered at an initial loading dose of 4 mg/kg as a 90 minutes IV infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute IV infusions until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs. Please refer to package insert for additional information.²⁵

17.0 DOSE ADJUSTMENT GUIDELINES
17.1 General Rules
If doses of investigational product (ie, neratinib, paclitaxel, or trastuzumab) are delayed or held, then study procedures for that cycle will proceed on schedule as planned, without any delay. This does not apply to tumor assessments, which should continue to be done every 8 weeks, regardless of any changes to dose administration, and AE assessment, which should be done continuously. Missed dose(s) of investigational product will not be made up. The dose adjustments presented below are to be used as a guideline for investigators, additional measures
may be taken as necessary for certain subjects per investigator’s medical judgment. All dose modifications/adjustments should be documented in subject’s source notes.

### 17.2 Dose Adjustments

Once a dose has been reduced for a subject, all subsequent cycles should be administered at that dose, unless further dose reduction is required. Dose reescalation is not permitted.

Subjects should discontinue an investigational product (ie, neratinib, paclitaxel) if they require more than 2 dose reductions of that investigational product or if subject has not recovered from a toxicity related to the investigational product after > 3 weeks. No dose reduction is planned for trastuzumab: treatment should be either temporarily or permanently discontinued in case of toxicity.

Once an investigational product has been discontinued, subjects may continue on the active treatment phase of the study receiving the other investigational product from the combination as monotherapy as per the investigator’s discretion. For example, if paclitaxel is discontinued for neuropathy, neratinib or trastuzumab may be continued as monotherapy if judged appropriate per the investigator’s assessment.

The recommended dose levels for toxicity-related dose reduction(s) are listed in the dose administration table below.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>80 mg/m²</td>
</tr>
<tr>
<td>-1</td>
<td>70 mg/m²</td>
</tr>
<tr>
<td>-2</td>
<td>60 mg/m²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Neratinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>240 mg</td>
</tr>
<tr>
<td>-1</td>
<td>160 mg</td>
</tr>
<tr>
<td>-2</td>
<td>120 mg</td>
</tr>
</tbody>
</table>
17.2.1 Dose Adjustment Guidelines for Subjects Enrolled in the Neratinib-Paclitaxel Arm

Neratinib-Related Toxicities

Diarrhea is the major DLT of neratinib. Subjects should have ready access to antidiarrheal agents (eg, loperamide) at home, starting on day 1 of treatment. Subjects should be encouraged to contact the site to report and discuss the severity of diarrhea and the appropriate course of treatment. Diarrhea should be treated at the very first occurrence with appropriate treatment.

Infectious causes of diarrhea should be excluded and documented in the source document for cases of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia). Stool cultures may be performed as a way of excluding infectious causes of diarrhea at per the investigator’s discretion. Results from occult blood, fecal leukocyte stain, clostridium difficile, campylobacter, salmonella, and shigella testings, when performed, should be reported using the appropriate eCRF..

General dietetic and pharmacologic recommendations are included in Attachment 3. Subjects with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction. Following treatment interruption and/or reduction, prophylactic antidiarrheal medication is recommended upon resumption of neratinib. Refer to the dose adjustment guidelines below for details.

Paclitaxel-Related Toxicities

Bone marrow suppression is the major DLT of paclitaxel. Neutropenia is the most important hematologic toxicity and is generally rapidly reversible. The use of supportive therapy, including G-CSF, should be considered for subjects who experience severe neutropenia.

Peripheral neuropathy is also frequently reported with the use of paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with cumulative dose.

Subjects receiving paclitaxel should be monitored prior to each dose with a complete blood count, including differential and platelet count. ANC must be $\geq 1000/mm^3 (1.0 \times 10^9/L)$ and
platelet count must be $\geq 75,000/\text{mm}^3$ ($75 \times 10^9/L$) in order to administer paclitaxel. Administration of the next weekly dose must be held until recovery to these levels, but not more than 3 weeks.

Paclitaxel has been associated with infusion reactions some of which were reported fatal despite premedication. Paclitaxel should be discontinued for infusion reactions manifesting as anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria. Please refer to package insert for additional information.\(^4\)

Dose modifications for subject experiencing acute hypersensitivity reaction despite premedication, neutropenia, or severe peripheral neuropathy during paclitaxel therapy are provided in the dose adjustment guidelines below.

**Dose Adjustment Guidelines for Subjects Receiving Neratinib + Paclitaxel**

<table>
<thead>
<tr>
<th>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</th>
<th>Action</th>
</tr>
</thead>
</table>
| **Diarrhea:** uncomplicated grade 1-2 diarrhea            | • Continue at full doses.  
• Provide dietetic recommendations (as defined in Attachment 3) to subjects.  
• Consider prophylactic anti-diarrheal medications with next neratinib administration. |
| **Diarrhea:** Grade 3 lasting $> 2$ days despite being treated with optimal medical therapy, or associated with fever, dehydration, or grade 3-4 neutropenia or any grade 4 diarrhea. | • Hold neratinib and paclitaxel until recovery to $\leq$ grade 1 or baseline.  
• Provide dietetic recommendations (as defined in Attachment 3) to subjects.  
• Consider prophylactic anti-diarrheal medications with next neratinib administration |
<table>
<thead>
<tr>
<th>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If recovery occurs:</td>
<td></td>
</tr>
<tr>
<td>o ≤1 week from treatment being held, resume at same doses of both investigational products.</td>
<td></td>
</tr>
<tr>
<td>o Within 1-3 weeks from treatment being held, reduce neratinib dose to the next lower dose level (maintain the same dose of paclitaxel).</td>
<td></td>
</tr>
<tr>
<td>• If event occurs a 2nd time and the neratinib dose has not already been decreased, reduce neratinib dose to the next lower dose level (maintain the same dose of paclitaxel). If neratinib dose has already been reduced, then reduce the dose of paclitaxel to the next lower dose level (maintain the same dose of neratinib)</td>
<td></td>
</tr>
<tr>
<td>• If subsequent events occur, reduce the dose of neratinib or paclitaxel to the next lower dose level in an alternate fashion (ie paclitaxel if neratinib was previously reduced or neratinib if paclitaxel was previously reduced).</td>
<td></td>
</tr>
<tr>
<td>Grade 2 neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Reduce paclitaxel by 1 dose level.</td>
<td></td>
</tr>
<tr>
<td>• Neratinib should be continued at the same dose level.</td>
<td></td>
</tr>
<tr>
<td>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</td>
<td>Action</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| Grade ≥ 3 neuropathy                                      | • Hold paclitaxel until event resolves or returns to baseline.  
• Decrease paclitaxel dose by 1 dose level  
• Neratinib should be continued at the same dose level. |
| Grade 3 or 4 acute hypersensitivity despite adequate premedication | • Discontinue paclitaxel and consider maintaining the subject on the active treatment phase of the study with neratinib monotherapy. |
| ANC <1000/mm³ (1.0 × 10⁹/L), or platelet <75,000/mm³ (75 × 10⁹/L) on day of scheduled paclitaxel treatment | • Hold paclitaxel until ANC ≥1000/mm³ (1.0 × 10⁹/L), and platelet ≥75,000/mm³ (75 × 10⁹/L)  
• Consider treatment with growth factor with next paclitaxel administration (eg, G-CSF)  
• If the event occurs a 2nd time, reduce paclitaxel by 1 dose level.  
• Neratinib should be continued at the same dose level. |
| Grade 4 neutropenia lasting ≥7 days, grade 4 febrile neutropenia, or grade 3 or 4 documented infection with neutropenia (ANC <1000). | • Hold paclitaxel until ANC ≥1000/mm³ (1.0 × 10⁹/L)  
• Reduce paclitaxel by 1 dose level.  
• Consider treatment with growth factor with next paclitaxel administration (eg, G-CSF)  
• Neratinib should be continued at the same dose level. |
Event on day of scheduled treatment (BASED ON NCI CTC 3.0) | Action |
---|---|
| | • If the event occurs a 2nd time, reduce paclitaxel to the next lower dose level or discontinue paclitaxel at the investigator’s discretion. |
| Other Grade 3 or 4 non-hematologic including nausea and/or vomiting despite optimal medical therapy; and asthenia lasting > 3 days | • Hold neratinib and paclitaxel until recovery to ≤ grade 1 or baseline.  
• Test-article dose adjustment and/or discontinuation should be performed according to the investigator’s best medical judgment. |
| QT/QTc >0.5 sec or QT/QTc increase of >0.06 sec over baseline | • Hold neratinib until recovery to ≤ grade 1 or baseline.  
• Test-article dose adjustment and/or discontinuation should be performed according to the investigator’s best medical judgment. |
| LVEF: Asymptomatic decline of ≥ 15% from baseline OR decline of ≥ 10% and below the lower limit of normal of 50% | A) If LVEF below 40%: Hold neratinib and seek cardiology input OR continue neratinib with great caution.  
Initiate monthly monitoring of LVEF  
• If while monitoring monthly LVEF remains < 40%: reconsider neratinib only if appropriate and after cardiology consult.  
• If while monitoring monthly LVEF increases to ≥ 40%: continue neratinib, monitor LVEF |
### Event on day of scheduled treatment (BASED ON NCI CTC 3.0)

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>every 12 weeks and consider cardiac support with input from cardiologist.</td>
</tr>
</tbody>
</table>

#### B) If LVEF between 40% to 50%: continue neratinib with caution and surveillance

**Initiate monthly monitoring of LVEF**

- If while monitoring monthly LVEF falls to < 40%: Follow bullet point A instructions described above.
- If while monitoring monthly LVEF remains ≥ 40%: continue neratinib, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.

<table>
<thead>
<tr>
<th>LVEF: Symptomatic cardiac failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neratinib should be held, LVEF measured and input from a cardiologist sought.</td>
</tr>
</tbody>
</table>

### 17.2.2 Dose Adjustment Guidelines for Subjects Enrolled in the Trastuzumab-Paclitaxel Arm

#### Paclitaxel-Related Toxicities

Subjects receiving paclitaxel should be monitored prior to each dose with a complete blood count, including differential and platelet count. ANC must be $\geq 1000/mm^3 \ (1.0 \times 10^9/L)$ and platelet count must be $\geq 75,000/mm^3 \ (75 \times 10^9/L)$ in order to administer paclitaxel.
Administration of the next weekly dose must be held until recovery to these levels, but not more than 3 weeks.

Please refer to package insert for additional information on dose modification. The guidelines below can serve as example of dose adaptations in subject acute hypersensitivity reaction despite premedication, neutropenia, or severe peripheral neuropathy during paclitaxel therapy.

**Paclitaxel Dose Adjustment Guidelines for Subjects Receiving Trastuzumab + Paclitaxel**

<table>
<thead>
<tr>
<th>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</th>
<th>Action</th>
</tr>
</thead>
</table>
| Grade 2 neuropathy                                        | • Reduce paclitaxel by 1 dose level  
|                                                          | • Trastuzumab should be continued at the same dose level |
| Grade ≥ 3 neuropathy                                      | • Hold paclitaxel until event resolves or returns to baseline.  
|                                                          | • Decrease paclitaxel dose by 1 dose level  
|                                                          | • Trastuzumab should be continued at the same dose level. |
| Grade 3 or 4 acute hypersensitivity despite adequate premedication | • Discontinue paclitaxel and consider maintaining the subject on the active treatment phase of the study with trastuzumab monotherapy. |
| ANC <1000/mm$^3$ (1.0 × 10$^9$/L), or platelet <75,000/mm$^3$ (75 × 10$^9$/L) on day of scheduled paclitaxel treatment | • Hold paclitaxel until ANC ≥1000/mm$^3$ (1.0 × 10$^9$/L), and platelet ≥75,000/mm$^3$ (75 × 10$^9$/L)  
|                                                          | • Consider treatment with growth factor with next paclitaxel administration (eg, G-CSF)  
|                                                          | • If the event occurs a 2nd time, reduce |
### Event on day of scheduled treatment (BASED ON NCI CTC 3.0) | Action
---|---
paclitaxel by 1 dose level.  
- Trastuzumab should be continued at the same dose level.  

| Grade 4 neutropenia lasting ≥7 days, grade 4 febrile neutropenia, or grade 3 or 4 documented infection with neutropenia (ANC <1000). | Hold paclitaxel until ANC ≥1000/mm³ (1.0 × 10⁹/L).  
- Reduce paclitaxel by 1 dose level.  
- Consider treatment with growth factor with next paclitaxel administration (eg, G-CSF).  
- Trastuzumab should be continued at the same dose level.  
- If the event occurs a 2nd time, reduce paclitaxel to the next lower dose level or discontinue paclitaxel at the investigator’s discretion. |

| Other Grade 3 or 4 non-hematologic including nausea and/or vomiting despite optimal medical therapy; and asthenia lasting > 3 days | Hold trastuzumab and paclitaxel until recovery to ≤ grade 1 or baseline.  
- Test-article dose adjustment and/or discontinuation should be performed according to the investigator’s best medical judgment. |

### Trastuzumab-Related Toxicities

Trastuzumab can specifically result in subclinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in subjects who have received trastuzumab concurrently with anthracycline-containing chemotherapy regimens. Trastuzumab has also been associated with infusion reactions and pulmonary toxicity. Trastuzumab infusion should be interrupted for subjects experiencing
Neratinib (HKI-272)
Protocol 3144A2-3005-WW
21 May 2009

dyspnea or clinically significant hypotension. Subjects should be monitored until signs and
symptoms completely resolve. Trastuzumab should be discontinued for infusion reactions
manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress
syndrome. Please refer to package insert for additional information on dose modification
following infusion reactions or cardiomyopathy events.25

Trastuzumab Dose Adjustment Guidelines for Subjects Receiving Trastuzumab +
Paclitaxel

<table>
<thead>
<tr>
<th>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Reactions</td>
<td></td>
</tr>
<tr>
<td>• Mild or moderate infusion reactions: decrease the rate of infusion.</td>
<td></td>
</tr>
<tr>
<td>• Interrupt the infusion in subjects with dyspnea or clinically significant hypotension.</td>
<td></td>
</tr>
<tr>
<td>• Discontinue trastuzumab for severe or life-threatening infusion reactions.</td>
<td></td>
</tr>
<tr>
<td>LVEF: Asymptomatic decline of ≥ 15% from baseline OR decline of ≥ 10% and below the lower limit of normal of 50%</td>
<td>A) If LVEF below 40%: Hold trastuzumab and seek cardiology input OR continue trastuzumab with great caution.</td>
</tr>
<tr>
<td></td>
<td>Initiate monthly monitoring of LVEF</td>
</tr>
<tr>
<td></td>
<td>• If while monitoring monthly LVEF remains &lt; 40%: reconsider trastuzumab only if appropriate and after cardiology consult.</td>
</tr>
<tr>
<td></td>
<td>• If while monitoring monthly LVEF increases to ≥ 40%: continue trastuzumab, monitor LVEF every 12 weeks and</td>
</tr>
<tr>
<td>Event on day of scheduled treatment (BASED ON NCI CTC 3.0)</td>
<td>Action</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>consider cardiac support with input from cardiologist.</td>
</tr>
<tr>
<td></td>
<td><strong>B)</strong> If LVEF between 40% to 50%: continue trastuzumab with caution and surveillance</td>
</tr>
<tr>
<td></td>
<td>Initiate monthly monitoring of LVEF</td>
</tr>
<tr>
<td></td>
<td>• If while monitoring monthly LVEF falls to &lt; 40%: Follow bullet point A instructions described above.</td>
</tr>
<tr>
<td></td>
<td>• If while monitoring monthly LVEF remains ≥ 40%: continue trastuzumab, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.</td>
</tr>
<tr>
<td>LVEF: Symptomatic cardiac failure</td>
<td>• Trastuzumab should be held, LVEF measured and input from a cardiologist sought.</td>
</tr>
</tbody>
</table>

**17.3 Subject Compliance**

For neratinib, compliance is monitored by study personnel at the site by using tablet counts and is recorded on source documents, the drug inventory record, and eCRFs. Paclitaxel and trastuzumab will be given by IV by site personnel at the site. Each study subject must have received 75% of the planned number of doses of primary therapy based on the number of days of actual dose administration to be considered compliant. Dose adjustments must follow the dose adjustment guidelines section.
Neratinib tablets will be counted by site personnel at the first study visit for each cycle to ensure subject compliance and will be documented on drug accountability forms provided to the sites. When paclitaxel and/or trastuzumab are supplied by Wyeth, dose administration will be recorded on Wyeth drug accountability forms. When paclitaxel and/or trastuzumab is not supplied by Wyeth, a drug accountability form from the site will be acceptable.

Any study medication not taken per protocol will be documented appropriately on the eCRF and in the source documents. All used, unused or partially used investigational products and their original containers should be kept on site for reconciliation by a site monitor prior to return to sponsor or destruction.

18.0 SAFETY
Refer to the flowchart(s) for time points. In this section, “investigational product” refers to neratinib, trastuzumab and paclitaxel.

Any subject who receives at least 1 dose of investigational product will be included in the evaluation for safety. The following safety parameters will be assessed as described in the Procedures section, Laboratory Determination section, and flowchart:

1. Medical history
2. Vital signs
3. Physical examinations
4. 12-lead ECGs
5. LVEF as measured by MUGAs/ECHOs
6. Laboratory evaluations (ie, serum chemistry panel, CBC with differential, coagulation panel, and β-HCG).

Changes in laboratory test results, including ECG and review of treatment-related adverse event incidence and severity will be reviewed. AEs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC) version 3. SAEs will be reported until
28 days after the last dose of investigational product(s) and will be followed until resolution. Any SAEs beyond 28 days after the last dose of investigational product(s) considered related to investigational product(s) will also be reported.

An Independent Data Monitoring Committee will meet approximately every 6 months to monitor safety and efficacy data.

19.0 EFFICACY

Refer to the flowchart(s) for time points: study flowchart for survival follow-up and tumor assessment flowchart for tumor assessments to be performed.

Tumor based efficacy endpoints (ie, PFS, ORR, DOR, and CBR) will be based on assessments performed by the investigators, and by an independent radiology vendor. The interim and primary analyses will be based on the independent vendor’s assessment.

Clinical activity will be assessed by performing tumor assessments for all subjects at screening, and then every 8 weeks throughout the active treatment phase until documented disease progression, or subject’s discontinuation from study (ie, lost to follow-up, subject’s request, or death), whichever occurs first. Additional evaluations of disease at baseline will be performed as clinically indicated. Missed tumor assessments must be performed as soon as possible. To be considered evaluable in terms of efficacy subjects must have no major protocol violations that could confound the interpretation of the study results, received at least 7 doses of neratinib or 2 doses of trastuzumab and at least 2 doses of paclitaxel, and undergo at least one follow-up tumor assessment approximately 8 weeks after starting treatment unless the subjects discontinued investigational product because of documented disease progression or death. As soon as evaluations for each tumor assessment are completed, the investigator should assess the subject response based on criteria defined in the Response Criteria section. Scans must be assessable for all evaluations.

Major protocol violations that will exclude subjects from the evaluable population include:
• Failure to meet any of the inclusion or exclusion criteria.
• Administration of any concurrent chemotherapy, radiotherapy, surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents and hormonal agents, before the last dose of investigational products, regardless of dose or number of days received.
• Subject remaining on study despite initiation of bisphosphonate therapy during the course of the study without documentation that disease progression was clearly ruled out.

For all subjects in the study, tumor site assessments (including copies of all radiology studies) will need to be prepared by the sites for evaluation by independent radiology review. Separate instructions will be provided to the sites on how and where to send these assessments.

All subjects will continue to have tumor assessments until documented progression of disease, initiation of a new anti-cancer treatment(s) or subject’s discontinuation from study (ie, lost to follow-up, subject’s request, or death). Follow-up after subject discontinuation of investigational product will also be conducted approximately every 3 months (ie, 12 weeks) to assess for survival until subject’s discontinuation from study (ie, lost to follow-up, subject’s request, or death).

Subjects who discontinue from study treatment for a reason other than radiographically confirmed objective disease progression will continue to have radiological tumor assessments performed approximately every 8 weeks (± 4 days) until documented progression, initiation of a new anti-cancer treatment, or subject’s discontinuation from study (ie, lost to follow-up, subject’s request, or death), whichever occurs first.

The evaluation of clinical activity for this study will use the RECIST guidelines, clarified by Wyeth Research as appropriate for this protocol (see following sections).

All subsequent measurements will be compared with the baseline measurement, thus establishing an objective review. Disease progression will be established by comparing all measurements with the smallest sum of longest diameter (SLD) recorded since randomization.
In order to estimate the overall tumor burden at baseline, a maximum of 5 measurable lesions per organ and 10 measurable lesions in total representative of all organs involved should be identified as target lesion(s) and recorded and measured at baseline. All sites of disease identified at screening must be followed for the duration of the study. Target lesions should be selected on the basis of their size (those with longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Their presence and absence should be noted throughout follow-up.

All lesions should be followed with the same method of assessment throughout the study.

- **Radiographic evaluations:**
  In case of spiral (helical) CT, acquisition should be performed with a maximum of 7-mm slice thickness (collimation) and reconstructing contiguously at 5-mm intervals. If conventional (axial) CT or MRI is used, contiguous images should be acquired at 10-mm or less.

- **Clinical examinations:**
  Clinically detected lesions will only be considered measurable if they are superficial (eg, skin nodules and palpable lymph nodes) and objective documentation can be provided, such as a caliper measurement, color photograph with a ruler, or scans. If such documentation is unavailable, these lesions will only be followed as non-target lesions.

The longest diameters for all target lesions will be recorded in millimeters and the sum of longest diameter (SLD) will be reported. The baseline sum of longest diameters will be used as the reference by which the objective tumor response will be characterized.
19.1 Definitions of Measurable Disease and Measurable Lesions

Measurable disease: The presence of at least 1 measurable lesion (defined below). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology and/or histology.

Measurable lesions: Lesions that can be accurately measured in at least 1 dimension, with the longest diameter being ≥20 mm for palpable skin nodules and/or lymph nodes, ≥ 10 mm for spiral CT (with 5-mm contiguous reconstruction), or ≥20 mm using standard CT or MRI (with 10 mm or less contiguous slices). Measurable lesions must be at least 2 times the slice thickness.

Nonmeasurable lesions: Lesions considered to be truly nonmeasurable include bone lesions, leptomeningeal disease, ascites, pleural and/or pericardial effusion, inflammatory breast disease, lymphangitis cutis and/or pulmonis, cystic lesions, as well as abdominal masses that are not confirmed and followed by imaging techniques.

19.2 Methods of Measurement

1. CT and MRI are the recommended methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed by using a 5-mm contiguous reconstruction algorithm. CT scans of the chest, abdomen and/or pelvis should be obtained as clinically indicated. Alternatively, CT scans of the chest and separate CT scans of the abdomen and/or pelvis may be obtained. Radiographs may be used during the study to follow lesions seen on bone scan and confirmed by radiographs at screening. In cases of CT contrast media allergy or renal insufficiency (creatine >2 mg/dL [176.8 μmol/L]) in which CT scans with contrast cannot be done, enhanced MRIs (for pelvis or abdomen) or CT without contrast (for chest) may be used instead, but the same method of assessment must be used throughout the course of the study.
2. The same method of measurement and the same technique of assessment should be used to characterize each identified and reported lesion at baseline through the final visit. The size of CT/MRI scan interval cuts must not change for a subject after screening.

3. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of the active drug phase and never more than 28 days before the beginning of the active drug phase.

4. Lesions noted on physical examination, such as skin nodules and lymph nodes, will be considered measurable only if they are superficial and are ≥ 20 mm at initial assessment. As often as possible, the same investigator using the same method of measurement should assess these lesions at all visits. Physical exam may not be the sole method of assessment for a solitary lesion.

5. For subjects with non-target skin lesions, photographs should be taken, if possible.

6. Lesions seen on chest radiographs, but not confirmed by CT or MRI scan, are not acceptable as measurable lesions.

7. Ultrasound should not be used for the purposes of measuring or evaluating tumors in this study.

8. Tumor markers alone cannot be used to assess response.

19.3 Documentation of “Target” and “Non-Target” Lesions

1. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, if possible, should be identified as target lesions and recorded and measured at baseline. In this context, organ systems are defined as group of related tissues or organs, performing a specific function. For example: lymph nodes represent one organ system, irrespective of their location in the body. Also, the left and right lobes of the lung belong to one single organ system.

2. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessment).
3. Target lesions at screening must have a unilateral tumor measurement of at minimum 10 mm and at least 2 times the size of the CT/MRI scan interval cut.

4. The longest diameters for all target lesions will be recorded and a sum of the longest diameter (SLD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum of LD will be used throughout the study as the reference by which the objective tumor response will be characterized. A target lesion that is present, but too small to measure accurately at evaluations after baseline (greater than 0 mm but less than 5 mm in unilateral dimension), will be classified as too small to measure (TSTM), and will by convention be assigned a value of 5 mm for the purposes of determining the sum of longest diameters.

5. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. This includes any lesions that do not meet measurable criteria as well as measurable lesions beyond the maximum number allowed for target lesions. Size determinations of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

19.4 Response Criteria

19.4.1 Clarifications to RECIST

The following clarifications have been provided in order to more accurately and consistently assess response for specific issues that are not addressed in the RECIST criteria (eg, missing data and lymph node measurements).

1. In general, if tumor response data is missing, an overall response assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data are available for all target lesions, the overall response for that time point will be assigned based on the target lesion assessment (sum of the longest diameter). The exception to this is the assessment of complete response (CR), when there is missing or unevaluable data for non-target lesions. In this case, an overall response of PR would be recorded at this time. Confirmation of overall response will require data for all lesions, both target and non-target, at a subsequent tumor assessment at least 4 weeks later. Repeat of all baseline assessments, including bone scan will also be required.
2. Lesion that have been previously irradiated or that have been treated with loco-regional treatment (eg, cryosurgery, arterial infusion, embolization etc…) cannot be selected as measurable lesion and must be selected and monitored as non measurable lesion to assess for disease progression.

3. A newly detected lymph node must have a diameter of ≥ 15 mm before it will be designated as new malignant tissue and assessed as progressive disease (PD).

4. Target lymph node lesions that become ≤ 10 mm will be considered normal (non-pathologic) and should be recorded as having a measurement of 0 mm. Thus, it follows that if all target node lesions have become ≤ 10 mm, and all other non-node lesions have disappeared (whether target or non-target type), the overall response can be considered a CR.

5. In order to avoid premature determination of PD, in instances where small tumors are target lesions, if the SLD is ≤ 20 mm at baseline, or becomes ≤ 20 mm during the course of the study, a ≥ 5 mm increase in SLD is required at subsequent tumor assessments before the target and overall response is assessed as PD.

6. Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

7. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (ie, fine needle aspiration/biopsy) to confirm the CR status.

8. Skin lesions will only be considered measurable disease if they are documented radiographically. Photography is not recommended as a means to follow measurable disease.

9. Bone lesions, if present should be identified as non-target lesions.

10. Subjects who require initiation of bisphosphonates for their cancer will be considered to have evidence of progressive disease and should discontinue from active treatment phase unless disease progression can be completely ruled out. Every effort should be made to evaluate subject for progressive disease prior to initiating bisphosphonates.
11. Subjects who require initiation of radiation for their cancer will be considered to have evidence of progressive disease and should discontinue from active treatment phase. Every effort should be made to evaluate subject for progressive disease prior to initiating radiation.

19.4.2 Evaluation of Target Lesions (Per Assessment)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR):</td>
<td>Disappearance of all target lesions</td>
</tr>
<tr>
<td>Partial response (PR):</td>
<td>At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD</td>
</tr>
</tbody>
</table>
| Progressive disease (PD):     | At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of recorded LDs since the treatment started, or the appearance of 1 or more new lesions
a. Any new lesion reported after screening must be documented as a non-target lesion. |
| Stable disease (SD):          | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment started |

19.4.3 Evaluation of Non-Target Lesions (Per Assessment)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR):</td>
<td>Disappearance of all non-target lesions and normalization of tumor marker level</td>
</tr>
<tr>
<td>Stable disease (SD)/Incomplete response:</td>
<td>Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above normal limits</td>
</tr>
<tr>
<td>Progressive disease (PD):</td>
<td>Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions</td>
</tr>
</tbody>
</table>
19.4.4 Evaluation of Overall Response

At designated time points, the investigator should assess the overall response on the basis of the target lesions, non-target lesions, and new lesions (if any). The best overall response is the best response recorded from randomization until disease progression/recurrence (taking as reference for PD) the smallest measurements recorded since randomization. In general, the subject’s best overall response assignment will depend on the achievement of both measurement and confirmation criteria.

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

19.4.5 Confirmation of Response

The main goal of confirmation of objective response is to avoid an incorrect estimation of the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of SD, measurements must have met the SD criteria at least once at a minimum of 8 weeks following first dose of study drug administration.
19.5 Primary Endpoints

Progression Free Survival

Progression-free survival is the interval from the date of randomization until the first date on which recurrence or progression, or death due to any cause, is documented, censored at the last assessable evaluation or at the initiation of new anticancer therapy.

19.6 Secondary Endpoints

Objective Response Rate

Objective response rate is the proportion of subjects who achieve confirmed tumor response (complete or partial response) per RECIST.

Duration of Response

The duration of response is measured from the time to which measurements criteria are met for CR or PR (whichever status is recorded first) until the first date on which recurrence or PD is objectively documented, taking as a reference for PD the smallest measurements recorded since randomization.

Duration of Stable Disease

SD is measured from randomization until the criteria for disease progression are met, taking as a reference the smallest measurements recorded since randomization. The minimal interval for duration of SD is 8 weeks.

Clinical Benefit Rate

Clinical benefit rate is the proportion of subjects who achieve a confirmed tumor response (CR or PR) or SD for at least 24 weeks.
Overall Survival

Overall survival is the time from the date of randomization until the date of death, censored at the last known date alive.

Frequency of Symptomatic or Progressive CNS Lesions

Incidence of subjects presenting with newly diagnosed symptomatic or progressive CNS lesions at the time of tumor progression.

Time to Symptomatic or Progressive CNS Lesions

Time from the date of randomization until the date of appearance of newly diagnosed symptomatic or progressive CNS lesions.

20.0 HEALTH OUTCOMES ASSESSMENT

The following questionnaires (see Attachment 6) will be used to collect patient-reported quality of life data:

1. Breast cancer specific quality of life - Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B)
2. Generic quality of life using the EuroQual 5 Dimension questionnaire (EQ-5D)

Patient-reported outcomes assessments will be performed at screening, day 1 of every other cycle (ie, cycle 2, 4, 6, etc), and at the time of treatment discontinuation.

Data on underlying disease related and non-disease related physician visits, emergency visits, nurse visits, and hospitalizations related to breast cancer diagnosis and treatment will be collected to assess impact on health care resource utilization. Health care resource utilization will be assessed on day 1 of every cycle starting with cycle 2, and at the end of treatment visit. Reasons for missing data will be documented and incorporated into the analysis as necessary.
A brief description of the questionnaires that will be used to collect patient reported outcomes in this study is given below.

**FACT-B**
The FACT-B (version 4) is a 38-item questionnaire with 6 subscales assessing physical, social, emotional, and functional well-being and additional concerns more specific to women with breast cancer (9 items). Subjects will be asked to indicate how true a statement had been for them over the past 7 days using a 5-point scale as follows: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All items receive equal weighting.

**EQ-5D**
The EQ-5D is a standardized instrument for use as a measure of general health states preferences and provides a simple descriptive profile and index value for health status and measures 5 dimensions of health including mobility, self-care, pain/discomfort, anxiety, and general health via a horizontal visual analog scale. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The patient-reported assessments are for the purpose of exploring the subject’s own perceptions about their symptoms and health-related quality of life and thus a proxy (ie, a caregiver or study personnel) should not complete the questionnaires. Additionally, the investigator must not influence the subject’s assessments. Every effort should be made to maintain an unbiased assessment.

If a subject cannot complete these assessments because of illiteracy or other documented reason, the assessments should be omitted. Reasons for missing data will be documented and incorporated into the analysis as necessary. Details of the algorithms that generate summary derived scores on each of the above health related quality of life scales and the statistical approach for each will be provided in the statistical analysis plan.
21.0 PHARMACOGENETIC ACTIVITY EVALUATION

ErbB-2 status will be confirmed by FISH using a central vendor for all subjects.

Original tumor biopsy sample, if available, will be studied for: PIK3CA mutations in hotspots (ie, exons 9,20 via gene sequencing), PIK3CA amplification (q-PCR or FISH), PTEN loss and erbB-family members (erbB-1, erbB-3, and erbB-4) (IHC), c-Myc amplification (q-PCR or FISH).

Formalin fixed, paraffin embedded tumor biopsy sample (original and/or fresh biopsy) can be sent (block or set of 5 μm sections on a total of 21 glass microscope slides).

Blood samples from patients at baseline, cycle 1, day 15 and cycle 2, day 1 of the active treatment phase will be obtained and tested for quantitative levels of soluble HER2/ECD.

Detailed information about pharmacogenetic sample collection, preparation, storage, labeling, and shipment is indicated in the Study Reference Manual.

Biomarker endpoints are optional and submission of samples for this testing is not required for study entry.

22.0 LABORATORY DETERMINATIONS

Refer to the flowchart(s) for time points.

As much as possible, only 1 laboratory will be used by each investigator for all determinations. Laboratory certification and laboratory normal ranges must be provided to the sponsor for all laboratories used.

All laboratory tests with values that become abnormal to a clinically significant degree after investigational product administration must be repeated and the investigator must continue to follow up as medically indicated until values have returned to baseline or until the condition
stabilizes. If laboratory values do not return to normal or baseline within a reasonable period, the etiology must be identified and the sponsor notified. All clinically significant abnormal laboratory tests will be recorded on the Adverse Event CRF.

Laboratory determinations will include the following:

1. Pregnancy test: For women of childbearing potential, a serum human chorionic gonadotropin test or urine pregnancy test will be performed at screening before investigational product administration and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the investigational product(s).

2. Serum chemistry: Serum chemistry tests consisting of sodium, potassium, chloride, calcium, creatinine, albumin, ALT/serum glutamic pyruvic transaminase (SGPT), AST/serum glutamic oxaloacetic transaminase (SGOT), glucose, total bilirubin, blood urea nitrogen (BUN; or urea), alkaline phosphatase, bicarbonate or carbon dioxide, total protein and magnesium will be performed at screening and on study day 1 of every cycle and at the end of treatment visit. Subjects do not need to fast prior to collection of the sample; however, the subject’s fasting status at the time the sample is collected will be recorded on the eCRF.

3. Hematology: White blood cell (WBC) count including differential, hemoglobin, hematocrit, platelet count, and ANC will be performed at screening and on study days 1, 8, 15 of every cycle and at the end of treatment visit.

4. Coagulation tests: Prothrombin time (PT, expressed in seconds) or INR, partial thromboplastin time (PTT, expressed in seconds) will be performed at screening and end of treatment visit. Subjects taking anticoagulants (heparin or coumarin derived) should be monitored closely and their anticoagulant dose adjusted as needed.

5. Pharmacogenetic blood draw (subject participating in pharmacogenetic portion of the study only) blood samples will be taken at baseline (screening) and cycle 1, day 15 and cycle 2, day 1 for assessment of serum HER2/ECD. Baseline sample may be drawn at anytime from the time of informed consent signing up to the administration of the first dose of investigational product.

6. Stool cultures will be performed as clinically indicated per investigator’s judgment. Results from occult blood, fecal leukocyte stain, clostridium difficile, campylobacter,
salmonella, and shigella testings, when performed to exclude infectious causes of diarrhea grade 3/4 or diarrhea of any grade with complicating features (dehydration, fever, grade 3/4 neutropenia) will be reported on the appropriate eCRF.

Laboratory values should be reviewed prior to each cycle and prior to dispensing investigational product(s) to the subject. Complete blood count (CBC) may be performed up to 3 days prior to paclitaxel/trastuzumab or paclitaxel infusions.

Sample collection, storage, and shipping information can be found in the study reference manual.

23.0 STATISTICS

Additional details of the analysis will be provided in the statistical analysis plan (SAP) and/or the clinical study report (CSR). This information may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the CSR.

23.1 Statistical Methods

Randomization is stratified by prior adjuvant trastuzumab exposure (yes/no), prior lapatinib exposure (yes/no), ER/PgR status (ER and/or PgR positive, ER and PgR negative), and region (1=United States; 2=Western Europe, Australia, South Africa, and Canada; 3=Asia-Pacific, India, Eastern Europe, Africa, and South America).

The primary endpoint is PFS, based on independent tumor assessments, defined as time from date of randomization to date of progressive disease (PD) or death if no documented progression, censored at the last assessable evaluation or at the initiation of new anticancer therapy. The secondary endpoints include OS, ORR, CBR, DOR, breast cancer specific quality of life, safety, CNS criteria, and biomarkers.

Efficacy analyses will be based on intent-to-treat (ITT) population, defined as all subjects randomized to the study. Efficacy analyses will also be performed on the evaluable population
defined in the Efficacy section. Safety analyses will be based on the safety population defined in the Safety section.

For the primary efficacy analysis, PFS, OS, and DOR will be compared using the stratified logrank test with prior exposure to erbB-2 inhibitor (prior adjuvant trastuzumab or prior lapatinib exposure, Yes/No) and ER/PgR (positive/negative) as stratification variables, where the strata will be the same as used for randomization. The hazard ratio and corresponding 95% 2-sided confidence interval using stratified Cox proportional hazard regression will be presented. The median time-to-event will be estimated using the Kaplan-Meier method and will be reported with two-sided 95% confidence intervals for each arm. Sensitivity analyses of the primary endpoint will be described in the SAP.

ORR and CBR will be compared between the 2 treatment arms using the generalized Cochran Mantel-Haenszel (CMH) test adjusted for prior exposure to erbB-2 inhibitor (prior adjuvant trastuzumab or prior lapatinib exposure, Yes/No) and ER/PgR (positive/negative). For each treatment arm, the rates along with the exact 95% confidence intervals will be computed.

AEs and SAEs will be summarized by arm. The incidence of grade 3 or higher diarrhea and cardiac failure events will be compared between the 2 treatment arms using the Fisher’s exact test.

Presence or absence of symptomatic or progressive CNS lesions will be assessed at tumor progression for each patient. Frequency of symptomatic or progressive CNS lesions at the time of tumor progression will be summarized by arm and compared between the 2 treatment arms using the generalized Cochran-Mantel-Haenszel test. The median time to symptomatic or progressive CNS lesions will be estimated for each arm using the Kaplan-Meier method and compared between the 2 treatment arms using the stratified log-rank test.

Breast cancer specific quality of life scores and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for pre-specified covariates.
Discontinuation from the study and dose reduction due to AEs and therapies implemented to treat some specific AEs will be compared between the treatment groups to assess the impact of AEs on treatment compliance. Physician visits, emergency visits, nurse visits, and hospitalizations related to breast cancer diagnosis and treatment will be compared between the two treatment groups as exploratory analysis.

23.2 Interim Analysis

Two (2) interim analyses will be performed. One (1) is for PFS and the other 1 is for OS. The interim analysis for PFS will occur when approximately 40% PFS events (300 PFS events) have been observed. The interim analysis is projected to occur at about 17.7 months from first randomization. Boundaries will be calculated based on the actual numbers of events observed. If the interim analysis is conducted as planned and p-value > 0.4207, then the trial may be stopped for futility based on PFS. The trial will not be stopped for efficacy at the interim PFS analysis. The stopping probability is 58% under the null hypothesis and 2% under the alternative hypothesis at the interim PFS analysis. The interim analysis for OS will be performed at the time of final PFS analysis. The efficacy on OS might be claimed if p-value < 0.0012.

The interim analysis will be conducted by an independent statistician outside of Wyeth and the results of the data analysis will be sent to the independent data monitoring committee (IDMC) for review. The summary data analyses will not be shared with the study team so that the trial may remain blinded.

The conduct of this trial (including the accrual/retention of subjects) will also be reviewed by the IDMC. The IDMC will meet approximately every 6 months depending upon enrollment or more frequently if required. However, any recommendation for early termination will be based upon the results of the planned interim analysis and/or safety concerns.
Final PFS analysis will be conducted when approximately 749 PFS events have been observed. If the interim and final analyses occur as planned, a p-value < 0.0249 will demonstrate the superiority of neratinib in combination with paclitaxel.

A follow-up analysis for overall survival will be conducted when approximately 631 OS events have been observed. If the interim and follow-up analyses for OS occur as planned, a p-value < 0.0249, will demonstrate the superiority of neratinib in combination with paclitaxel for OS.

### 23.3 Statistical Power and Sample Size Considerations

**Sample size:** This is a group sequential design with 1 interim analysis intended for stopping for futility. The power family (delta=0.3) beta spending function is employed for futility analysis. The Lan-Demets O’Brien-Flemming (OF) alpha spending function is used for controlling the type I error rather than early stopping for efficacy on PFS.

The assumptions for sample size calculations are the following. Median PFS of the trastuzumab plus paclitaxel arm is 9 months\(^{11,12}\) and median PFS of neratinib + paclitaxel arm is 11.7 months (30% improvement in median PFS, hazard ratio [HR]=0.77). Enrollment rate is expected to be about 60 per month. The design is based on 1-sided log-rank test with alpha=0.025, power=90% (adjusted per Carroll 2007)\(^{26}\), and an interim analysis when 40% of required PFS events are observed. The 2-year dropout rate is assumed to be 15%. Taking into account the power loss due to time lapse between tumor assessments, a total of 749 PFS events will be needed. With 1200 subjects enrolled in 23.5 months, the final PFS analysis will be about 30.5 months (2.5 years) from the date of first subject randomization.

**Power for OS Analysis:** Assume median OS of 24 months for the trastuzumab plus paclitaxel arm and 30 months for neratinib plus paclitaxel arm (25% improvement on median OS, HR=0.8). With 1200 subjects enrolled in about 23.5 months, there will be about 631 observed OS events in about 44 months from the date of first subject randomization. This provides 80% power for a 1-sided log-rank test with alpha=0.025. One (1) interim analysis for OS will be
performed at the time of final PFS analysis. Type I error will be controlled through a power family (delta=-0.5) alpha spending function.

24.0 SUBJECT IDENTIFICATION
Subjects will be numbered sequentially via Clinical Operations Randomization Environment (CORE) within the eClinical system. Each subject must be assigned a unique subject number. The subject must keep that number throughout the study even if he or she transfers to another site. A subject who discontinues or is withdrawn from the study before meeting inclusion and exclusion criteria and who reenrolls at a later time must be assigned a new subject number. A number must never be reassigned or reused for any reason. The investigator must follow all applicable privacy laws in order to protect a subject’s privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

25.0 INVESTIGATIONAL PRODUCT ACCOUNTABILITY, RECONCILIATION, AND RETURN
The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

All used, unused or partially used investigational products and their original containers should be kept on site for reconciliations by a site monitor prior to return to sponsor or destruction.

The site may destroy unused investigational product and investigational product containers after accountability has been performed. Investigational product destruction must be documented on the dispensing and inventory record. Investigational product is destroyed at the site only with the sponsor’s permission. This may be done when a investigational product is a hazardous substance or its shipment may expose humans to risk, or it is not classified as a controlled or isotopically labeled substance.

Shipment of a investigational product that is a hazardous substance or whose shipment may expose humans to risk will be done according to local laws and regulations.
26.0 RANDOMIZATION AND BLINDING

This is an open-label, phase 3, randomized study. Subjects who give informed consent and meet eligibility criteria will be randomized in a 1:1 ratio to arm A or B no more than 2 business days before administration of the first dose of investigational product. Randomization will be stratified by prior adjuvant trastuzumab exposure, prior lapatinib exposure, ER/PgR status and region and the investigators are not blinded to study treatment. However, the independent radiologists assigned to review the images of tumor assessments will be blinded to study treatment. In addition, all sponsor personnel who are directly involved in the conduct of the study will be blinded to any summary results by treatment arm.

Allocation of subjects to treatment groups will proceed through the use of an IVRS that is accessible 24 hours a day, 365 days a year. The dispenser will be required to enter or select information that will include the user ID and password, the investigator site number, the subject number, and the date of birth of the subject. The dispenser will then be provided with a subject randomization number and treatment assignment. This randomization number must be recorded on the eCRF. Once subject numbers and randomization numbers have been assigned, they cannot be reassigned. The randomization system will also send confirmation of the randomization, by fax, to the user. Specific instructions will be provided in the IVRS study reference guide.

27.0 ADVERSE EVENTS

27.1 Safety

For safety information on neratinib, refer to the most recent version of the investigator’s brochure.

For safety information on paclitaxel and trastuzumab, refer to the most recent version of the US FDA approved product labeling for the safety information.
27.2 Definitions

An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given an investigational product or in a Wyeth clinical study. The event does not need to be causally related to the investigational product or Wyeth clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of an investigational product, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
- An AE occurring from abuse (eg, use for nonclinical reasons) of an investigational product.
- An AE that has been associated with the discontinuation of the use of an investigational product.
- For reports from postmarketing studies, any failure of expected pharmacologic action of an investigational product.
- A protocol-related adverse event is an AE occurring during a clinical study that is not investigational product related, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

A serious adverse event (SAE) is defined by Wyeth as an AE that:

- Results in death.
- Is life-threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in cancer.
- Results in a congenital anomaly or birth defect.
Important medical events are AEs that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is an official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the investigator through a serious adverse event form 7443. Situations include, but are not limited to, the following:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.
Disability is defined as a substantial disruption in a person’s ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

**Other Reportable Information.** Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

- Pregnancy exposure to an investigational product, except for exposure to prenatal vitamins. If a pregnancy is confirmed, use of the investigational product must be discontinued immediately. Information about use in pregnancy encompasses the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there were no abnormal findings. Both maternal and paternal investigational product exposures are collected. Pregnancy exposure information is collected even if the investigational product is not contraindicated for use in pregnancy. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.

- Lactation exposure to an investigational product, with or without an AE.

- Overdose of an investigational product as specified in this protocol, with or without an AE. Baby formula overdoses without any AEs are excluded.

- Inadvertent or accidental exposure to an investigational product, with or without an AE. Nutritional product inadvertent or accidental exposures without AEs are excluded.

- Medication errors with or without an AE (including product confusion and potential product confusion).

- Death with or without an AE.

### 27.3 Overdose

For paclitaxel and trastuzumab, overdose is defined as a dose greater than that specified in this protocol. For neratinib, an overdose is defined as any additional neratinib tablets taken by the subject, which is higher than that prescribed by the investigator.
All investigational product overdoses, whether or not associated with an AE/SAE, will be reported on the serious adverse event form 7443 and sent to the fax number indicated in the Emergency Contacts section.

27.4 Medication Errors

A medication error is any preventable event that may cause or lead to inappropriate investigational use or subject harm while the investigational product is in control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Medication errors will be collected/reported only for neratinib, the Wyeth product under investigation, and not for paclitaxel or trastuzumab.

Examples for medication error that will require reporting to the sponsor:

2. Administration of expired neratinib, when associated with an AE/SAE.

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the serious adverse event form 7443. All other medication errors will be reported by faxing the Clinical Study Medication Error Incident Report, form 15701, to the fax number indicated in the Emergency Contacts section.
27.5 Efficacy Endpoints and Disease Progression Events

The term “disease progression” as defined by RECIST should not be reported as an AE or SAE. However, events or symptoms associated with hospitalization and caused by disease progression should be reported with the appropriate term describing the symptoms (eg, bone pain, pleural effusion, etc).

Disease progression will either be reported based on radiographic assessments by the sites (thus documented as “PD” on the tumor assessment and completion of treatment eCRFs), or based on symptoms of disease deterioration (thus documented as “symptomatic deterioration” on the completion of treatment eCRF). However, every effort must be made to confirm PD radiographically. If a subject discontinues the treatment period of the study due to symptomatic deterioration, 1 single AE should be identified as primary symptom of nonradiographic PD, and the subject should continue with radiographic assessments at least every 8 weeks (± 4 days) during the survival follow-up period of the study until radiographic disease progression, new anticancer treatment, or death, whichever occurs first.

27.6 Adverse Event and Serious Adverse Event Recording and Reporting

Determination of AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked a nonspecific question such as: "How have you been feeling since your last visit?" Signs and symptoms must be recorded using standard medical terminology. For subjects incapable of giving consent, the legally acceptable representative may be asked this question regarding the subject.

AEs and SAEs will be collected from the signing of the informed consent form to 28 days after the last dose. The investigator must instruct the subject to report AEs and SAEs during this time period. During the time period specified above, the investigator will:

- Record all AEs and SAEs on source documents.
- Record all AEs and SAEs in the CRFs for subjects who are not screen failures.
- Report all SAEs on form 7443.
An AE’s causal relationship to the product has no bearing on the AE’s reportability.

The investigator must follow up on all AEs and SAEs until the events have subsided, until values have returned to baseline, or, in case of permanent impairment, until the condition has stabilized.

Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC. The sponsor will maintain detailed records of all AEs and SAEs reported by an investigator in accordance with good clinical practice and applicable local regulations including, but not limited to, regulations implementing the requirements of Directive 2001/20/EC.

27.7 Serious Adverse Event Reporting Requirements

All SAEs, including other information reportable as SAEs, and follow-up information must be reported to the sponsor within 1 business day after learning of the event by faxing a completed serious adverse event form 7443 to the fax number indicated in the Emergency Contacts section and confirming by phone or e-mail that the fax was received. A business day is defined as any day except weekends, December 25, and January 1.

Suspected adverse reactions that are both serious and unexpected are subject to expedited reporting in accordance with all applicable global laws and regulations. In the European Economic Area (EEA), the sponsor will ensure reporting of suspected unexpected serious adverse drug reactions (SUSARs), for the investigational medicinal product(s) used in a clinical study to the IECs and competent authorities of the EEA Member States where the study is being conducted. SUSARs will be reported in accordance with the requirements and provisions of Directive 2001/20/EC and relevant implementing guidelines and as transposed into the applicable national laws.
28.0 SUBJECT DISCONTINUATION OR WITHDRAWAL

Reasons why a subject may discontinue or be withdrawn from the **active treatment phase** include, but are not limited to:

- Documented disease progression as determined by the investigator (following the definitions provided in the Response Criteria section)
- Adverse event
- Symptomatic deterioration
- Subject request\(^a\)
- Investigator request (with detailed documentation of reasoning)
- Protocol violation
- Discontinuation of the study by the sponsor
- Lost to follow-up\(^b\)
- Death

\(a\): Consent withdrawal by the subject must be documented in writing by the subject or her legal representative.

\(b\): Lost to follow-up is defined as after 3 attempts by phone followed by 1 attempt of sending a certified letter.

Subjects may discontinue or be withdrawn from the **study** for the following reasons:

- Subject request\(^a\)
- Lost to follow-up\(^b\)
- Discontinuation of the study by the sponsor
- Death

\(a\): Consent withdrawal by the subject must be documented in writing by the subject or her legal representative.

\(b\): Lost to follow-up is defined as after 3 attempts by phone followed by 1 attempt of sending a certified letter.

When a subject discontinues or is withdrawn from treatment or study, the investigator will notify the sponsor and every effort must be made to perform the procedures indicated for the end of treatment visit or last survival contact. The CORE system will also need to be updated as outlined in the Randomization section.
If a subject is lost to follow-up, or voluntarily withdraws from any study participation, every effort must be made to perform a final visit. Every effort should be made to determine why a subject is lost to follow-up or withdraw consent. This information, including the date, should also be recorded on the subject's conclusion of subject participation eCRF.

Subjects discontinuing the treatment period of the study, will be contacted every 3 months for survival information (and new anticancer therapy) until a cutoff time when a total of approximately 631 deaths have been observed.

29.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION
The sponsor may suspend or terminate the study or part of the study at any time for any reason.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all investigational products, investigational product containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. For investigational new drug application (IND) studies, the investigator must submit a written report to the sponsor and the IRB/IEC within 3 months after the completion or termination of the study. A sample of this final study report can be found in the study reference manual.

30.0 INFORMED CONSENT
The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The informed consent form(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.
Before any protocol-required procedures are performed, a subject must:

- Be informed of all pertinent aspects of the study and elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC-approved informed consent form.
- Provide a separate consent signature to participate in the voluntary pharmacogenetic testing. Subjects may abstain from the voluntary pharmacogenetic testing but still participate in the main study.

31.0 PROTOCOL AMENDMENTS

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

32.0 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the investigator’s brochure, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these site visits, information recorded in the CRFs is verified against source documents.
33.0 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

33.1 Investigator
The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. CRFs must be fully completed and include all required data. All CRF data must be submitted to the sponsor throughout and at the end of the study. Remote data capture will be used to record and transmit data electronically to the sponsor.

The health outcomes questionnaires will be transferred from an electronic handheld device directly into the database and will be considered source data. There will be no prior written record for these data.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

An updated statement of investigator form (ie, FDA form 1572 or GCT Alternate Statement of Investigator Form 17026 and, if required by local regulations, an equivalent) will be filed with the sponsor for any changes in the study personnel reported in the current statement of investigator form.

Investigators must notify their IRB/IEC of protocol violations in accordance with local regulatory and IRB/IEC requirements.

33.2 Sponsor
The eCRF data are stored in a database and processed electronically. The sponsor medical monitor reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs identify missing data, out-of-range data,
and other data inconsistencies. Data from vendors performing biomarker analyses (including erbB-2 status analysis), radiology assessments and ECG data will be processed electronically. Requests for data clarification are forwarded to the investigative site for resolution.

34.0 SUBJECT INJURY
In general, subject to specific provisions in the clinical study agreement (CSA), if a subject is injured as a direct result of an investigational product, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject’s medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

35.0 PRESTUDY DOCUMENTATION
The investigator must provide the sponsor with the following documents BEFORE enrolling any subjects:

- Completed and statement of investigator form (ie, FDA form 1572 or GCT Alternate Statement of Investigator Form 17026 and, if required by local regulations, an equivalent).
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the principal investigator, subinvestigators, and nonphysicians having significant investigator responsibility (ie, those related to final determination of eligibility, efficacy, or safety) who are listed on the statement of investigator form (ie, FDA form 1572 or GCT Alternate Statement of Investigator Form 17026 and, if required by local regulations, an equivalent).
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually)
and, where required, a copy of the annual progress report submitted to the IRB/IEC must also be provided to the sponsor.

- Copy of the IRB/IEC-approved informed consent document to be used.
- If applicable, a list of the IRB/IEC members and their qualifications and a description of the committee’s working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Fully executed CSA.
- If applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

### 36.0 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by Good Clinical Practice (GCP) as essential, for the longer of (a) 2 years after the last marketing authorization for the study drug has been approved or the sponsor has discontinued its research with respect to such drug or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator’s notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor’s expense.
37.0 BIOLOGICAL SAMPLES

Blood and tissue samples will be used only for scientific research, including pharmacogenetic testing. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject’s identity. Some of the samples may be stored for additional analyses on inherited factors/biomarkers related to breast cancer that could be identified in future research. After the study ends, the samples will be retained for a period of 10 years (or less as per local regulation) for research purposes, after which time the samples will be destroyed. Tissue blocks will be retained by the central vendor for as long as it is useful for research purposes, after which time the blocks will be returned to sites. The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from that sample will still be used for this research. The biological samples will remain the property of the sponsor, and may be shared with other researchers as long as confidentiality is maintained.

38.0 CLINICAL STUDY REPORT

As appropriate, an investigator will be selected to act as the signatory for the clinical study report. This investigator will be selected based on clinical experience and understanding of the product.

39.0 PUBLICATION POLICY

39.1 Sponsor’s Publication Policy

The sponsor’s policy is to publish or otherwise communicate the results of its hypothesis-testing clinical studies, regardless of outcome, for marketed products, compound(s) or product(s) being investigated that are later approved for marketing. Hypothesis-testing clinical studies are those studies intended to provide meaningful results by examining prestated questions using predefined statistically valid plans for data analysis, thereby providing firm evidence of safety and/or efficacy to support product claims.
Exploratory studies, in contrast, serve to set direction for possible future studies. They have significant statistical limitations, provide only preliminary information about a disease, condition, or product, and are not designed to provide final conclusions on product claims. The sponsor does not commit to publish or otherwise communicate the results of every exploratory study, because this information is of an exploratory nature and often highly proprietary. However, if information from an exploratory study is of significant medical importance, the sponsor will publish or otherwise communicate the results.

The sponsor’s decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

39.2 Investigator’s Ability to Publish

Upon completion of the study, the investigator may publish or otherwise publicly communicate the results, subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 calendar days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except that the investigator shall delete any confidential information from such proposed publication. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 calendar days in order to have a patent application(s) filed.
40.0 REFERENCES


16 Xia W, Liu LH, Ho P, Spector NL. Truncated ErbB-2 receptor (p95ErbB-2) is regulated by heregulin through heterodimer formation with ErbB-3 yet remains sensitive to the dual EGFR/ErbB-2 kinase inhibitor GW572016. Oncogene. 2004;23(3):646-653.


41.0 ATTACHMENTS

41.1 Attachment 1: Sponsor Approved erbB-2 Assays

ErbB-2 results based on 1 of the following commercial kit assays are acceptable (for the purposes of study entry)

<table>
<thead>
<tr>
<th>IHC Approved Assay</th>
<th>FISH Approved Assay</th>
<th>CISH Approved Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>HercepTest</td>
<td>Pathvysion HER2 DNA Probe Kit</td>
<td>SPOT-Light® HER2 CISH™ Kit</td>
</tr>
<tr>
<td>Pathway</td>
<td>INFORM HER2/neu Probe</td>
<td>-</td>
</tr>
</tbody>
</table>
### 41.2 Attachment 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

<table>
<thead>
<tr>
<th>Description</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry on all predisease performance without restriction.</td>
<td>0</td>
</tr>
<tr>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.</td>
<td>1</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>2</td>
</tr>
<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
<td>3</td>
</tr>
<tr>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>4</td>
</tr>
</tbody>
</table>
41.3 Attachment 3: Guidelines for the Management of Neratinib-Induced Diarrhea for Investigators in 3144A2-3005-WW

Diarrhea should be treated at the very first occurrence with appropriate treatment. Subjects should be encouraged to contact the site to report and discuss the severity of diarrhea and the appropriate course of treatment. Additional recommendations include common dietetic rules to avoid diarrhea. The following recommendations were developed based on the Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea (Journal of Clinical Oncology, Vol 22, No 14 (July 15), 2004: pp. 2918-2926), and previous study protocol and case reports experience with neratinib.

UNCOMPLICATED GRADE 1-2

Dietetic measures

- Stop all lactose-containing products
- Drink 8 to 10 large glasses of clear liquids per day
- Eat frequent small meals
- Recommend low fat regimen enriched with rice, bananas, and applesauce

Pharmacological treatment

Administer standard dose of loperamide: initial dose, 4 mg, followed by 2 mg every 4 hours or after every unformed stool – consider continuation of loperamide until diarrhea-free for 12 hours. Some investigators reported successful management of the diarrhea with the use of diphenoxylate hydrochloride and atropine sulfate formula (LOMOTIL®, DIARCED®, CO-PHENOTROPE®).

GRADE 3 or 4 or ANY GRADE WITH COMPLICATING FEATURES (DEHYDRATION, FEVER, AND/OR GRADE 3-4 NEUTROPENIA)

Infectious causes of diarrhea should be excluded and documented in the source document for cases of grade 3/4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3/4 neutropenia). Stool cultures may be performed as a
way of excluding infectious causes of diarrhea at per the investigator’s discretion. Results from the stool cultures should be documented on the appropriate eCRF as applicable.

**Dietetic measures (same as above)**

**Pharmacological treatment**

- Administer standard dose of loperamide: initial dose, 4 mg, followed by 2 mg every 4 hours or after every unformed stool – consider continuation of loperamide until diarrhea-free for 12 hours. Some investigators reported successful management of the diarrhea with the use of diphenoxylate hydrochloride and atropine sulfate formula (LOMOTIL®, DIARCED®, CO-PHENOTROPE®).
- Administer octreotide (SANDOSTATINE®) [100–150 μg SC BID or IV (25–50 μg/h)] if dehydration is severe, with dose escalation up to 500 μg TID; use intravenous fluids as appropriate.
- Consider prophylactic antibiotics as needed (eg, fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3–4 neutropenia.
### 41.4 Attachment 4: List of Inhibitors and Inducers of the Cytochrome P450 CYP3A4, 5, 7 Isoenzymes

<table>
<thead>
<tr>
<th><strong>INHIBITORS</strong></th>
<th><strong>INDUCERS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin (3A4)</td>
<td>Carbamazepine (3A4)</td>
</tr>
<tr>
<td>Ritonavir (3A4)</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Saquinavir (3A4)</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Troleandomycin (3A4)</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Voriconazole (3A4)</td>
<td>Troglitazone</td>
</tr>
</tbody>
</table>

- Clarithromycin (3A4)
- Erythromycin (3A4)
- Fluconazole (3A4)
- Fluvoxamine (3A4)
- Grapefruit juice (3A4)
- Grapefruit-containing products (3A4)
- Indinavir (3A4)
- Itraconazole (3A4)
- Ketoconazole (3A4)
- Mibefradil (3A4)
- Miconazole (3A4)
- Nelfinavir (3A4)

- Amiodarone
- Amiodarone
- Cannabinoids
- Fluoxetine
- Lopinavir
- Metronidazole
- Quinine
- Sertraline
- Zafirlukast

In boldface are identified strong CYP3A4 inducers/inhibitors.

This list is not meant to be considered all inclusive.

### Attachment 5: Summary of Drugs That Are Generally Accepted to Have a Risk of Causing QT/QTc Prolongation Potentially Causing torsade de pointes

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Cordarone/Pacerone</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Trisenox</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Vascor</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Aralen</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Norpace</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Tikosyn</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Motilium</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Inapsine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythrocin/E.E.S.</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Halfan</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Corvert</td>
</tr>
<tr>
<td>Levomethadyl</td>
<td>Orlaam</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Serentil</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadose/Dolophine</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Avelox</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>NebuPent/Pentam</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Pronestyl/Procan</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Cardioquin/Quinaglute</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Betapace</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>Zagam</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
</tr>
</tbody>
</table>

Adapted from the University of Arizona Center for Education and Research on Therapeutics. This list is not meant to be considered all inclusive.

See the following Web site for an updated list of Drugs With Risk of torsade de pointes (list 1):

http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm#
41.6 Attachment 6: Health Outcome Assessments

Health Questionnaire

*English version for the UK (validated for Ireland)*

© 1999 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group
By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-Care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

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To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

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FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1 I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2 I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3 Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP4 I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5 I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6 I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7 I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL/FAMILY WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP8 I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP9 I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP10 I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP11 My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP12 I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP13 I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP14 Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP15 I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
FACT-B (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

### EMOTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
FACT-B (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have been short of breath.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am self-conscious about the way I dress.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>One or both of my arms are swollen or tender.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel sexually attractive.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by hair loss.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that other members of my family might someday get the same illness I have</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about the effect of stress on my illness.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by a change in weight.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to feel like a woman.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have certain parts of my body where I experience significant pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
STATISTICAL ANALYSIS PLAN

Protocol Title: A Randomized, Open Label, Two-Arm Study of Neratinib Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel For The First-Line Treatment of ERBB2-Positive Locally Recurrent or Metastatic Breast Cancer

Study Protocol No: 314A2-3005-WW
Disease Condition: Metastatic Breast Cancer
Sponsor: Puma Biotechnology, Inc.
10880 Wilshire Blvd, Suite 2150
Los Angeles, CA 90024 USA
Phone: +1 424.248.6500
Fax: +1 424.248.6501

Date of SAP: v 4.0 06 February 2015
## DOCUMENT VERSION CONTROL

<table>
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<th>Version Number</th>
<th>Date</th>
<th>Comments/Changes</th>
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<td>1.0</td>
<td>16-FEB-2009</td>
<td>Initial draft</td>
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<td>2.0</td>
<td>16-JUN-2011</td>
<td>Modified to accommodate protocol amendment 5</td>
</tr>
<tr>
<td>3.0</td>
<td>01-AUG-2013</td>
<td>Modified to accommodate protocol amendment 6</td>
</tr>
<tr>
<td>3.1</td>
<td>21-NOV-2013</td>
<td>Further modified to accommodate protocol amendments 5 and 6</td>
</tr>
<tr>
<td>4.0</td>
<td>06-FEB-2015</td>
<td>Removed the interval-censoring based analyses</td>
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<table>
<thead>
<tr>
<th>Abbreviation or Term</th>
<th>Definition/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CBR</td>
<td>Clinical benefit rate</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine phosphokinase</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran Mantel-Haenszel</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical study report</td>
</tr>
<tr>
<td>CTCAE</td>
<td>NCI Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DOR</td>
<td>Duration of response</td>
</tr>
<tr>
<td>ECHO</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>AESIs</td>
<td>Adverse Events of Special Interest</td>
</tr>
<tr>
<td>EOS</td>
<td>End of study</td>
</tr>
<tr>
<td>ERBB2+</td>
<td>Human epidermal growth factor receptor 2 positive</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent to treat</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multiple-gated acquisition scan</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred term</td>
</tr>
<tr>
<td>QW</td>
<td>Once weekly</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-Emergent Adverse Event</td>
</tr>
<tr>
<td>WHODrug</td>
<td>World Health Organization Drug Reference List</td>
</tr>
</tbody>
</table>
1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical methodology to be used for analysis of data from study 3144A2-3005-WW. This analysis plan is meant to supplement the study protocol. Any deviations from this plan will be described in the Clinical Study Report (CSR).
2. **PROTOCOL SUMMARY**

2.1. **Study Objectives**

The purpose of this study is to gain preliminary understanding of the efficacy and safety of neratinib in combination with paclitaxel in the context of a randomized study.

2.1.1. **Primary Objective**

The primary objective of this study is to compare investigator assessed progression-free survival (PFS) following treatment with neratinib in combination with paclitaxel versus trastuzumab plus paclitaxel in patients who have not received previous treatment for ERBB2-positive locally recurrent or metastatic breast cancer (MBC).

2.1.2. **Secondary Objectives**

The secondary objectives of this study are:

- To compare investigator assessed clinical activity between treatment arms by measuring the following clinical endpoints:
  - Objective response rate (ORR)
  - Duration of response (DOR)
- To compare safety (adverse events [AEs] and serious adverse events [SAEs]) between treatment arms
- To compare the frequency and time to symptomatic or progressive central nervous system (CNS) lesions in both treatment arms

2.1.3. **Exploratory Objective**

The exploratory objectives of this study are:

- To compare patient reported breast specific quality of life between treatment arms
- To compare health care utilization (including hospitalization and physician visits) between treatment arms
- To identify biomarkers predictive of neratinib response/resistance (apart from ERBB2)
2.2. Overall Study Design and Plan

2.2.1. Features of the Study Design

This is a randomized multi-center, multinational, open-label active-controlled, parallel design study of the combination of neratinib with paclitaxel versus the combination trastuzumab plus paclitaxel in first line treatment for women with metastatic or recurrent ERBB2+ breast cancer. Approximately 480 subjects were to be randomized in a 1:1 manner to receive neratinib plus paclitaxel or trastuzumab plus paclitaxel.

The study initially included the following phases: screening, treatment, and long-term follow-up. Following a 28-day screening phase, eligible patients were randomized to Arm A or Arm B. Baseline assessments were performed prior to randomization and Cycle 1/Day 1 dosing. Patients then participated in the active treatment phase, consisting of 28-day treatment cycles. Patients were anticipated to participate in the study for an average of 13 months. This includes approximately 1 month for screening and an estimated average of 12 months for treatment. Post Amendment 6 approval, long-term follow-up for survival, after discontinuation from active treatment, is no longer part of the study. Patients that were in the long-term follow-up phase ended the study at the time of Amendment 6 approval. All other patients will continue to receive treatment until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs which will conclude their study participation.

2.3. Study Population

The patient population will include all patients that sign and date an approved informed consent form and are eligible per the criteria defined in the protocol. A full list of the inclusion and exclusion criteria can be found in the 3144A2-3005-WW study protocol.

2.4. Treatment Regimens

Patients in the Neratinib + Paclitaxel combination arm will receive their therapy as described below:

- Neratinib: Six 40 mg tablets (240 mg) taken orally once daily with food, preferably in the morning, continuously until treatment discontinuation.
- Paclitaxel: Administered IV (80 mg/m²) over approximately 1 hour on days 1, 8, and 15 of a 28-day cycle. Patients will receive paclitaxel treatment for at least 6 cycles. Additional cycles may be given at the investigator’s discretion.

Therapy continues until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

Patients in the trastuzumab + paclitaxel combination arm will receive their treatment as follows:

- Trastuzumab: Administered at an initial loading dose of 4 mg/kg as an approximately 90 minute IV infusion followed by subsequent once weekly doses of 2 mg/kg as 30-90 minute IV infusions
- Paclitaxel: Administered IV (80 mg/m²) on days 1, 8, and 15 of a 28-day cycle.

Patients received paclitaxel treatment for at least 6 cycles. Additional cycles may have been given at the investigator’s discretion.

Treatment continues until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

2.5. **Treatment Group Assignments or Randomization**

Patients will be randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Neratinib (240 mg per day) + Paclitaxel (IV 80 mg/m2 on days 1, 8, and 15 of a 28-day cycle)
- Arm B: Trastuzumab (initial IV infusion dose 4mg/kg with subsequent once weekly IV infusion doses of 2 mg/kg) + Paclitaxel (IV 80 mg/m² on days 1, 8, and 15 of a 28-day cycle)

Patient randomization will be stratified according to:

- Prior trastuzumab exposure (yes or no)
- Prior lapatinib exposure (yes or no)
- Estrogen receptor+ (ER+) and/or progreserone receptor (PR+) (i.e. hormone receptor +) versus ER- and PR- (ie, hormone receptor -)
2.6. **Sample Size Determination**

The study was initially designed as a Phase 3 trial to determine whether the combination of neratinib + paclitaxel was superior to the combination of trastuzumab + paclitaxel as first line treatment for women with metastatic or recurrent ERBB2+ breast cancer. The initial assumptions made in designing this trial were that the median progression-free survival (PFS) for the experimental arm of neratinib + paclitaxel would reach 11.7 months and that the median PFS in the control arm of trastuzumab + paclitaxel would be 9 months. However, based upon recent publications, median PFS in patients treated with trastuzumab + taxane-based therapy in the first line metastatic setting is closer to 12 months rather than 9 months. Consequently, the anticipated difference between treatment arms may be considerably smaller. Rather than substantially increasing the sample size to accommodate this smaller difference, the statistical analysis plan has been revised to be consistent with the Sponsor intent to gain an earlier, preliminary understanding of the safety and efficacy of neratinib + paclitaxel in the first line treatment of women with locally recurrent or MBC.

The accrual goal for this study was reduced from 1200 patients to 480 patients. For the assessment of the primary endpoint, PFS, a one-sided log-rank test with 304 confirmed PFS events achieves 80% power at a 7.5% significance level to detect a 30% improvement in the experimental arm median PFS assuming the control arm median PFS is 12 months. If confirmed PFS events are reported for all 480 enrolled patients, with the aforementioned power and significance levels, a one-sided log-rank test will be able to detect a 24% or greater improvement in experimental arm median PFS in comparison to a median PFS of 12 months assumed for the control arm.
3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

Categorical variables will be summarized using counts and percentages. Percentages will be displayed to 1 place after the decimal point (xx.x), with the exception of 100%, which will be displayed without additional decimal places. Continuous variables will be summarized using number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Mean and median will be reported at 1 more significant digit than the precision of the data; standard deviation will be reported at 2 more significant digits than the precision of the data. Minimum and maximum will be reported to the same level of precision as the original observations. In general, any calculated values, such as those due to unit conversion, will be rounded to the same number of decimal places as the original data. P-values will be reported to 3 decimal places, with values less than 0.001 displayed as ‘<0.001.’

In general, the baseline value will be considered the last measurement observed prior to taking the first dose of study treatment.

SAS statistical software (version 9.2 or later) and R (version 3.0 or later) will be used for all analyses.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.
4. ANALYSIS POPULATIONS

Three analysis populations will be used for this study: the Intent to treat (ITT) population, Efficacy Evaluable population, and the Safety population.

4.1. Intent to treat (ITT) Population

The intent to treat population is defined as all patients who are randomized into the study. Patients will be analyzed in the treatment arm to which they were randomly assigned regardless of which treatment they received.

4.2. Efficacy Evaluation Population

The efficacy evaluable population is defined as all patients who meet all of the following criteria:

- Randomized and received at least 7 doses of neratinib or 2 doses of trastuzumab and at least 2 doses of paclitaxel
- Patients must have completed at least one valid follow-up radiological tumor assessment based upon independent reviewer’s assessment, after at least 8 weeks from the first dose of investigational product. This is not required for patients who discontinued investigational product because of documented disease progression or died prior to the second scheduled tumor assessment
- No major protocol violations

4.3. Safety Population

The safety population is defined as all patients who received at least one dose of investigational product. Patients will be analyzed based upon the treatment they received regardless of the treatment to which they were randomized.

The analysis of the primary and secondary efficacy endpoints as well as exploratory endpoints will be performed on the ITT. Selected analysis will be performed using the efficacy evaluable population when is appropriate. The analysis based upon the ITT population will be considered the primary analysis. All safety analyses will be performed using the safety population.
5. **STUDY PATIENTS**

5.1. **Disposition of Patients**

The number and percentage of patients entering and completing each study phase (ie, screening, active treatment, long-term follow-up) will be presented, stratified by treatment. Reasons for ending treatment and study will also be summarized.

5.2. **Protocol Deviations**

Protocol deviations will be classified and monitored regularly during the duration of the study. Among other reasons, failure to meet any of the protocol inclusion or exclusion criteria will be considered a protocol deviation. Important protocol deviations will be summarized by type and treatment group.
6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided for all demographic and baseline characteristics based upon the ITT population. Demographic data, medical history, cancer history, prior anti-cancer therapy, and tumor burden will be summarized by means of descriptive statistics or frequency tables. For categorical variables, the number and percentage of patients in each category will be presented. For continuous variables, summaries will include the number of patients with data, mean, median, standard deviation, Q1, Q3, minimum, and maximum.

6.1. Demographic and baseline characteristics

The following demographic and baseline variables will be summarized by treatment group:

- Age (years)
- Age group (<65 years, ≥65 years)
- Race and ethnicity (per CRF)
- Height (cm)
- Weight (kg)
- Body mass index (BMI)

BMI will be calculated as: \( \text{BMI} \ (\text{kg/m}^2) = \frac{\text{Weight (kg)}}{\text{Height (cm) x 0.01}}^2 \)

6.2. Medical History

Medical history data including: chronic conditions, relevant surgical procedures, symptoms experienced during the previous 30 days prior to randomization, symptoms ongoing at the time of screening, any medical conditions that require medication and cancer history will be collected at screening, within 28 days before Cycle 1/ Day 1 in accordance with the Schedule of Procedures included in the protocol.

Cancer history variables include date of first diagnosis, nodal status, histology, tumor stage at diagnosis, previous chemotherapy/biotherapy/immunotherapy, previous adjuvant therapy, previous radiation, and prior cancer related surgical therapies.

Medical history and cancer history data will be summarized.
6.3. Prior and Concomitant Medications

Concomitant medications will be defined as medications documented on the Concomitant Medications CRF. Concomitant medications will be coded using the World Health Organization (WHODrug) dictionary and summarized.
7. **MEASUREMENTS OF TREATMENT COMPLIANCE**

Duration of treatment will be summarized separately for each study compound by treatment group. In addition, the cumulative quantity, dose intensity (quantity per unit time), and the relative dose intensity (dose intensity/schedule dose per unit time) will be summarized.

The number of patients with dose holds or dose reductions will be tabulated for each experimental article by treatment group.
8. **Efficacy Evaluation**

8.1. **Overview of Efficacy Analysis Issues**

8.1.1. **Handling of Dropouts or Missing Data**

Missing assessments for PFS, the number of patients who drop out prior to PFS, and the length of follow-up for dropouts will be summarized by treatment group. Sensitivity analyses will not be performed to assess the impact of patient dropout or missing assessments on the primary and secondary efficacy nor exploratory endpoint analyses.

8.1.2. **Multicenter Studies**

Data from all sites will be pooled for the purpose of analyses. Exploratory analyses by site are not an objective of this study and are not currently planned.

8.2. **Efficacy Endpoints**

*Table 8-1* gives an overview of the efficacy endpoints and the analysis methods that will be implemented.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free Survival (PFS)</td>
<td>• Kaplan-Meier estimates and survival curves</td>
</tr>
<tr>
<td></td>
<td>• Log-rank test</td>
</tr>
<tr>
<td></td>
<td>• Cox proportional hazards model</td>
</tr>
<tr>
<td>Objective Response Rate (ORR)</td>
<td>Cochran-Mantel-Haenszel test</td>
</tr>
<tr>
<td>Duration of Response (DOR)</td>
<td>• Kaplan-Meier estimates and survival curves</td>
</tr>
<tr>
<td></td>
<td>• Log-rank test</td>
</tr>
<tr>
<td></td>
<td>• Cox proportional hazards model</td>
</tr>
<tr>
<td>Clinical Benefit Rate (CBR)</td>
<td>Cochran-Mantel-Haenszel test</td>
</tr>
<tr>
<td>Time to symptomatic or progressive CNS lesions</td>
<td>• Kaplan-Meier estimates and survival curves</td>
</tr>
<tr>
<td></td>
<td>• Log-rank test</td>
</tr>
<tr>
<td></td>
<td>• Cox proportional hazards model</td>
</tr>
<tr>
<td></td>
<td>• Cumulative incidence function for time to symptomatic or progressive CNS lesion stratified by treatment with competing risks</td>
</tr>
<tr>
<td>Proportion of patients with symptomatic or progressive CNS lesions</td>
<td>Cochran-Mantel-Haenszel test</td>
</tr>
</tbody>
</table>

*Table* Error! No text of specified style in document.-1. Efficacy Endpoints and Analysis Methods
8.2.1. **Definitions and criteria used in the determination of primary and secondary efficacy endpoints**

The following definitions and criteria are used, with respect to target lesions, in the determination of PFS, and the secondary efficacy endpoints ORR, DOR, and CBR per RECIST (v1.0) and the frequency and time to symptomatic or progressive CNS lesions.

**Complete Response (CR):** Disappearance of all target lesions.

**Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded since treatment started.

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

**Frequency of Symptomatic or Progressive CNS Lesions:** Incidence of patients presenting with newly diagnosed symptomatic or progressive CNS lesions at the time of tumor progression.

**Time to Symptomatic or Progressive CNS Lesions:** Time from randomization until the date of appearance of newly diagnosed symptomatic or progressive CNS lesions.

8.2.2. **Progression Free Survival (PFS)**

Progression free survival (PFS) is defined as the time interval from the date of randomization until the first date on which recurrence, progression or death due to any cause, is documented, or is censored at the last assessable evaluation prior to new anti-cancer therapy.

Progression is assessed by the investigator and it is not necessary to confirm disease progression.

PFS is censored on the date of the last overall tumor assessment (which encompasses both target and non-target tumor assessments) on study for patients who did not have progressive disease (PD) and who did not die while on study or who started a new anti-cancer therapy prior to documented PD. Additionally, patients lacking an evaluation of tumor response after
randomization have their PFS time censored on the date of randomization with duration of 1 day. If an overall tumor assessment is a PD and missing its date, then the earlier date of the target or non-target tumor assessments used in the determination of the overall assessment of PD will be used. If the overall tumor assessment date of a PD still cannot be determined, then the date of previous tumor assessment will be used for the PD date.

Assessment of PFS will be performed by the study investigators for all patients at screening, and then every 8 weeks from the first dose of investigational product until the occurrence of documented disease progression, or patient withdrawal from the study (i.e., PD, lost to follow-up, withdrawal of consent, or death), whichever occurs first. If patients remain on active treatment post Amendment 6 approval, the first planned tumor assessment will be performed every 12 weeks of treatment throughout the remaining active treatment phase until documented disease progression or a patient’s discontinuation from study, whichever occurs first. PFS will be assessed using the modified Response Evaluation Criteria in Solid Tumors (RECIST v1.0).

8.2.3. Objective Response Rate (ORR)

ORR is defined as the proportion of patients who achieve confirmed complete responses (CR) or partial responses (PR), per RECIST (v1.0) criteria, as their best overall response. The best overall response is the best response recorded from randomization until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since randomization). To be assigned a status of PR or CR, the response must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are initially met.

8.2.4. Duration of Response (DOR)

Duration of response is measured from the time at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date of recurrence, PD or death is objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment, per RECIST (v1.0). This value is censored at the last valid tumor assessment. Patient dropout includes patients that are lost to follow up or that start other anticancer therapy. The duration of overall complete response is measured from the time
measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.2.5. **Clinical Benefit Rate (CBR)**

The CBR is defined as the proportion of patients who achieve overall tumor response (CR or PR) or SD for at least 24 weeks. Patients who drop out prior to 24 weeks and have not achieved CR, PR, or SD prior to their withdrawal will not be considered successes for the calculation of CBR. Stable disease is measured from randomization until the criteria for disease progression or response are met per RECIST (v1.0) criteria.

8.2.6. **Health Outcomes Assessment**

A brief description of the questionnaires used to collect patient reported outcomes in this study is given below. A full description of the questionnaires is provided in Appendix 6 of the study protocol. With the approval of Amendment 5, the collection of patient reported outcomes questionnaires and data on underlying disease and non-disease related health care resource utilization were discontinued. All data collected up to the time of implementation of Amendment 5 will be used for exploratory descriptive analyses. Missing data prior to approval of Amendment 5 will not be imputed. No sensitivity analyses will be performed to determine the impact of missing data.

8.2.6.1. **FACT-B**

FACT-B is a validated instrument used to measure disease-specific quality of life in breast cancer patients (Brady et al., 1997). Patients will be asked to indicate how true a statement had been for them over the past 7 days using a 5-point scale: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All items on the questionnaire receive equal weighting.

The FACT-B (version 4) is a 37-item questionnaire with 5 subscales. The FACT-B (version 4) consists of two parts:

1) The general questionnaire on cancer (FACT-G), which includes the following 4 subscales:
   a. Physical well-being (PWB) consisting of 7 statements (GP1 – GP7)
   b. Social/Family well-being (SWB) consisting of 7 statements (GS1 – GS7)
c. Emotional well-being (EWB) consisting of 6 statements (GE1 – GE6)

d. Functional well-being (FWB) consisting of 7 statements (GF1 – GF7)

2) An additional breast cancer-specific subscale (BCS) consisting of 10 statements of which 9 are used in scoring (B1 – B9)

The overall total score is the sum of the 5 subscale scores based upon the following formularies:

\[
PWB = \frac{[(4-GP1)+(4-GP2)+(4-GP3)+(4-GP4)+(4-GP5)+(4-GP6)+(4-GP7)]\times7}{\text{# responses}}
\]

\[
SWB = \frac{[GS1+GS2+GS3+GS4+GS5+GS6+GS7]\times7}{\text{# responses}}
\]

\[
EWB = \frac{[(4-GE1)+GE2+(4-GE3)+(4-GE4)+(4-GE5)+(4-GE6)]\times6}{\text{# responses}}
\]

\[
FWB = \frac{[GF1+GF2+GF3+GF4+GF5+GF6+GF7]\times7}{\text{# responses}}
\]

\[
BCS = \frac{[(4-B1)+(4-B2)+(4-B3)+B4+(4-B5)+(4-B6)+(4-B7)+(4-B8)+B9]\times9}{\text{# responses}}
\]

*An item is only used if the patient responded to the question, i.e. an item is not used in scoring when there is no response to the question.

These formularies account for missing responses via proration, i.e. multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items responded to by the patient. This is an acceptable method for obtaining the subscale scores when more than 50% of the items in the subscale receive a patient response.

The total score is calculated as the sum of the subscale scores:

\[
\text{FACT-B} = \text{FACT-G} + \text{BCS} = (\text{PWB} + \text{SWB} + \text{EWB} + \text{FWB}) + \text{BCS}.
\]

The FACT scale is considered to be an acceptable indicator of patient quality of life as long as the overall response rate is greater than 80%, i.e., 22 of 27 FACT-G items completed or 29 of 36 FACT-B items completed. The greater the FACT-B score, the better the breast cancer patient’s quality of life.

8.2.6.2. EQ-5D

The EQ-5D is a standardized instrument that provides a simple descriptive profile and index value for health status. The EQ-5D consists of 6 items: 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score. Each dimension has 3 levels:
1) No problem
2) Some problem
3) Extreme problem

Patients are asked to select the level most descriptive of their current state of function or experience on each dimension. The following algorithm is used to derive the health utility index. An initial score of 1 will be assigned to each patient then a series of deductions will be made according to Table 8-2 based upon the levels of the responses within each dimension. Furthermore, for any combination of responses other than 11111, which indicates ideal health, will have a constant of 0.081 subtracted from the total score. A response of 3 in any of the dimensions indicates a poor quality of life. If at least one dimension includes a response of 3, then 0.269 will be subtracted from the total score.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Coefficient for Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>0</td>
</tr>
<tr>
<td>Self-care</td>
<td>0</td>
</tr>
<tr>
<td>Usual Activity</td>
<td>0</td>
</tr>
<tr>
<td>Pain/Discomfort</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety/Depression</td>
<td>0</td>
</tr>
</tbody>
</table>

*Constant deduction for any combination of responses other than 11111 is 0.081 and if at least 1 dimension includes a response of 3, subtract 0.269 from the total score.

For example, the calculation of a patient health index with responses 11223 is as follows:

Health Index = 1 – 0.081 – 0 – 0 – 0.036 – 0.123 – 0.236 – 0.269 = 0.255.

The health index will be based only on a complete set of patient responses. Missing responses will not be imputed. Baseline values will be determined by the last health index value prior to study medication intake. If a patient has no baseline value prior to study medication intake, then the patient will be excluded from the analysis.

8.3. Analysis Methods

The following represents an overview of the planned statistical analysis. Additional analyses may be performed if deemed appropriate. All analyses will be carried out using untransformed data (i.e. original scale) unless otherwise specified.
Categorical variables will be presented as counts and percentages and continuous variables will be presented using descriptive statistics (N, mean, std dev, median, Q1, Q3, min, and max). Tables will be summarized by treatment arm as well as overall.

**8.3.1. Primary Efficacy Analyses**

Progression free survival (PFS) is defined as the time interval from the date of randomization until the first date on which recurrence, progression or death due to any cause, is documented, or is censored at the last assessable evaluation on study or prior to new anti-cancer therapy, if applicable.

The log-rank test (stratified by randomization factors) will compare the PFS distributions between the treatment arms. The following hypothesis will be tested:

H₀: There is no difference in progression-free survival between the treatment arms

H₁: Progression-free survival is longer for patients randomized to the neratinib plus paclitaxel arm compared to the trastuzumab plus paclitaxel arm.

The primary efficacy analysis will be evaluated via the ITT population and will be considered the primary analysis. The analysis may be performed on the efficacy evaluable population as a sensitivity and supportive analysis. Survival analyses using interval censoring may also be employed as sensitivity analysis.

**8.3.2. Secondary Efficacy Analyses**

ORR, CBR, and the proportion of patients with symptomatic or progressive CNS lesions at the time of tumor progression will be compared between the two treatment groups using a generalized Cochran Mantel-Haenszel (CMH) test adjusted for prior exposure to ERBB2 inhibitors (prior adjuvant trastuzumab or prior lapatinib exposure, Yes/No), ER/PgR status (positive/negative), and geographic region. Estimates of ORR, CBR, and the proportion of patients with symptomatic or progressive CNS will be determined as well as their associated 95% confidence intervals for each treatment group.

DOR is measured from the time at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date of recurrence or PD or death is
objectively documented. DOR will be descriptively analyzed as per the primary analysis of
PFS (see Section 8.3.1).

Time to symptomatic or progressive CNS lesions is defined as the time interval from the date
of randomization until the first date on which a scheduled or unscheduled visit documents
CNS symptoms, the imaging examination shows CNS progression or is censored at the last
assessable evaluation on study or prior to new anti-cancer therapy, if applicable. Time to
symptomatic or progressive CNS lesions will be analyzed using Kaplan Meier method, Cox
proportional hazards model, and log-rank test (see Section 8.3.1). Additionally, other PDs
and death will be considered as competing risks for CNS progression to determine the
cumulative incidence function.

8.3.3. Other Efficacy Analyses

8.3.3.1. Health Outcome Assessments

Health outcomes in this study consist of the two questionnaires: FACT-B and EQ-5D.

The analysis will consist of patients that were enrolled into the study prior to Amendment 5
and will not include health outcome assessment information post-Amendment 5. For each
treatment arm descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum,
and maximum) will be presented for FACT-B and the total of all scales for EQ-5D at each
visit (baseline, every other cycle visit, and final visit). Differences between the treatment
arms will be tested using a random effects mixed model with change from baseline total
score as the outcome variable and the following covariates: treatment, treatment by time
interaction, and baseline total score as fixed effects, and site as a random intercept effect. The
results from the differing covariance structures will be compared and contrasted.

No sensitivity analyses will be performed to quantify the impact of missing values on the
results of the exploratory analysis of the health outcome assessments.

8.3.3.2. Health Care Utilization

Health care utilization including hospital and physician visits between treatment arms will be
described and compared. The analyses will consist of patients that were enrolled into the
study prior to Amendment 5. For each treatment group, descriptive statistics will be
presented, in addition to totals across the treatment groups.
8.3.3.3. **Biomarkers Predictive of Neratinib Response**

Nonparametric maximum likelihood estimated PFS curves (interval censored) stratified by biomarker presence/absence and treatment will be created to describe differences in PFS that may be related to the presence/absence of a particular biomarker.

No sensitivity analyses will be performed to quantify the impact of missing values on the results of the exploratory analysis of biomarkers predictive of neratinib response.

8.4. **Examination of Subgroups**

Subgroup analyses of the efficacy endpoints may be performed for the baseline covariates defined as following:

- Age group (<65 years, ≥65 years)
- Race (Asian, Black or Other, White)
- Prior trastuzumab exposure (yes or no)
- Prior lapatinib exposure (yes or no)
- Estrogen receptor+ (ER+) and/or progesterone receptor (PR+) (i.e. hormone receptor +) versus ER- and PR- (i.e. hormone receptor -)
- Geographic region (1 = United States; 2 = Western Europe, Australia, South Africa, and Canada; 3 = Asia Pacific, India, Eastern Europe, Africa, and South America)
9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

All safety analyses will be performed for all subjects in the Safety Population by the actual treatment received. The following assessments will be used to evaluate the safety of neratinib in combination with paclitaxel as first-line treatment for ERBB2 positive locally recurrent or MBC:

- Adverse events (AEs)
- Medical history
- Vital sign measurements
- Physical examination findings
- Electrocardiogram (ECG)
- LVEF results from MUGA or ECHO
- ECOG performance status
- Laboratory assessments.

All safety endpoints will be summarized by actual treatment group and visit when appropriate.

9.2. Extent of Exposure

Extent of exposure to each investigational product will be summarized by total dose, average dose, duration, relative dose intensity, number of missed doses, number of dose delays, and number of dose reductions.

9.3. Adverse Events, Serious Adverse Events, and Deaths

All AEs and SAEs will be reported until 28 days after the last dose of investigational product(s) and will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAE occurring any time after the reporting period, it must be promptly reported. The patient diary card used for recording of investigational product intake will also be used by patients to document any AEs experienced during study treatment. In the case of diarrhea, it also serves to document the number of loose stools per day and use of loperamide/other antidiarrheal treatments taken.
Adverse events and serious adverse events will be coded using MedDRA v17.0 or later. All AEs will be graded by the Investigator according to the NCI CTCAE v4.03. Summaries will in general focus on treatment-emergent adverse events (TEAEs). A TEAE is any adverse event that occurs or worsens on or after first dose of investigational product and up to 28 days after the last dose.

Subject incidence of all TEAEs, SAEs, treatment related TEAEs, treatment related SAEs, TEAEs leading to IP changes, grade 3 or 4 TEAEs, and fatal AEs will be tabulated by SOC, PT, and Grade, and by treatment group. Similar AE tables will be generated by descending order of PT only.

Hospitalizations due to TEAE will be summarized descriptively including the number of days by treatment arms.

Separate summaries will be presented for treatment emergent diarrhea events leading to treatment discontinuation, dose holds and dose reductions. Therapies used to treat diarrhea will also be summarized.

TEAEs, Serious Adverse Events (SAEs), TEAEs leading to discontinuation will be listed in by patient listings sorted by treatment, patient identifier and study day; SAEs will be flagged. All AE listings will include study day, SOC, PT, reported term, dose, Cycle/day, AE onset date, AE resolution date, outcome, duration, relationship to drug, action taken, and severity.

Patient deaths are recorded on the End of Study CRF page. The frequency and incidence of death will be summarized by cause of death overall, treatment arm, and on-study status at time of death (within 28 days of last dose vs. more than 28 days after last dose).

Patient death listings will include all death data available including date of death, cause of death and any AEs resulting in death.

Partial dates will be defined as dates that are missing certain elements of the date field. This may include missing information for the month, date or year, or two of these elements, but not all three. The patient diary card used for recording investigational product intake was also used to record AEs during study treatment. In some instances, this card may have partial dates recorded where the exact start or end date of the adverse event was not recalled. In these instances where the start day is missing, the day will be imputed as the first day of the
month unless the day of the first dose date is more appropriate. If the end day is missing then the day will be imputed as the last day of the month. If the month, year, both month and year, or the entire date is missing then no data imputation will be used, but these events will be counted with regard to frequency but the duration will be defined as unknown.

The Adverse Events of Special Interest (AESI) for the neratinib and paclitaxel combination therapy will be based on SMQ or the complete list of the Sponsor-defined group of preferred terms. Subject incidence of each AESI will be summarized by category, preferred terms, and grade.

9.4. **Clinical Laboratory Evaluation**

Blood samples for clinical chemistry and hematology will be collected during screening, before study drug administration, on Day 1 of each treatment cycle and at the treatment discontinuation visit. Samples for pregnancy test and urinalysis will be collected at screening, before study drug administration.

Laboratory data will be summarized in tables using descriptive statistics calculated on both the actual score and the change from baseline score for selected laboratory parameters. Lab shift tables using the CTCAE v4.03 or later grading will be used for the select analytes of interest, when applicable.

In addition, liver function test (LFT) abnormality will be summarized by treatment groups.

9.5. **Vital Signs, Physical Findings, and Other Observations Related to Safety**

9.5.1. **Vital Signs**

Vital signs, including systolic and diastolic blood pressure, pulse, and body temperature, as well as weight will be collected during Screening, on Day 1 of each treatment cycle and at the treatment discontinuation visit.

Summary tables will include descriptive statistics calculated on both the actual score and the change from baseline score.

A second summary will focus on the individual subject measures with the intent of identifying post-baseline abnormalities defined as clinically significant. Using clinically
significant ranges for each vital sign measure, descriptive statistics will summarize the post-baseline subject frequencies (percentages) that are outside the range defined.

9.5.2. **Physical Examinations**

Complete physical examinations (including a full neurological exam) will be collected during Screening and the Treatment Discontinuation Visit. Detailed/brief (system-guided) physical examinations will be done at subsequent time points to evaluate any clinically significant abnormalities, including worsening of conditions included in the patient’s medical history.

Changes in weight will be summarized across time on study and the frequency of clinically significant changes will be tabulated overall and by treatment.

9.5.2.1. **Electrocardiograms**

Single standard 12 lead digital ECGs will be performed during Screening, at Cycle 1 Day 1, at every 4 cycles starting with Cycle 4, and on the Treatment Discontinuation Visit.

The EKG (measured after resting in a supine position for 5 minutes) will include heart rate, PR, QRS, QT and QTc intervals. The ECG will be read and interpreted at the investigational site for patient safety monitoring, and documentation stored with the source documents.

All ECG parameters and their change from baseline will be summarized by treatment arm and overall using descriptive statistics. The frequency of abnormal ECG events will be tabulated by treatment arm and overall.

9.5.2.2. **Left Ventricular Ejection Fraction (LVEF)**

Multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO) scans to determine LVEF will be performed during Screening and repeated at Cycle 2 Day 1, Cycle 4 Day 1, and every 12 weeks thereafter and at treatment discontinuation, if not done within the previous 12 weeks.

MUGA scans or ECHO scans to determine LVEF will be performed as part of Screening procedures within 4 weeks before Cycle 1/Day 1, unless results are already available from within 6 weeks before Cycle 1/Day 1.

The mean LVEF and mean LVEF change from baseline will be summarized by treatment arm and overall using descriptive statistics.
10. OTHER ASSESSMENTS

10.1. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at Screening, on Day 1 of each treatment cycle and at the Treatment Discontinuation Visit (in accordance with the Schedule of Procedures in the study protocol). The ECOG categories are also summarized in the study protocol.

Screening ECOG performance status may be accepted as the Baseline status if the assessment was performed within 14 days of initiation of investigational product and there are no clinically significant findings.

The ECOG status will be included in the baseline and demographic variables. The number and percentages of subjects in each ECOG category will be presented by treatment and overall.
11. **INTERIM ANALYSES AND DATA MONITORING**

No interim analysis for early stopping is planned.

An Independent Data Monitoring Committee (IDMC) will meet approximately every 6 months to monitor safety data.
12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

None
REFERENCES

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## Protocol amendment history

<table>
<thead>
<tr>
<th>Amendment Date</th>
<th>Summary of Important Amendment Changes Affecting the Conduct of the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original 21-MAY-2009</td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>
| Amendment 1 (Country specific for Japan) 03-AUG-2009 | The key change was wording added in accordance with the Health Authority and Ethics Committees requirements in Japan, as follows:  
- Inclusion criterion 1 was revised to state “Female subjects aged 20 years or older”  
- In coagulation panel tests aPTT was added instead of PTT  
- A rationale for each inclusion/exclusion criterion was provided  
- The timing and process for obtaining informed consent for Japan was described  
- Monetary payment for insurance and compensation for study-related injuries were described  
- The process for records retention was described. |
| Amendment 2 (Country specific for Portugal) 24-NOV-2009 | The key changes were:  
- Serological testing for immunocompromised patients in Portugal was made mandatory.  
- The volume of blood to be collected at screening was changed from 7 to 14 mL for patients in Portugal.  
- Bicarbonate or carbon dioxide testing was to be performed if available only. |
| Amendment 3 04-FEB-2010 | The key changes were:  
- The design changed from a ~350-site study to a ~400-site study.  
- Inclusion criterion 8 was revised as follows: Eastern Cooperative Oncology Group (ECOG) status of 0 to 2 (not declining within 2 weeks prior to signing informed the first dose of investigational product).  
- Analysis of serum ERBB2/ECD levels was added to the baseline assessments.  
- Concomitant medication guidelines were added for patients taking anticoagulants or digoxin.  
- Guidelines for evaluating liver function test changes were added for patients experiencing Grade 3 diarrhea or hepatotoxicity.  
- New patient monitoring and dose adjustment guidelines were added for patients experiencing the following events: Grade 2 Pneumonitis/Interstitial Lung Disease; Grade ≥3 Pneumonitis/Interstitial Lung Disease; Grade 3 ALT or Grade 3 bilirubin; Grade 4 ALT or Grade 4 bilirubin; and ALT > 3x ULN and total bilirubin > 2x ULN and alkaline phosphatase < 2x ULN.  
- Analysis of phosphorus levels was added to the serum chemistry panel. |
| Amendment 4 18-FEB-2011 | Not applicable. This amendment was not implemented. |
| Amendment 5 09-JUN-2011 | The key changes were:  
- The design changed from a 1,200-subject Phase 3 study to a 480-subject Phase 2 study.  
- Analysis of p95ERBB2 levels with an antibody-based assay was added to the biomarkers evaluation.  
- The guidelines for diarrhea management were revised. |
- Primary prophylactic use of antidiarrheal medication was mandated.
- A diarrhea management decision-tree schematic was added.
- The dose adjustment guidelines for diarrhea were revised to align with changes made in the sister study (adjuvant study B1891004).
- The guidelines for calculating LVEF decline were clarified.
- New guidelines for selecting lymph nodes as target or non-target lesions at screening were added.
- The requirement to collect health outcomes questionnaires was discontinued.
- Adverse event and serious adverse event reporting procedures were revised to reflect process changes at Pfizer.
- The use of subject diaries and the distribution of subject diarrhea management cards were made mandatory for all subjects enrolled in the neratinib arm.

**Amendment 6 22-MAR-2012**

The key changes were:
- Study sponsorship was changed from Wyeth, a Pfizer Company, to Puma Biotechnology, Inc.
- Biomarker samples collected for p95ERBB2 levels as initially introduced per Amendment 5 were no longer to be analyzed.
- Overall survival was removed from the secondary endpoints of the study. As a result, the study no longer included a long-term follow-up for survival period.
- The frequency of tumor assessment was changed from every 8 weeks to every 12 weeks from first dose of investigational product.
- PK sample collection was stopped.
- The scenario for possible use of locally supplied trastuzumab and paclitaxel was expanded.

**Amendment 6.1**

Country-specific amendment for China.
There were no changes, except for transfer of sponsorship to Puma.