An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

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Study Protocol Number:	PUMA-NER-6203
Disease Condition:	HER2 Amplified (HER2+) Breast Cancer
Sponsor's Investigational Product Name/Formulation:	Neratinib Tablets
US IND Number	066783
EudraCT Number	2019-001896-35
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STUDY CONTACTS

Refer to the study reference manuals.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Puma Biotechnology, Inc.

Name of Investigational Product: Neratinib tablets

Name of Active Ingredient: Neratinib

Title of Study: An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

Condition or Disease: HER2 Amplified (HER2+) breast cancer

Approximate Values			
Number of Patients	3-5	**Duration of Patient Participation**	1 year
Number of Centers	2 sites	**Duration of Study**	1.5 years

Objectives:

Primary: The primary objective of this study is to characterize and understand colon pathogenesis related to neratinib-induced diarrhea through biopsies and images obtained by colonoscopy study.

Secondary: The secondary objectives are:

- To characterize the incidence and severity of diarrhea during the first 28-day cycle
- To analyze changes in serological and fecal inflammatory markers from baseline to second colonoscopy

Study Design:

This is an open-label, phase 2 study that will investigate colon pathology in patients with HER2-positive breast cancer treated with neratinib as monotherapy.

All patients will receive neratinib for the first 28 days as a single daily dose of 240mg.

Colonoscopy will be performed after eligibility has been confirmed, but prior to administration of the first dose of neratinib and at Day 30 (± 3 days) the conclusion of Cycle 1 (28 days).

Following the second study colonoscopy procedure:

- For patients being treated for stage 1 to 3c breast cancer in the extended adjuvant setting, neratinib will continue to be administered at a single daily dose of 240 mg until completion of one year of therapy from start of treatment, or until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.
- For patients being treated for metastatic breast cancer (mBC), capecitabine will be introduced after the second study colonoscopy procedure at a dose of 750mg/m^2 twice daily for 14 days of each 21 day treatment cycle, with neratinib administered continuously throughout at 240mg daily, until disease progression, death, unacceptable toxicity, or other specified withdrawal criterion.

All patients will receive loperamide diarrhea prophylaxis daily for one (1) 28-day cycle and then as needed.

Patients being treated for stage 1 to 3c breast cancer receiving extended adjuvant treatment will return to the clinic approximately every 3 months for safety assessments. Patients with mBC will return to the clinic at scheduled cycles. End of Treatment (EOT) visit is planned on upon completion of 1 year of treatment, followed by Safety Follow-up Visit 28 days after the last dose of neratinib.

The primary analysis will be conducted after all patients have completed two consecutive colonoscopies with biopsies. The final analysis will be conducted when all patients have completed study treatment, discontinued treatment or met other specified withdrawal criterion.

The study will end when all patients have been followed-up for 28 days after the last dose of neratinib.

Clinical care beyond the scope of this protocol remains the responsibility of the treating physician..

Study Endpoints:

- The primary endpoint is change from baseline in pathological findings in colon biopsies after the first 28 days of neratinib monotherapy.
- The secondary endpoint will be the incidence and severity of diarrhea during the first 28-day cycle of neratinib monotherapy.

Neratinib and Loperamide Dose and Administration:

- Neratinib: Six (6) 40 mg tablets (total dose 240 mg) will be self-administered orally by patients once daily with food, preferably in the morning
    - In patients with stage 1 to 3c breast cancer receiving extended adjuvant treatment with neratinib monotherapy, neratinib will be administered as a single 28-day cycle (Cycle 1) followed by continuous daily dosing for up to 1 year or until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.
    - In patients with mBC, neratinib will be administered as monotherapy for a single 28-day cycle (Cycle 1). Beginning in Cycle 2 following the completion of the second study colonoscopy procedure and in all subsequent cycles, neratinib will be administered continuously in 21-day cycles and capecitabine twice daily for 14 days of each 21 day treatment cycle until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.
- Loperamide:
    - Loperamide should be taken as instructed, titrating to 1-2 bowel movements per day.
    - The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
    - During weeks 1-2 (day 1 – 14) of Cycle 1 loperamide 4 mg will be self-administered administered three times daily (TID).
    - During weeks 3-4 (days 15 – 28) of Cycle 1 loperamide 4 mg will be self-administered twice daily (BID).
    - After the first 28 day Cycle, loperamide will be self-administered as needed (PRN) (not to exceed 16 mg per day).

Additional instructions regarding loperamide dosing are provided in Section 6.2.

During the first 28 days of treatment, patients must use a paper diary to record their intake of neratinib and loperamide, as well as the use of other antidiarrheals.

Capecitabine Dose and Administration (mBC patients only)

- Capecitabine therapy will not begin until the second study colonoscopy procedure has been completed.
- Capecitabine (total daily dose of 1500 mg/m^2 daily, administered as 750 mg/m^2 orally twice daily as approximately evenly divided doses) will be self-administered on Day 1-14 of each cycle, beginning after completion of the second study colonoscopy procedure and biopsy on Day 30 ± 3 days.
- Capecitabine should be taken with water within 30 minutes after a meal.

Diagnosis and Main Criteria for Inclusion:

Study Population:

Inclusion Criteria

1. Aged ≥18 years at signing of informed consent.
2. Histologically confirmed stage 1 through stage 4 primary adenocarcinoma of the breast (Edge and Compton, 2010).
3. Documented HER2 overexpression or gene-amplified tumor by a validated approved method (Wolff et al, 2013).
4. Patients with confirmed stage 1 to stage 3c breast cancer receiving extended adjuvant treatment with neratinib monotherapy must have completed a course of prior adjuvant trastuzumab or experienced side effects that resulted in early discontinuation of trastuzumab that have since resolved.

5. Patients with mBC must have had at least 2 prior HER2-directed regimens.
6. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
7. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
8. Negative β-human chorionic gonadotropin (hCG) pregnancy test for premenopausal women of reproductive capacity (those who are biologically capable of having children) and for women less than 12 months after menopause. [Women are considered postmenopausal if they are ≥12 months without menses, in the absence of endocrine or anti-endocrine therapies.]
9. Women of childbearing potential must agree and commit to the use of a highly effective non-hormonal method of contraception, i.e., intrauterine device, bilateral tubal ligation, vasectomized partner, or abstinence (only when it is the preferred lifestyle of the patient), from the time of informed consent until 28 days after the last dose of the investigational products. Men (male patient) with a female partner of childbearing potential must agree and commit to use condom and the female partner must agree and commit to use a highly effective method of contraception (i.e., any of the above methods, or for females, hormonal contraception associated with inhibition of ovulation) while on treatment and for 3 months after last dose of investigational products.
10. Recovery (i.e., to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).
11. No major bleeding diathesis or use of anticoagulants that would pose a high risk for endoscopic procedure.
12. Provide written, informed consent to participate in the study and follow the study procedures.

Exclusion Criteria

A patient will be excluded from this study if she/he meets any of the following criteria:

1. Patients with confirmed stage 1 to stage 3c currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.
2. Patients with mBC who have received prior capecitabine or HER2 directed TKI therapy.
3. Currently using drugs that have been implicated as causing microscopic colitis/watery diarrhea, such as acarbose, aspirin, proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), histamine H2-receptor antagonists, selective serotonin reuptake inhibitors, and ticlopidine (Pardi, 2017).
4. Major surgery within <28 days of starting treatment or received chemotherapy, investigational agents, or other cancer therapy, except hormonal therapy (e.g., tamoxifen, aromatase inhibitors), <14 days prior to the initiation of investigational products.
5. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2; including individuals who currently use digitalis, beta-blockers, or calcium channel blockers specifically for congestive heart failure), unstable angina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.
6. QTc interval >0.450 seconds (males) or >0.470 (females), or known history of QTc prolongation or Torsade de Pointes (TdP).
7. Diagnosis of inflammatory bowel disease
8. Screening laboratory assessments outside the following limits:

Laboratory Parameters	**Required Limit for Exclusion**
Absolute neutrophil count (ANC)	≤1,000/µl (≤1.0 x 10^9/L)
Platelet count	≤50,000/µl (≤100 x 10^9/L)
Hemoglobin	≤8 g/dL (transfusions allowed) Transfusions must be at least 14 days prior to initiation of treatment
Total bilirubin	>1.5 x institutional upper limit of normal (ULN) (in case of known Gilbert's syndrome, <2 x ULN is allowed)

Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	>2.5 x institutional ULN (>5 x ULN if liver metastases are present)
Creatinine	Creatinine clearance <30 mL/min (as calculated by Cockcroft-Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])
International Normalized Ratio (INR)	>1.5

[a] Cockcroft and Gault, 1976

[b] Levey et al, 1999

9. Active, unresolved infections.
10. Patients with a second malignancy, other than adequately treated non-melanoma skin cancers, in situ melanoma or in situ cervical cancer. Patients with other non-mammary malignancies must have been disease-free for at least 5 years.
11. Currently pregnant or breast-feeding.
12. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline).
13. Clinically active infection with hepatitis B or hepatitis C virus.
14. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that could, in the Investigator's judgment, make the patient inappropriate for this study.
15. Known hypersensitivity to any component of the investigational products; known allergies to any of the medications or components of medications used in the trial.
16. Unable or unwilling to swallow tablets

Safety Assessments:

The primary endpoint is descriptive assessment of colon pathology during the first 28 days of neratinib therapy.

The secondary endpoint is the incidence and severity of diarrhea during the first 28-day cycle. The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) for Cycle 1 through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and in Cycle 2 in patients with mBC will also be reported. AEs and SAEs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE), version 4.0 or higher.

After28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and in Cycle 2 in patients with mBC through 28 calendar days after the last administration of neratinib, only SAE data will be collected and summarized. SAEs will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to administration of neratinib, it should be promptly reported. All SAEs must be reported within 24 hours of awareness of the event using the SAE Report Form.

Safety will also be assessed based on medical history, vital sign measurements, physical examination findings, electrocardiogram results, MUGA or ECHO, and laboratory assessments.

Colonoscopy:

Microscopic colitis (MC) is a relatively common cause of chronic watery diarrhea. The diagnosis is based upon characteristic histological findings in the presence of diarrhea. The symptoms of MC are non-specific, and many patients meet the diagnostic criteria for irritable bowel syndrome; therefore, colon biopsies are required to definitively distinguish MC from the much more common irritable bowel syndrome (Pardi, 2017).

MC has two main subtypes, lymphocytic colitis and collagenous colitis, with the main distinction being histological. The characteristic biopsy finding in lymphocytic colitis is intraepithelial lymphocytosis, defined as >20 intraepithelial lymphocytes per 100 surface epithelial cells. In addition, the lamina propria contains a mixed infiltrate of acute and chronic inflammatory cells. Collagenous colitis has similar inflammatory findings, although the intraepithelial lymphocyte infiltrate tends to be less prominent. The distinguishing histological feature of

collagenous colitis is a thickened subepithelial collagen band (>7 μm, compared with normal of ≤5 μm). Despite the normal appearance grossly, biopsies often show surface epithelial damage (Pardi, 2017).

The ideal location in the colon to obtain biopsies is not clear. The inflammation and collagen thickening are not always uniform throughout the colon, and inflammation in lymphocytic colitis and collagen thickening in collagenous colitis may be worse in the right versus left colon. It is well established that distal colon biopsies are not sufficiently sensitive to make the diagnosis and that proximal and distal biopsies are standard of care.

To characterize pathology of the colonic mucosa in HER2 amplified (HER2+) breast cancer treated with neratinib, colonoscopy in this study will be performed at before initiation of neratinib in Cycle 1 and on Day 30 (± 3 days) (Appendix 1). During colonoscopy, photographs of the colonic mucosa will be taken along with approximately 8 biopsies from the terminal ileum, cecum, ascending colon, proximal transverse colon, splenic flexure, sigmoid colon, and rectum. If any abnormal appearing colon mucosa is identified endoscopically, it will be noted and biopsied in a separate jar. Biopsy material will be analyzed in a central laboratory. If polyps are identified, they will be removed during the examination; if cancer is identified, it will be sampled. Usual, standard clinical care will be provided for endoscopic findings unrelated to the study aims.

At the time of colonoscopy, serological inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) will be sampled and stool markers for diarrhea (fecal calprotectin, fecal elastase) will be collected.

Statistical Methods:

Sample Size: Approximately 3-5 patients will be enrolled.

Statistical Analysis:

Given the limited number of patients in the study, listing of the data and narratives will be the primary means to present the data. Descriptive summary statistics may be used if warranted. Demographic data, medical history, concomitant disease, and concomitant medication will be included in the analyses.

Safety:

All patients who receive a dose of neratinib will be analyzed for safety. The incidence of TEAEs and SAEs for Cycle 1 through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and following the completion of Cycle 2 in patients with mBC will be summarized after all biopsies have been completed. Following 28 days of neratinib monotherapy after the completion of the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and Cycle 2 in patients with mBC through 28 calendar days after the last administration of neratinib, only SAE data will be collected and summarized.

Final Analysis:

The final analysis will be conducted when all extended adjuvant patients with stage 1 to3c disease have completed 1 year of study treatment or discontinued the study, and have completed the Safety Follow-up Visit, and patients with mBC have completed study treatment or have discontinued the study, and have completed the Safety-Follow-up Visit.

Schedule of Procedures:

A schedule of procedures is included in Appendix 1.

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Abbreviation	Term/Definition
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [Classification System]
BID	twice daily
BUN	blood urea nitrogen
C	cycle
CBC	complete blood count
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
D	day
DCIS	ductal carcinoma in situ
DFS	disease-free survival
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor (also known as HER)
EIU	exposure-in-utero
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ERBB	epidermal growth factor family of trans-membrane receptors (also known as HER)
ERBB2	avian erythroblastic leukemia viral oncogene homolog 2, HER2
ESR	erythrocyte sedimentation rate
ExteNET	Extended Adjuvant Treatment with Neratinib, study 3144A2-3004-WW
FDA	Food and Drug Administration (United States)
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	gastrointestinal
GLP	Good Laboratory Practice

Abbreviation	Term/Definition
Hb	hemoglobin
hCG	β-human chorionic gonadotropin
Hct	hematocrit
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2; also known as c-erB2, ERBB2, or p185
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC_{50}	concentration at which there is 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IM	intramuscular(ly)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous(ly)
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MC	microscopic colitis
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multiple-gated accession scan
NCI	National Cancer Institute
NERLYNX	neratinib
NP	nurse practioner
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PA	physician's assistant
PB-272	neratinib
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PPE	palmar-plantar erythrodysesthesia
PPI	proton pump inhibitor
PRN	pro re nata (as needed)
PT	preferred term
QTc	QT interval, corrected for heart rate
RBC	red blood cell
SAE	serious adverse event

Abbreviation	Term/Definition
SC	subcutaneous(ly)
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TdP	Torsade de Pointes
TID	three times daily
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States (of America)
WBC	white blood cell

2. INTRODUCTION

2.1. Background

Breast cancer is the most frequently diagnosed malignancy in women and still the second leading cause of death in developed countries despite the advances made in the field over the past years (Ginsburg et al, 2017). In fact, more than 250,000 new cases of breast cancer were diagnosed in the United States in 2017 (Waks and Weiner, 2019). Globally, there were over 2 million new cases accounted for in 2018 (Bray et al, 2018).

2.2. ERBB2 Gene and Cancer

2.2.1. The Epidermal Growth Factor Receptor Family

Members of the epidermal growth factor family of trans-membrane receptors (ERBB family) are potent mediators of normal cell growth and development and are expressed in various tissues of epithelial, mesenchymal and neuronal origin (Baselga et al, 2009). The ERBB family consists of 4 closely related type 1 trans-membrane tyrosine kinase receptors: epidermal growth factor receptor (EGFR; also known as HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4).

Aberrant expression of HER1, HER2, and HER3 are linked to development of many epithelial cancers including colorectal, gastric, breast, and head and neck cancers. These membrane-spanning proteins receive extracellular signals from small peptide-ligand molecules, including epidermal growth factor-like molecules, transforming growth factor-α and neuregulins. Under normal physiological conditions, activation of the ERBB receptors is controlled by the spatial and temporal expression of their ligands (Yarden and Sliwkowski, 2001). Ligand binding triggers intracellular signaling through a complex and tightly controlled array of signaling pathways that together drive and regulate many cellular functions, including cell proliferation and organ development and repair. Binding of ligands to extracellular parts of HER1, HER3 and HER4 will result in dimerization and initiates a series of signaling cascades that includes mitogen-activated protein kinase, phosphoinositide 3-kinase (PI3K), Akt, and mammalian target of rapamycin (mTOR) (Garrett and Arteaga, 2011).

Each receptor comprises an extracellular domain at which ligand binding occurs, an alpha-helical trans-membrane segment and an intracellular protein tyrosine kinase domain (Olayioye et al, 2000). Receptor dimerization is an essential requirement for signaling activity of these receptors and can occur between two different ERBB receptors (hetero-dimerization) or between two molecules of the same receptor (homo-dimerization) (Olayioye et al, 2000; Ferguson et al, 2003). ERBB homodimers weakly perpetuate signals compared with heterodimers (Yarden and Sliwkowski, 2001). As the natural ligand for HER2 has not been identified, the receptor is presumed to exert its effects via formation of heterodimers with other HER family members and it is thought to be the preferred dimerization partner for the other receptors (Rosen et al, 2010). In fact, heterodimer formation with HER2 has been shown to increase the affinity of ligand binding to the dimerization partner (Graus-Porta et al, 1997). Dimerization of HER3, which lacks intrinsic kinase activity, with HER2 induces phosphorylation of HER3, which then activates the PI3K and Akt pathways (Graus-Porta et al, 1997).

2.2.2. ERBB2-positive Cancers

ERBB2 amplification and over-expression have been reported in 18 to 25% of human breast cancers and subsets of patients with ovarian and salivary gland tumors (Slamon et al, 1987; Vermeij et al, 2008; Cornolti et al, 2007). Approximately 15 to 20% (Ahn et al, 2012; Saini et al, 2011) of women with breast cancer are ERBB2-positive, which is associated with aggressive disease and poor prognosis (Slamon et al, 1987), including enhanced cell proliferation, reduced progression-free survival (PFS), and reduced overall survival (OS) (Slamon et al, 1987; Zhang et al, 2007; Badache and Goncalves 2006; Slamon et al, 1987). Compared with female breast cancer, male breast cancer cases are more often hormonal receptor (estrogen receptor/progesterone receptor) positive and HER2 negative, but treatment of male breast cancer patients follows the same indications as female postmenopausal breast cancer with surgery, systemic therapy and radiotherapy (Ottini et al, 2010). These observations have motivated the development of therapies targeting HER2.

2.3. Neratinib

Neratinib (HKI-272) is a potent irreversible pan ERBB inhibitor. Neratinib is an orally available small molecule that inhibits ERBB1, ERBB2, and ERBB4 at the intracellular tyrosine kinase domains, a mechanism of action that is different from trastuzumab. Neratinib reduces ERBB1 and ERBB2 autophosphorylation, downstream signaling, and the growth of ERBB1 and ERBB2 dependent cell lines. Preclinical data suggest that neratinib has antitumor activity in ERBB1- and/or ERBB2-expressing carcinoma cell lines, with cellular IC_{50} <100 nM (Rabindran et al, 2004).

Neratinib have advantages over other HER2 inhibitors due to its ability to irreversibly inhibit both HER1 and HER2. Breast cancer cells become resistant to trastuzumab over-time on the basis of extracellular domain truncation of HER2 receptor, which can no longer be recognized by the antibody (Xia et al, 2004), or because of coactivation of HER1 signaling (Rampaul et al, 2005; Zaczek et al, 2005). However, since neratinib acts on the intracellular tyrosine kinase domain, such cells are likely to maintain sensitivity to neratinib (Mosesson and Yarden, 2004).

A summary of preclinical studies, human pharmacokinetic studies, and previous clinical studies of neratinib for treatment of HER2 positive breast cancer are provided in the neratinib Investigator's Brochure (IB).

2.3.1. Clinical Activity of Neratinib

In Phase 1 and 2 clinical studies as a single agent or in combination with other anti-cancer agents, neratinib has shown anti-tumor activity in patients with HER2-positive/amplified breast cancer (Awada et al, 2013; Burstein et al, 2010; Chow et al, 2013; Saura et al, 2014). Analyses of the primary efficacy endpoint (disease-free survival, DFS) data from a pivotal, randomized Phase 3 ExteNET trial (Extended Adjuvant Treatment with Neratinib [3144A2-3004-WW, 'Study 3004'], (Chan et al, 2016; Martin et al, 2017); showed that neratinib reduced the risk of DFS events by 33% compared with placebo in women with HER2-positive locally advanced breast cancer who were treated with neratinib for 1 year after adjuvant trastuzumab. The one-sided p-value from the stratified log rank test was 0.005 indicating that DFS was significantly prolonged for patients randomized to the neratinib arm compared with the placebo arm. Furthermore, neratinib resulted in a statistically significant improvement in the secondary

efficacy endpoint, DFS including ductal carcinoma in situ (DFS DCIS). Neratinib reduced the risk of DFS DCIS events by 37% compared with placebo. The one-sided-p value from the stratified log rank test was <0.001 indicating that DFS DCIS was significantly prolonged for patients randomized to the neratinib arm compared with the placebo arm.

On 17-JUL-2017, the United States (US) Food and Drug Administration (FDA) approved neratinib (NERLYNX®) for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy (Singh et al, 2018).

On 31-AUG-2018, the European Commission (EC) granted marketing authorization for neratinib (NERLYNX®) for the extended adjuvant treatment of adult patients with early stage hormone receptor-positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

2.3.1.1. Neratinib in Combination with Capecitabine

In a Phase 1/2 clinical study investigating the combination of neratinib plus capecitabine, the maximum tolerated dose (MTD) of neratinib 240 mg was established in combination with capecitabine 1500 mg/m^2 in patients with solid tumors. Subsequent investigation of this dose regimen in patients with HER2+ advanced breast cancer demonstrated that this combination treatment was clinically active and has a manageable toxicity profile.

In the study, clinical responses at the MTD were observed in 63% of patients (64% of those with no prior lapatinib exposure and 57% of those with prior lapatinib), while median durations of response were 46 and 48 weeks, respectively. This is a slightly higher response rate and similar duration of response to that observed in previous neratinib monotherapy studies, but in a full study population previously treated with trastuzumab (Burstein et al, 2010; Wong et al, 2009); an objective response rate (ORR) of 29% with neratinib monotherapy has also been reported (Martin et al, 2011). In this study, all patients progressed to previous trastuzumab-based therapy, and median PFS with neratinib plus capecitabine was 40 weeks in the lapatinib-naive cohort and 36 weeks in the lapatinib-treated cohort. These results compare favorably with those previously observed in the monotherapy study for patients who received prior trastuzumab (22 weeks) (Geyer et al, 2006). The results of this study suggest that the combination of neratinib plus capecitabine may have superior efficacy in patients with prior therapy with anti HER2-targeted therapies.

The results of this Phase 1/2 study also compare favorably with results obtained from the combination of lapatinib plus capecitabine in an indirect comparison. In a Phase 3 study, ORR (44.2%), clinical benefit rate (57.7%), and PFS (6.34 months) with lapatinib plus capecitabine were lower than was observed with neratinib plus capecitabine in the Phase 1/2 study (Xu et al, 2011).

The combination of neratinib plus capecitabine was associated with an acceptable safety and tolerability profile in the Phase 1/2 study. Diarrhea was the most common Grade 3/4 AE in the study (reported by 23% of patients), although only 4 patients discontinued treatment due to the event (6%), which is similar to previous experience in neratinib monotherapy studies (Burstein et al, 2010; Wong et al, 2009). Diarrhea typically occurred within a few days of neratinib initiation (median, 2 days) and was most often managed by a dose delay or reduction. Across previous

neratinib studies, diarrhea typically occurred within 2 to 8.5 days of neratinib initiation and was generally managed with dose adjustments or antidiarrheal medications (Burstein et al, 2010; Wong et al., 2009).

The most frequent toxicities reported with capecitabine monotherapy are palmar-plantar erythrodysesthesia syndrome (PPE) and gastrointestinal events. While the incidence of PPE (all grades, 47%) in this study was similar to the range reported in capecitabine monotherapy studies (37% to 60%), the incidence of diarrhea was higher (all grades, 88% compared with 5% to 58% reported in monotherapy studies) (Burstein et al, 2010; Wong et al, 2009), as may be expected from the combination of two drugs that are associated with gastrointestinal effects. Overall, no unexpected toxicity was observed in patients receiving neratinib plus capecitabine, and few patients discontinued treatment due to toxicity.

2.3.2. Safety Profile of Neratinib in Monotherapy and Combination Therapy Studies

Safety results from completed and ongoing clinical studies conducted in patients with breast cancer or other solid tumors show that neratinib is generally well tolerated with a consistent safety profile. Gastrointestinal (GI) disorders, such as diarrhea, nausea, and vomiting, account for the most-frequently reported treatment-emergent adverse events. Fatigue, decreased appetite, abdominal pain, headache, rash, and hepatotoxicity (abnormal liver function test) have also been reported in patients treated with neratinib. Refer to the neratinib Investigator Brochure (IB) for more detailed information regarding benefits and identified and potential risks for patients, as well as for a summary of findings from neratinib nonclinical studies that potentially have clinical significance.

Refer to Appendix 2 (Dose Adjustment Guidelines) for further information regarding the management of neratinib-related toxicities.

2.3.3. Diarrhea Management Without Anti-diarrheal Prophylaxis

As the mechanism of action of neratinib targets EGFRs, which are present in high numbers in the GI tract, diarrhea is a predicted on-target effect. Consistent with neratinib binding to the target receptors in the GI tract, diarrhea was the most common treatment-emergent adverse event (TEAE) leading to discontinuation in the Phase 3 ExteNET trial (Study 3004), in which 2,840 women with early-stage HER2 positive breast cancer who had completed adjuvant treatment with trastuzumab were randomized 1:1 to receive either neratinib or placebo daily for one year. Anti-diarrheal prophylaxis to prevent the neratinib related diarrhea was not mandated in Study 3004; however, patients were allowed the use of anti-diarrheal agents after experiencing diarrhea at any time during the study. Thus, Study 3004 patients initiated neratinib dosing without concomitant anti-diarrheals and only took anti-diarrheal agents after diarrhea had occurred.

In Study 3004, 95.4% of patients experienced diarrhea of any grade and 39.8% of patients experienced Grade 3 diarrhea. The majority of patients reporting Grade 3 diarrhea experienced the event in the first month of treatment. Although diarrhea was a frequent adverse event (AE), diarrhea episodes were predominately short in duration and rarely associated with severe or serious complications. Diarrhea due to neratinib was managed with anti-diarrheals and/or with dose adjustments. These diarrhea management techniques resulted in 95.0% of the diarrhea in the neratinib arm being resolved, similar to the 96.8% in the placebo arm. Only 1.6% of patients

treated with neratinib had diarrhea that was categorized as a serious adverse event (SAE). All AEs related to diarrhea were reversible with supportive care, treatment interruption, and/or discontinuation. The median cumulative duration of Grade 2 or higher diarrhea was 10 days and the discontinuation rate due to diarrhea was 16.8% in patients receiving neratinib in Study 3004 (Table 1).

Table 1: Characteristics of Diarrhea in Study 3004 (No Anti-diarrheal Prophylaxis)

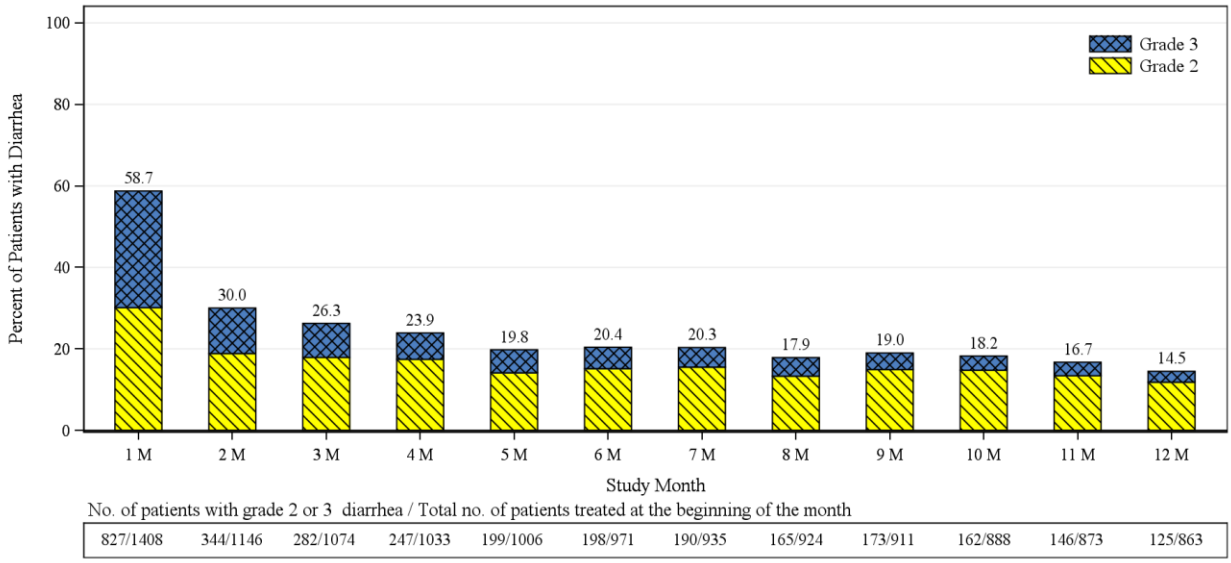
	Neratinib Arm (N=1408)	**Placebo Arm (N=1408)**
Duration of treatment (months)		
Median (Min, Max)	11.6 (0.03, 13.3)	11.8 (0.1, 13.2)
Incidence of diarrhea by worst grade – n (%)		
Any Grade	**1343 (95.4)**	**499 (35.4)**
Grade 1	323 (22.9)	382 (27.1)
Grade 2	458 (32.5)	94 (6.7)
Grade 3	561 (39.8)	23 (1.6)
Grade 4	1 (0.1)	0 (0.0)
Cumulative duration of grade 2 or higher per patient (days)		
Median	10	3
Cumulative duration of grade 3 or higher per patient (days)*		
Median	5	2
Action taken		
Dose hold due to diarrhea-n (%)	**477 (33.9)**	**26 (1.8)**
Dose reduction due to diarrhea -n (%)	**372 (26.4)**	**8 (0.6)**
Discontinuation due to diarrhea – n (%)	237 (16.8)	3 (0.2)
Diarrhea leading to hospitalization - n (%)	20 (1.4)	1 (0.1)

* Includes one episode of Grade 4 diarrhea

2.3.3.1. Incidence of Grade 3 Diarrhea in Study 3004

In Study 3004 neratinib arm, 95.4% of patients experienced diarrhea of any grade and 39.8% of patients experienced Grade 3 diarrhea (Table 1). The majority of patients reporting Grade 3 diarrhea experienced the event in the first month of treatment. The incidence of Grade 3 diarrhea decreased in subsequent months (Figure 1).

Figure 1: Incidence of Treatment-emergent Grade 2 or Grade 3 Diarrhea Over Time in Study 3004 Neratinib Arm (No Prophylaxis)



The severity grade for diarrhea is the worst grade during the treatment month.
One month is defined as 30 days.

2.3.4. Diarrhea Management With Anti-diarrheal Prophylaxis

While Study 3004 was ongoing, trials in metastatic breast cancer showed that administering anti-diarrheal agents on the same day as initiating neratinib therapy helped to reduce neratinib-related diarrhea (Ustaris et al, 2015). In these studies, neratinib and loperamide were given together on Day 1 and then continued to be given together for the first month of treatment. After the first month, the prophylactic loperamide was stopped and neratinib continued to be given daily with loperamide given as needed (PRN) after diarrhea occurred.

Based on the results obtained in the metastatic setting demonstrating a reduction in the incidence of diarrhea with the prophylactic use of loperamide, study PUMA-NER-6201 (Study 6201) was initiated in the extended adjuvant breast cancer setting to assess the effectiveness of multiple prophylaxis regimens on reducing the incidence of neratinib-related diarrhea. Study 6201 enrolled the same patient population and had the same dose, frequency of administration, and duration of neratinib treatment as in the pivotal efficacy Study 3004. The first cohort in Study 6201 was designed to confirm the previous results by using loperamide anti-diarrheal prophylaxis.

In Study 6201 loperamide cohort, 79.6% of patients experienced diarrhea of any grade and 30.7% of patients experienced Grade 3 diarrhea. The median cumulative duration of Grade 2 or higher diarrhea was 5 days and the discontinuation rate due to diarrhea was 20.4% (Table 2).

Table 2: Characteristics of Diarrhea in Study 6201 (Prophylaxis Months 1 and 2)

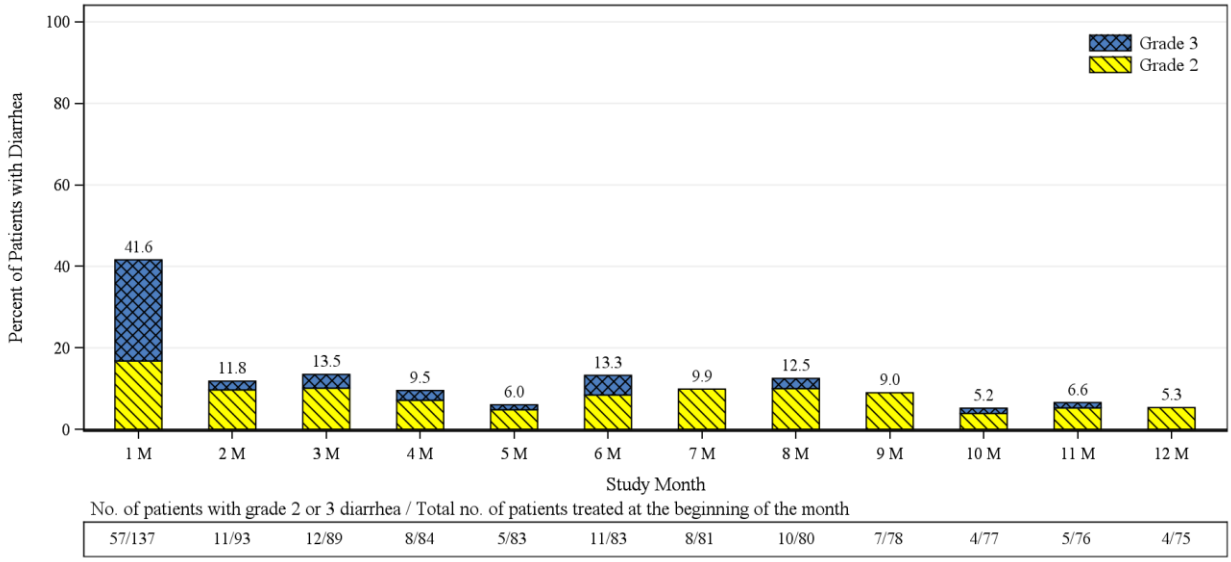
	Loperamide Cohort* (N=137)
Duration of treatment (months)	
Median (Min, Max)	11.63 (0.1, 13.1)
Incidence of diarrhea by worst grade – n (%)	
Any Grade	**109 (79.6)**
Grade 1	**33 (24.1)**
Grade 2	**34 (24.8)**
Grade 3	**42 (30.7)**
Grade 4	**0 (0.0)**
Cumulative duration of grade 2 or higher per patient (days)	
Median	5.0
Cumulative duration of grade 3 or higher per patient (days)	
Median	3.0
Action taken	
Dose hold due to diarrhea-n (%)	**20 (14.6)**
Dose reduction due to diarrhea -n (%)	**11 (8.0)**
Discontinuation due to diarrhea – n (%)	**28 (20.4)**
Diarrhea leading to hospitalization - n (%)	**2 (1.5)**

* In the loperamide cohort of Study 6201, 2 different prophylaxis regimens were evaluated; values presented in the table combine the data from the 2 regimens.

2.3.4.1. Incidence of Grade 3 Diarrhea in Study 6201

The data from Study 6201 suggest that the use of antidiarrheal prophylaxis with loperamide reduces the diarrhea experienced by the patients taking neratinib compared to that seen in Study 3004. The data from Study 6201 also confirm the previous observation made in Study 3004 that the highest incidence of Grade 3 diarrhea with neratinib therapy is observed in the first month of treatment and that the incidence is reduced in subsequent months (Figure 2).

Figure 2: Incidence of Treatment-emergent Grade 2 or Grade 3 Diarrhea Over Time in Study 6201 With Loperamide Prophylaxis



1 month = 30 days

2.4. Study Rationale

A rat model for neratinib-associated diarrhea has identified inflammation of the terminal ileum and proximal colon as a potential cause of the neratinib-related diarrhea. Studies conducted in this model demonstrated that budesonide, a locally acting corticosteroid used for inflammatory GI conditions, and colesevelam, a bile acid sequestrant, each reduced the amount of days with moderate diarrhea compared with neratinib alone. In the proximal colon, rats treated with neratinib had higher levels of apoptosis compared with controls; budesonide significantly reduced histopathological injury in the proximal and distal colon in rats (Secombe et al, 2017; Secombe et al, 2019).

Microscopic colitis (MC) is a relatively common cause of chronic watery diarrhea. The diagnosis is based upon characteristic histological findings in the presence of diarrhea. The symptoms of MC are non-specific, and many patients meet the diagnostic criteria for irritable bowel syndrome; therefore, colon biopsies are required to definitively distinguish MC from the much more common irritable bowel syndrome.

MC has two main subtypes, lymphocytic colitis and collagenous colitis, with the main distinction being histological. The characteristic biopsy finding in lymphocytic colitis is intraepithelial lymphocytosis, defined as >20 intraepithelial lymphocytes per 100 surface epithelial cells. In addition, the lamina propria contains a mixed infiltrate of acute and chronic inflammatory cells. Collagenous colitis has similar inflammatory findings, although the intraepithelial lymphocyte infiltrate tends to be less prominent. The distinguishing histological feature of collagenous colitis is a thickened subepithelial collagen band (>7 µm, compared with normal of ≤5 µm). Despite the normal appearance grossly, biopsies often show surface epithelial damage.

The ideal location in the colon to obtain biopsies is not clear. The inflammation and collagen thickening are not always uniform throughout the colon, and inflammation in lymphocytic colitis and collagen thickening in collagenous colitis may be worse in the right versus left colon. It is

well established that distal colon biopsies are not sufficiently sensitive to make the diagnosis and that proximal and distal biopsies are standard of care.

This study aims to characterize the pathology of colonic mucosa in patients with HER2 positive breast cancer treated with neratinib by performing a colonoscopy at before the initiation of neratinib in Cycle 1 and on Day 30 (± 3 days) (Appendix 1). During colonoscopy, photographs of the colonic mucosa will be taken along with approximately 8 biopsies from the terminal ileum, cecum, ascending colon, proximal transverse colon, splenic flexure, sigmoid colon, and rectum. If any abnormal appearing colon mucosa is identified endoscopically, it will be noted and biopsied in a separate jar. Biopsy material will be analyzed in a central laboratory. If polyps are identified, they will be removed during the examination; if cancer is identified, it will be sampled. Usual, standard clinical care will be provided for endoscopic findings unrelated to the study aims.

At the time of colonoscopy, serological inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) will be sampled and stool markers for diarrhea (fecal calprotectin, fecal elastase) will be collected.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to characterize and understand colon pathogenesis related to neratinib-induced diarrhea through biopsies and images obtained by colonoscopy study

3.2. Secondary Objectives

The secondary objectives of this study are:

- To characterize the incidence and severity of diarrhea during the first 28-day cycle.
- To analyze changes in serological and fecal inflammatory markers from baseline to second colonoscopy.

3.3. Exploratory Objectives

None.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, phase 2 study that will investigate colon pathology in patients with HER2-positive breast cancer treated with neratinib as monotherapy.

All patients will receive neratinib for the first 28 days as a single daily dose of 240mg.

Following the second study colonoscopy procedure:

- For patients being treated for stage 1 to 3c breast cancer in the extended adjuvant setting, neratinib will continue to be administered at a single daily dose of 240mg until completion of one year of therapy from start of treatment , or until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.
- For patients being treated for metastatic breast cancer (mBC), capecitabine will be introduced after the second study colonoscopy procedure at a dose of 750mg/m^2 twice daily for 14 days of each 21 day treatment cycle, with neratinib administered continuously throughout at 240mg daily, until disease progression, death, unacceptable toxicity, or other specified withdrawal criterion.

All patients will receive loperamide diarrhea prophylaxis daily for one (1) 28-day cycle and then as needed.

Following a 28-day screening period (Section 9.1), eligible patients will be enrolled. Baseline assessments will be performed prior to Cycle 1/Day 1 dosing. Patients will then participate in the active treatment phase, consisting of, in both groups, a single 28-day cycle of neratinib monotherapy (Section 9.2). Neratinib and loperamide will be administered orally by patients as described in Section 6. The morning dose of neratinib will be held on the day of the second study colonoscopy procedure (Section 6.1).

Colonoscopy will be performed after eligibility has been confirmed, but prior to administration of the first dose of neratinib on Day 1 of Cycle 1, and at Day 30 (± 3 days). Thereafter, extended adjuvant patients with stage 1 to 3c breast cancer will continue to receive neratinib monotherapy for 1 year or until progression of disease, death, or intolerance to study prescribed therapy. Patients with mBC will continue to receive neratinib in 21-day cycles, beginning in Cycle 2, after completion of the second study colonoscopy procedure, in combination with capecitabine administered on Day 1-14 of each cycle, until progression of disease, death, or intolerance to study prescribed therapy.

NOTE; patients with mBC cannot be exposed to capecitabine until after completion of the second study colonoscopy procedure.

In extended adjuvant patients with stage 1 to 3c breast cancer, patients will return to the clinic approximately every 3 months for safety assessments. End of Treatment (EOT) visit is planned on upon completion of 1 year of treatment, followed by Safety Follow-up Visit 28 days after the last dose of neratinib.

In patients with mBC, clinic visits during the active treatment phase are planned on Day 1 of Cycle 1, Cycle 2, and each subsequent cycle. Treatment discontinuation visit is planned 0-3 days after the last dose, followed by a Safety Follow-up Visit 28 days after the last dose of neratinib.

Assessments required throughout the study are summarized in the Schedule of Study Procedures (Appendix 1).

Patients may be discontinued from investigational product or from the study, as described in Section 10 and Section 11.

The primary endpoint of the study is change from baseline in pathological findings in colon biopsies after the first 28 days of neratinib. The secondary endpoint is the incidence and severity of diarrhea during the first 28-day cycle.

The study will end when all patients have been followed-up for 28 days after the last dose of neratinib.

Approximately 3-5 patients will be enrolled at approximately 2 centers.

4.2. Study Duration and Termination of Study

The approximate duration of the study is 1.5 years.

Patients with stage 1 to 3c disease receiving extended adjuvant therapy are anticipated to participate in the study for approximately 1 year. This includes 1 month for screening, approximately 12 months for the active treatment phase until progression of disease or intolerance to study prescribed therapy, and safety follow-up visit 28 days after the last dose of neratinib.

Patients with mBC are anticipated to participate in the study for an average of 12 months. This includes approximately 1 month for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 1 month for initial Safety Follow-up. Patients who permanently discontinue treatment due to unacceptable toxicity will be followed-up for 28 days after the last dose of neratinib to collect any adverse events (AEs) (Section 9.4).

The primary analysis will be conducted after all patients have completed two sets of colon biopsies. The final analysis will be conducted when all patients with stage 1 to 3c breast cancer have completed 1 year of study treatment or have met other specified withdrawal criteria and patients with mBC have discontinued therapy or have met other specified withdrawal criteria (see Section 10).

The study will end when all patients have been followed up for 28 days after the last dose of neratinib.

In the event that end of treatment (EOT) is declared earlier by the Sponsor, patients will be offered the opportunity to complete treatment through a treatment extension study.

4.3. Randomization and Blinding

This is a non-randomized, open-label study.

5. STUDY POPULATION

5.1. Inclusion Criteria

Each patient will be entered into this study only if she/he meets all of the following criteria:

1. Aged ≥18 years at signing of informed consent.
2. Histologically confirmed stage 1 through stage 4 primary adenocarcinoma of the breast (Edge and Compton, 2010).
3. Documented HER2 overexpression or gene-amplified tumor by a validated approved method (Wolff et al, 2013).
4. Patients with confirmed stage 1 to 3c breast cancer receiving neratinib monotherapy must have completed a course of prior adjuvant trastuzumab or experienced side effects that resulted in early discontinuation of trastuzumab that have since resolved.
5. Patients with mBC must have had at least 2 prior HER2-directed regimens.
6. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
7. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
8. Negative β-human chorionic gonadotropin (hCG) pregnancy test for premenopausal women of reproductive capacity (those who are biologically capable of having children) and for women less than 12 months after menopause. Women are considered postmenopausal if they are ≥12 months without menses, in the absence of endocrine or anti-endocrine therapies.
9. Women of childbearing potential must agree and commit to the use of a highly effective non-hormonal method of contraception, i.e., intrauterine device, bilateral tubal ligation, vasectomized partner, or abstinence (only when it is the preferred lifestyle of the patient), from the time of informed consent until 28 days after the last dose of the investigational products. Men (male patient) with a female partner of childbearing potential must agree and commit to use condom and the female partner must agree and commit to use a highly effective method of contraception (i.e., any of the above methods, or for females, hormonal contraception associated with inhibition of ovulation) while on treatment and for 3 months after last dose of investigational products.
10. Recovery (i.e., to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).
11. No major bleeding diathesis or use of anticoagulants that would pose a high risk for endoscopic procedure.
12. Provide written, informed consent to participate in the study and follow the study procedures.

5.2. Exclusion Criteria

A patient will be excluded from this study if she/he meets any of the following criteria.

1. Patients with confirmed stage 1 through stage 3c breast cancer currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.
2. Patients with mBC that have received prior capecitabine or HER2 directed TKI therapy.
3. Currently using drugs that have been implicated as causing microscopic colitis/watery diarrhea, such as acarbose, aspirin, proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), histamine H2-receptor antagonists, selective serotonin reuptake inhibitors, and ticlopidine (Pardi, 2017).
4. Major surgery within <28 days of starting treatment or received chemotherapy, investigational agents, or other cancer therapy, except hormonal therapy (eg, tamoxifen, aromatase inhibitors), <14 days prior to the initiation of investigational products.
5. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2; including individuals who currently use digitalis, beta-blockers, or calcium channel blockers specifically for congestive heart failure), unstable angina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.
6. QTc interval >0.450 seconds (males) or >0.470 (females), or known history of QTc prolongation or Torsade de Pointes (TdP).
7. Diagnosis of inflammatory bowel disease.
8. Screening laboratory assessments outside the following limits:

Laboratory Parameters	**Required Limit for Exclusion**
Absolute neutrophil count (ANC)	≤1,000/µl (≤1.0 x 10^9/L)
Platelet count	≤50,000/µl (≤100 x 10^9/L)
Hemoglobin	≤8 g/dL (transfusions allowed) Transfusions must be at least 14 days prior to initiation of treatment
Total bilirubin	>1.5 x institutional upper limit of normal (ULN) (in case of known Gilbert's syndrome, <2 x ULN is allowed)
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	>2.5 x institutional ULN (>5 x ULN if liver metastases are present in mBC patients)
Creatinine	Creatinine clearance <30 mL/min (as calculated by Cockcroft-Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])
International Normalized Ratio (INR)	≥1.5

[a] Cockcroft and Gault, 1976
[b] Levey et al, 1999

9. Active, unresolved infections.
10. Patients with a second malignancy, other than adequately treated non-melanoma skin cancers, in situ melanoma or in situ cervical cancer. Patients with other non-mammary malignancies must have been disease-free for at least 5 years.

11. Currently pregnant or breast-feeding.
12. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline).
13. Clinically active infection with hepatitis B or hepatitis C virus.
14. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that could, in the Investigator's judgment, make the patient inappropriate for this study.
15. Known hypersensitivity to any component of the investigational products; known allergies to any of the medications or components of medications used in the trial.
16. Unable or unwilling to swallow tablets.

5.3. Patient Enrollment

Enrollment will occur only after the patient has given written informed consent, all screening assessments have been completed, and the patient meets all eligibility criteria.

6. ADMINISTRATION OF NERATINIB AND LOPERAMIDE TREATMENTS

6.1. Neratinib

Neratinib will be supplied as 40-mg, film-coated tablets packaged in bottles with desiccant.

Neratinib (240 mg; provided as six 40-mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. Neratinib must be taken with food, preferably in the morning.

In patients with stage 1 to 3c disease, extended adjuvant treatment with neratinib will be given continuously as a single 28-day cycle followed by continuous daily dosing for up to 1 year

In patients with mBC, following completion of a 28-day cycle of neratinib monotherapy and completion of the second study colonoscopy procedure, neratinib will be given continuously in 21-day cycles in combination with capecitabine. On the day of the second study colonoscopy procedure in both groups, the morning dose of neratinib will be held. Neratinib will be resumed the day following the second study colonoscopy procedure. In both groups, daily dosing should continue until disease recurrence or progression (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion is met (see Section 10).

During the first 28 days, patients must use a diary to record their intake of neratinib (see Section 8.5.2).

6.1.1. Neratinib Dose Adjustment

Neratinib dose adjustment and/or discontinuation and/or management of toxicity should be performed according to Appendix 2 and Section 10.1.

Recommended dose reductions for the -1 and -2 dose levels of neratinib are listed in Table 3.

Table 3: Dose Reduction Levels for Neratinib-Related Toxicity

Dose Level	Neratinib
Recommended Starting Dose	240 mg
First dose reduction	200 mg
Second dose reduction	160 mg
Third dose reduction	120 mg

mg = milligrams

If doses of neratinib are held, study procedures for that cycle will proceed on schedule as planned, without any delay. Missed dose(s) of neratinib (i.e., any dose that is not administered within the protocol-defined administration window) will not be made up. **Note: Patients should take one dose per calendar day.** The dose adjustment guidelines represent the minimum set of measures the Investigator must follow. However, additional measures may be taken, as necessary, for certain patients per the Investigator's medical judgment. All dose modifications/adjustments should be documented in the patient's source file.

Once the neratinib dose has been reduced for a patient, all subsequent cycles must be administered at that dose, unless further dose reduction is required. Dose re-escalation will only be permitted if explicitly approved in advance by the Sponsor. Evidence of this approval must be contained within the patient's source file.

Patients must discontinue the investigational product if a criterion for withdrawal is met (see Section 10.1).

Reintroduction of the discontinued investigational product at a later time during the active treatment phase is not permitted.

Detailed rules for dose adjustments of neratinib in case of toxicity, including the dose levels to which the investigational product should be adjusted, are provided in Appendix 2.

6.2. Loperamide

Detailed dosing instructions and recommendations for management of diarrhea are provided in Section 7.2. Prior to initiation of study drug in Cycle 1.

- Inform patients that they will experience diarrhea while taking neratinib.
- Loperamide should be taken as instructed
- The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
- During weeks 1-2 (day 1 – 14) of Cycle 1 loperamide 4 mg will be self-administered administered three time daily.
- During weeks 3-4 (days 15 – 28) of Cycle 1 loperamide 4 mg will be self-administered twice daily
- After the first 28 days, loperamide will be self-administered as needed (PRN) (not to exceed 16 mg per day).

Recommended loperamide dosing is listed below in Table 4.

Table 4: Loperamide Dosing

Day	Loperamide Dose
1-14	Daily dose of 12 mg in 3 divided doses of 4 mg
15-28	Daily dose of 8 mg in 2 divided doses of 4 mg
29+	Daily dose as needed (not to exceed 16 mg per day)

During the first 28 days, patients must use a diary to record their intake of loperamide as well as the use of other antidiarrheals. Loperamide pill counts will be conducted only during the first cycle (28 days) of therapy.

Documentation of the number of stools at baseline should be captured in the patient's record. Any occurrences of loose stools, diarrhea or constipation must be documented by the patient and captured in the Patient Diary (see Section 8.5.2) during Cycle 1. The entries in the Patient Diary should be reviewed by the study staff together with the patient.

The Patient Diary will contain details of the daily number of unformed stools the patient has experienced since the last visit. Documenting the toxicity grade of the diarrhea or constipation by the study staff needs to be reported accurately on the Case Report Form (CRF) using the NCI CTCAE version 4.0 criteria.

Loperamide Dose Adjustment

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose (up to a maximum dose of 16 mg per day).

- For patients who develop diarrhea during Cycles 1, loperamide should be increased up to a maximum of 16 mg a day.
- If a patient is unable to tolerate loperamide due to symptomatic constipation, loperamide should be held until after the first bowel movement and then resumed at a dose reduced by one level.
- For recurrent symptomatic constipation events, hold loperamide until after the first bowel movement and then resume at a dose reduced to the next lower dose level.
- If a patient is unable to tolerate once-daily loperamide due to constipation, hold loperamide and discuss subsequent loperamide dosing with the Medical Monitor.
- Neratinib dosing should continue if loperamide is held.

Recommended dose reductions for loperamide are listed in Table 5.

Table 5: Loperamide Dose Reduction Levels for Constipation

Dose Level	Loperamide Dose	Tablets/Capsules per Day
0	4 mg TID	6 tablets/capsules a day
-1	4 mg BID	4 tablets/capsules a day
-2	2 mg TID	3 tablets/capsules a day
-3	2 mg BID	2 tablets/capsules a day
-4	2 mg once a day	1 tablet/capsule a day

Abbreviations: BID = twice daily; mg = milligrams; TID = three times daily

If a patient experiences an AE leading to dose interruption of neratinib for reasons other than diarrhea, consider holding loperamide until neratinib treatment is resumed.

6.3. Capecitabine

Patients with mBC will receive capecitabine, beginning in Cycle 2 of treatment (i.e., following completion of the second study colonoscopy procedure and biopsy).

Capecitabine is available at 150 mg and 500 mg film-coated tablets.

Capecitabine (total dose of 1500 mg/m^2 daily, administered as 750 mg/m^2 in approximately evenly divided doses) will be self-administered orally by patients starting with Cycle 2/Day 1 (i.e. following completion of the second study colonoscopy procedure and biopsy). Doses are to

be taken daily on Days 1 to 14 of each 21-day cycle. Capecitabine should be taken with water within 30 minutes after a meal.

During treatment with neratinib plus capecitabine, patients should be monitored for conditions that may require dose to be held or discontinued as described in Appendix 2. Careful attention should be paid to the onset of diarrhea or hand-foot syndrome in particular, and early dose adjustment or prophylactic therapy should be implemented as described in Appendix 2.

Daily dose of neratinib plus capecitabine should continue until a criterion for treatment withdrawal or study withdrawal is met (see Section 10.1 and Section 10.2, respectively).

Refer to the capecitabine (Xeloda®) US Package Insert and/or the SPC for further information on dosing, safety assessments and toxicity management.

6.3.1. Dose Adjustment

Investigational product dose adjustment and/or discontinuation should be performed according to Appendix 2 and Section 10.1.

Recommended dose reductions for the -1 and -2 dose levels of capecitabine in combination with neratinib are listed in Table 6.

Table 6: Dose Reduction Levels for Capecitabine-Related Toxicity (When Administered in Combination with Neratinib)

Dose Level	Capecitabine (administered in combination with neratinib)
Starting Dose	1500 mg/m^2, 750 mg/m^2 BID
-1[aa]	1100 mg/m^2, 550 mg/m^2 BID
-2[a]	750 mg/m^2, 375 mg/m^2 BID

Abbreviation: BID: twice daily

[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) (to 75% [level -1] or 50% [level -2] of the starting dose) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

6.4. Packaging, Labeling, and Storage

6.4.1. Neratinib

Neratinib will be supplied as 40-mg, film-coated tablets packaged in bottles with desiccant.

Neratinib should be stored at 25°C (77°F) or below; do not freeze. Neratinib should be stored with desiccant. Excursions are permitted from 15°C (59°F) to 30°C (86°F). Neratinib should be stored in a secure location with limited access. Patients should be instructed to store neratinib in a safe place at room temperature.

Detailed packaging information is available in the study reference manuals. Neratinib will be labeled according to local regulations and include the study number.

6.4.2. Loperamide

Commercially available loperamide will be provided to the subjects by the study sites.

6.4.3. Capecitabine

Commercially available capecitabine will be provided to the subjects with mBC by the study sites.

6.5. Drug Accountability and Treatment Compliance

The study site must maintain accurate records documenting dates and quantities of investigational product, capecitabine and loperamide supplied/ reimbursed by the Sponsor. Records must also be maintained documenting dates and quantities (i.e., pill counts) of neratinib, capecitabine and loperamide received, dispensed (per-patient), and returned (per-patient). Such documentation should permit a running log of the receipt and per-patient disposition of all investigational products on site. Any investigational product, capecitabine or loperamide accidentally or deliberately destroyed must also be documented.

Throughout the study, reconciliation will be made between the amounts of neratinib, capecitabine and loperamide supplied, dispensed, returned, and subsequently destroyed or returned to the Sponsor. All investigational products, capecitabine and loperamide will be returned to Sponsor or its representative, or destroyed at the site in accordance with local standard operating procedures, as specified in writing by the Sponsor.

Individual patient dosing compliance should be reviewed and documented at each study visit by study site staff. If patient non-compliance is noted, the patient should be re-instructed regarding proper dosing procedures in order to continue in the study. If repeated non-compliance is noted, additional steps may be taken, including withdrawal of the patient from the study (see Section 10.2).

7. CONCOMITANT MEDICATIONS

All concomitant medications and concomitant nonpharmacological treatments/therapies will be recorded at screening from 28 days prior to the signing of the informed consent form (ICF), on Day 1 of Cycle 1 through completion of the second study colonoscopy procedure. This will include the start date, stop date, generic name, route of administration, dose and indication for treatment. At screening, patients will be asked what medications they have taken during the previous 28 days and which medications are ongoing at the time of screening.

7.1. Permitted Concomitant Treatment

Any palliative and/or supportive care for cancer-related symptoms, which are not otherwise specified in the list of prohibited medications (Section 7.3), or drugs with potential for drug-drug interactions (Section 7.4), or in the associated Appendices (Appendix 4, Appendix 5, Appendix 6), including hormonal therapy (eg, tamoxifen, aromatase inhibitors) is permitted at the Investigator's discretion.

Specifically, the following treatments are permitted during the study:

- Standard therapies for preexisting medical conditions and for medical and/or surgical complications. All medication(s) as well as dose and length of therapy should be recorded in the case report form (CRF).
- Adjuvant endocrine therapy is allowed for hormone receptor-positive disease.
- Bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors (eg, denosumab), are allowed regardless of indication.
- Secondary prophylactic use of growth factors (e.g., granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) may be implemented per the American Society of Clinical Oncology guidelines at the Investigator's discretion, if significant neutropenia or febrile neutropenia/infection is observed.

7.2. Required Loperamide Antidiarrheal Therapy

Diarrhea is the major dose-limiting toxicity of neratinib with onset typically occurring early in the course of treatment (during the first few weeks of treatment). Primary prophylactic use of antidiarrheal medication is **mandatory** for all enrolled patients taking neratinib.

As noted in Section 6.2, loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is proposed, this should be discussed with the Medical Monitor and the reason documented in the source documents. Second-line antidiarrheal treatments (diphenoxylate hydrochloride and atropine sulfate) may be used in Cycle 1. Adjunctive therapies (eg, octreotide [SANDOSTATIN®] (or equivalent as approved by the Sponsor) are also recommended for use when appropriate; however, the use of octreotide should be avoided in Cycle 1.

The Investigator must review with the patient the **Patient Instructions** for the management of diarrhea and the **Patient Diary** used by the patient to record daily the number of stools, use of loperamide and/or other anti-diarrheals, and the use of investigational product for the first cycle (28 days) of the study (see Section 8.5.2). Both the patient and the Investigator must sign the

patient instructions for the management of diarrhea. The Patient Instructions and Patient Diary are to be handed to the patient before leaving the site with investigational product on or before Cycle 1/Day 1, with clear instructions to contact the Investigator in the event of *de novo* onset or persistent Grade ≥2 diarrhea to discuss the appropriate course of treatment. The Investigator must also complete and sign the **Investigator Checklist** on or before Cycle 1/Day 1.

Documentation of any occurrences of loose stools or diarrhea must be as precise as possible and captured in the Patient Diary. For AE recording, documentation of "Intermittent" events of diarrhea is limited to Grade 1. If events of Grade 1 diarrhea are separated by 3 days without any diarrhea, then each event must be documented as separate AEs with corresponding start and stop dates.

The entries on the Patient Diary should be reviewed together with the patient. If the patient has experienced diarrhea since the last visit, details of the daily number of unformed stools provided on the diary help to grade the diarrhea as precisely as possible (per NCI CTCAE v.4.0). Also, the daily dose of loperamide (or other antidiarrheals, if applicable) noted on the diary will be reviewed and recorded on the CRF.

Loperamide (along with neratinib) will be dispensed directly by the site on or before Cycle 1/Day 1 and during subsequent visits as needed. It is very important to initiate treatment with loperamide concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

Loperamide Prophylactic Dosing Instructions (Cycle 1)

- Inform patients that they will experience diarrhea while taking neratinib.
- Administer loperamide:
  - The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
  - For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients TID (total 12 mg a day).
  - During weeks 3-4 (days 15-28) loperamide 4 mg will be self-administered BID
  - After the first 28 days, loperamide will be self-administered as needed (PRN) (not to exceed 16 mg/day)
- For patients who develop diarrhea during Cycle 1, loperamide should be increased up to a maximum of 16 mg a day.
- At any time during the study, for patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) on a maximum dose of loperamide (16 mg a day), Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by Sponsor).
- For Grade 2 diarrhea during the 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, or during Cycle 2 in patients with mBC and beyond (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection TID, or after initial dose of

short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by intramuscular (IM) injection (equivalent medication may be used with approval of the Sponsor).

- After resolution of diarrhea, loperamide prophylaxis can be increased in 2 mg increments with the goal of titrating to 1-2 bowel movements a day.
- Instruct patients to promptly report diarrhea symptoms.
- Instruct patient to record the number of stools per day and the dose of any anti-diarrheal medication taken each day (see Section 8.5).

For new onset uncomplicated Grade 1 or Grade 2 diarrhea

Dietetic measures

- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day (~2000 mL).
- Eat frequent small meals.
- Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.

Pharmacological treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea-free for 12 hours.
- At any time during the study, for patients with persistent Grade 1 diarrhea on loperamide, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 hours to 8 hours may be added (or equivalent as approved by the Sponsor).
- For 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, or during Cycle 2 in patients with mBC and beyond, for Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneously (SC) TID; or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscularly (IM) (equivalent medication may be used with approval of the Sponsor).

For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia

Dietetic measures (same as above)

Pharmacologic treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea-free for

12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).

- Administer octreotide [100-150 µg SC BID or intravenously (IV) (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID].
- Use IV 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.

The Investigator or designee should contact the Sponsor or the Medical Monitor for advice if at any time there is a concern for the appropriate course of action for the management of diarrhea.

Stool cultures should be done to exclude infectious causes of Grade 3 or Grade 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or Grade 4 neutropenia) per the Investigator's discretion. Results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella*, and *Shigella* testing, when performed, should be reported using the appropriate CRF.

Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction.

7.3. Prohibited Concomitant Treatment

The following treatments are prohibited throughout the duration of the active (treatment) stage/phase of the study:

- Any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments, except hormonal therapy (eg, tamoxifen, aromatase inhibitors), including other investigational agents.
- Acarbose, aspirin, proton pump inhibitors, NSAIDs, histamine H2-receptor antagonists, selective serotonin inhibitors, and ticlopidine (See Section 5.2 Exclusion Criterion 2) are excluded in Cycle 1 and until after the completion of the second study colonoscopy procedure.
- Systemic steroid use, by oral or parenteral route, including budesonide in Cycle 1 until after the completion of the second study colonoscopy procedure.

7.4. Potential for Drug-Drug Interactions

Patients should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (eg, ketoconazole) for the duration of the active stage/phase of the study. Patients should also avoid grapefruit/grapefruit juice and herbal remedies, including St John's Wort. Refer to Appendix 4 for a list of inhibitors and inducers of CYP isoenzymes. If unavoidable, patients taking such agents should be monitored closely.

Patients using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECG) at the Investigator's discretion. Refer to Appendix 6 for a

summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing Torsade's de Pointes (TdP).

Patients taking digoxin, a P-glycoprotein (P-gp) substrate with a narrow therapeutic window, should be monitored closely. The digoxin dose should be adjusted as needed, since neratinib is an inhibitor of P-gp. Co-administration of neratinib with digoxin could result in increased digoxin levels and associated digoxin toxicity. Refer to Appendix 5 for a list of substrates and inhibitors of P-gp.

Patients taking oral coumadin-derivative anticoagulants (i.e., warfarin and phenprocoumon) should be monitored closely and their anticoagulant dose adjusted as needed.

The solubility of neratinib is pH dependent and treatments that alter gastrointestinal pH such as proton pump inhibitors (PPIs), histamine H2-receptor antagonists, and antacids may lower the solubility of neratinib. It has been observed that a single 240-mg dose of neratinib combined with lansoprazole may decrease neratinib AUC by up to 70%. It is unknown whether separating PPI and neratinib doses reduce the interaction. If an H2-receptor antagonist such as ranitidine is required, neratinib should be taken at least 2 hours before the next dose of the H2-receptor antagonist and 10 hours after the H2-receptor antagonist dosing. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 3 hours.

7.5. Treatment Compliance

Refer to Section 6.5.

8. STUDY ASSESSMENTS

8.1. Efficacy Assessment

There are no study mandated imaging requirements. Clinical care is within the purview of the investigator and patient.

8.2. Safety Assessments

8.2.1. Safety Endpoints

- The primary endpoint is descriptive assessment of colon pathology during the first 28 days of neratinib therapy.
- The secondary endpoint is the incidence and severity of diarrhea during the first 28-day cycle.

The incidence of TEAEs and SAEs for Cycle 1 through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and in and Cycle 2 in patients with mBC will also be reported. AEs and SAEs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE), version 4.0 or higher.

After the completion of 28 days following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting and in Cycle 2 in patients with mBC through 28 calendar days after the last administration of neratinib, only SAE data will be collected and summarized. SAEs will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to administration of neratinib, it should be promptly reported. All SAEs must be reported within 24 hours of awareness of the event using the SAE Report Form. More details on AEs can be found in Section 13.

SAEs will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to administration of neratinib, it should be promptly reported. All SAEs must be reported within 24 hours of awareness of the event using the SAE Report Form. More details on AEs can be found in Section 13.

Safety will also be assessed based on medical history, vital sign measurements, physical examination findings, and laboratory assessments. Refer to the Schedule of Procedures (Appendix 1) for time points.

The diary used for recording of investigational product intake will also be used by patients to document any other study treatment. In case of diarrhea, it also serves to document the number of loose stools per day, and use of loperamide/other antidiarrheal treatments taken.

8.2.2. Colonoscopy

Microscopic colitis (MC) is a relatively common cause of chronic watery diarrhea. The diagnosis is based upon characteristic histological findings in the presence of diarrhea. The symptoms of

MC are non-specific; therefore, colon biopsies are required to definitively distinguish MC from the much more common irritable bowel syndrome.

To characterize pathology of the colonic mucosa in patients with HER2 positive breast cancer treated with neratinib, colonoscopy in this study will be performed prior to the first dose of neratinib (Cycle 1 Day 1) and on Day 30 (± 3 days) (Appendix 1).

During colonoscopy, photographs of the colonic mucosa will be taken along with approximately 8 biopsies from the terminal ileum, cecum, ascending colon, proximal transverse colon, splenic flexure, sigmoid colon, and rectum. If any abnormal appearing colon mucosa is identified endoscopically, it will be noted and biopsied in a separate jar. If polyps are identified, they will be removed during the examination; if cancer is identified, it will be sampled. Usual, standard clinical care will be provided for endoscopic findings unrelated to the study aims. Biopsy material will be analyzed in a central laboratory. At the time of colonoscopy, serological inflammatory markers (ESR, CRP) will be sampled and stool markers for diarrhea (fecal calprotectin, fecal elastase) will be collected.

Results for appearance, histology, and pathology should be reported using the appropriate CRF.

Descriptions of photography, biopsy and tissue collection, and histology procedures are provided in the Biopsy Collection and Processing Manual.

8.2.3. Laboratory Assessments

Laboratory testing will be performed in accordance with the Schedule of Procedures (Appendix 1).

The institutional laboratory will analyze all laboratory endpoints from samples collected.

Screening laboratory results may be accepted as the baseline assessment if they are performed within 72 hours of initiation of enrollment.

The following laboratory endpoints will be determined, as summarized in Table 7.

Table 7: Laboratory Parameters

Hematology	Hematocrit (Hct) Hemoglobin (Hb) Platelet count Red blood cell (RBC) count White blood cell (WBC) count, with differential	
Clinical chemistry	Albumin Alkaline phosphatase ALT AST Blood urea nitrogen (BUN) Calcium Chloride Creatinine Glucose (non-fasting)	Lactate dehydrogenase (LDH) Magnesium Phosphorus Potassium Sodium Total bilirubin Serum lipase Serum amylase

Table 7: Laboratory Parameters (Continued)

Hematology	Hematocrit (Hct) Hemoglobin (Hb) Platelet count Red blood cell (RBC) count White blood cell (WBC) count, with differential
Serum or urine pregnancy test	In women of child-bearing capacity (at screening and second test within 72 hours prior to C1D1).
Coagulation	International Normalized Ratio (INR)
Inflammatory markers	ESR, CRP, fecal calprotein, fecal elastase

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a nonclinically significant level deemed acceptable by the Investigator and the Sponsor Medical Monitor (or his/her designated representative), or until a diagnosis that explains them is made.

Criteria for reporting abnormal laboratory values as AEs are summarized in Section 13.1.2.

The total volume of blood collected from each patient during the course of the study will be dependent upon the number of treatment cycles the patient completes. For patients receiving neratinib as monotherapy in the adjuvant setting who complete 1 year of treatment, approximately 50 mL of blood, corresponding to approximately 15 mL blood during screening, 15 mL on Day 1/Cycle 1 and 5 mL blood approximately every 3 months up to 1 year will be sampled. For patients with mBC, 15 mL of blood will be sampled at screening and on Day 1 of each treatment 21-day treatment cycle.

8.2.4. Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Appendix 1):

- Blood pressure (systolic and diastolic; mmHg)
- Resting heart rate (beats per minute)
- Body temperature (°C), [oral]
- Respiration rate
- Weight (kg)
- Height (screening only)

Vital signs will be measured after resting in a seated position for 5 minutes, prior to dosing.

8.2.5. Physical Examination

Physical examinations will be performed in accordance with the Schedule of Procedures (Appendix 1).

8.2.6. Electrocardiogram

Single standard 12-lead digital ECGs will be performed in accordance with the Schedule of Procedures (Appendix 1).

The ECG (measured after resting in a supine position for 5 minutes) will include heart rate, rhythm and RR, PR, QRS, 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.

8.2.7. Left Ventricular Ejection Fraction (LVEF)

MUGA scan or ECHO scans to determine LVEF will be performed in accordance with the Schedule of Procedures (Appendix 1). It is strongly recommended to use the same method of measurement for the same patient throughout the duration of the study.

8.3. Other Study Assessments

8.3.1. Health Outcomes Assessments

None.

8.3.2. Disease Recurrence or Progression

Clinical documentation of recurrence or progression, including date and site of recurrence or progression, will be collected at the EOT visit.

8.4. Protocol Deviations

Protocol deviations should be reported to the Sponsor (or designee) as they occur or are discovered and should be captured in CRFs at the time of monitoring and medical review of data line listings.

8.5. Study Drug Accountability/Patient Diary

8.5.1. Study Medication Accountability

The study site must maintain accurate records documenting dates and quantities of medicinal product received from the Sponsor. On a per patient basis, records must be maintained documenting dates and quantities of medicinal product dispensed and returned at each study visit. Any medicinal product accidentally or deliberately destroyed must be documented.

Throughout the study, reconciliation will be made between the amount of medicinal product supplied, dispensed, returned, and subsequently destroyed or returned to Sponsor. All medicinal products will be returned to Sponsor or its representative, or destroyed at the site in accordance with local standard operating procedures (SOPs), as specified in writing by the Sponsor.

8.5.2. Patient Diary

A paper patient diary will be provided by the Investigator for the patient to record daily study medication intake for the first cycle. The number of stools per day and the use of antidiarrheal treatment will be recorded in the patient diary during the first 28-day treatment cycle.

9. STUDY CONDUCT

A Schedule of Procedures is provided in Appendix 1.

In addition to the procedures listed below, unscheduled clinic visits and procedures should be performed at the Investigator's discretion to assess symptoms and concerns newly reported by the patient to rule out or confirm potential recurrence, or for the purpose of assessing the patient's safety.

9.1. Screening/Baseline

Screening activities are to be conducted within 28 days prior to Cycle 1/Day 1, except for serum or urine pregnancy test for women of child-bearing potential (see Inclusion Criterion 7 in Section 5.1), which should be performed, both, at screening and repeated within 72 hours prior to Cycle 1/Day 1.

Documentation of locally assessed ERBB2-amplified status by fluorescence in situ hybridization (FISH) (>2.2) or ERBB2 overexpression by immunohistochemistry (IHC) (3+) by a validated approved method (Wolff et al, 2013) must be confirmed.

The following information/assessments will be collected/recorded at Screening:

- Medical history:
  - Presence of chronic conditions and/or medical history of significance (include review of history of cardiac, pulmonary, and gastrointestinal disease) including relevant surgical procedures.
  - Assessment of bowel movements experienced during the previous 28 days as well as those ongoing at the time of screening
  - Cancer history, including but not limited to, date of first diagnosis, histology, tumor stage, and previous chemotherapy/biotherapy/immunotherapy exposure.
  - Other previous and concomitant medication will be documented, as described in Section 7.
- Demography: sex, ethnicity, and race (Asian, Black or African American, White, Other).
- Physical examination; refer to Section 8.2.5.
- Vital signs, including height and weight; refer to Section 8.2.4.
- ECG; refer to Section 8.2.6.
- LVEF; refer to Section 8.2.7.
- Laboratory tests; refer to Section 8.2.3.
- Colonoscopy; refer to Section 8.2.2.
- ECOG status will be assessed in accordance with the Schedule of Procedures (Appendix 1). The ECOG categories are summarized in 0.

The Cycle 1/Day 1 physical examination and blood sample may be omitted if the screening values were obtained within 72 hours prior to initiation of treatment.

9.2. Active Treatment Phase

Neratinib will be self-administered by patients daily during each 28-day cycle.

The following will be performed in accordance with the Schedule of Procedures (Appendix 1):

- Serum or urine pregnancy testing; refer to Inclusion Criterion 7 in Section 5.1 and Section 8.2.3.
- Brief, symptom-guided physical examination; refer to Section 8.2.5.
- Vital signs, including height and weight; refer to Section 8.2.4.
- Laboratory tests; refer to Section 8.2.3.
- Concomitant medication assessment. Refer to Section 7.
- AE assessment. Refer to Section 13.
- Colonoscopy; refer to Section 8.2.2.
- Treatment compliance assessment; refer to Section 6.5.
- Collect Patient Diary at C2D1 visit.

9.3. Treatment Discontinuation or End-of-Treatment Assessments

The EOT visit will occur within 5 business days of the last dose of neratinib monotherapy in patients with Stage 1 to 3c disease receiving extended adjuvant therapy and within 0-3 days after the last dose neratinib in patients with mBC. When a patient discontinues study treatment for reasons of toxicity, disease progression, or other reasons, an EOT visit will occur within 5 business days of last dose of neratinib.

The following will be performed in accordance with the Schedule of Procedures (Appendix 1):

- AE assessment; refer to Section 13.
- Physical examination; refer to Section 8.2.5.
- Vital signs, including weight. Refer to Section 8.2.4.
- Disease recurrence as applicable. Refer to Section 8.3.2.

9.4. Safety Follow-up Visit

Patients who complete the active treatment phase or who discontinue due to unacceptable toxicity will be followed-up for 28 days after the last dose of neratinib to collect SAEs.

9.5. Long-term Follow-up

Not applicable for this study.

9.6. End of Study

The study will end when all patients have been followed-up for 28 days after the last dose of neratinib. The end of study (EOS) is defined as the last safety follow-up visit of the last patient or the completion of any/all follow-up monitoring and data collection described in the protocol.

In the event that EOS is declared earlier other than safety, patients with stage 1 to 3c disease will be offered the opportunity to complete the 1-year course of treatment while patients with mBC will be offered the opportunity to complete therapy until disease progression or unacceptable toxicity.

10. PATIENT WITHDRAWAL AND REPLACEMENT

10.1. Investigational Product Discontinuation

Patients **must** be discontinued from **investigational product** under the following circumstances listed below and in Appendix 2, unless otherwise agreed with the Medical Monitor:

- If the patient requires more than 2 dose reductions of neratinib (see Appendix 2)
- If neratinib is withheld due to an SAEs for >28 days. Patients who are clinically benefiting from therapy with neratinib may be resumed on therapy after 28 days if approved in advance by the Sponsor
- Disease recurrence
- Initiation of alternative anti-cancer therapy. Any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents (see Section 7.3).
- Pregnancy (see Section 13.4)
- Investigator request
- Patient request (i.e., withdrawal of consent for treatment)
- AEs/toxicity

Withdrawal due to AE should be distinguished from withdrawal due to other causes, and recorded on the appropriate AE page of CRF. If a patient withdraws due to toxicity, even if discontinuation is not otherwise required per protocol guidelines, the withdrawal should be classified as withdrawal due to AE.

10.2. Withdrawal from the Study

Patients may withdraw from the entire study including follow up at any time without penalty and for any reason without prejudice to his or her future medical care.

Patients may be required to withdraw from the study after discussion with the Sponsor and/or Investigator (whenever possible) for the following reasons:

- At the discretion of the Investigator
- At patient's request (withdrawal of consent for the study) (see Section 10.3)
- Lost to follow-up (defined as after three attempts at contact by phone followed by one attempt by sending a certified letter)
- If the entire study is terminated prematurely as described in Section 11
- Inability to complete a second study colonoscopy procedure

A patient may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or IRBs/IECs.

10.3. Procedures for Investigational Product Discontinuation/Study Withdrawal

When a patient is withdrawn from the study, the Investigator will notify the Sponsor. In all cases, the reason(s) for premature discontinuation/withdrawal, and the primary reason, must be recorded on the CRF. If a patient is prematurely withdrawn from the investigational product or the study for any reason, the Investigator must make every effort to perform the evaluations described for the EOT visit (performed within 5 days of the last dose of investigational product as appropriate). If a patient discontinues due to an AE, he/she should be strongly encouraged to undergo the EOT assessments and continue to be under medical supervision until symptoms cease or the condition becomes stable.

If a patient is lost to follow-up, or voluntarily withdraws from study participation, every effort should be made to determine why a patient is lost to follow-up or withdraws consent. This information, including the date, should also be recorded on the patient's conclusion of patient participation CRF.

All patients will remain on active study treatment until a cause of early treatment discontinuation occurs; these include disease progression, unacceptable toxicity, and withdrawal of consent (Section 10), or until study closure.

10.4. Patient Replacement

Patients who do not complete 2 consecutive colonoscopies with successful biopsy collection will be replaced.

11. PREMATURE TERMINATION OF STUDY

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. Investigational product will be available to patients to complete treatment as described in Section 4.2.

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 or have them destroyed locally according to Sponsor guidelines. 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 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.

12. STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

12.1. Study Patients

Descriptive statistics will be used to characterize the patient cohort. Demographic data, medical history, concomitant disease, and concomitant medication will be summarized by means of descriptive statistics for continuous variables (n, mean, standard deviation, median, minimum and maximum) and frequency tables for categorical variables.

Duration of treatment will be summarized. The number of patients with dose holds, dose reductions, a summary of diarrhea and other GI events will be tabulated. Treatment discontinuation and the reasons for discontinuation will be summarized.

12.2. Efficacy Analyses

Not applicable for this study.

12.3. Safety Analyses

All patients who receive a dose of neratinib will be analyzed for safety. The incidence of TEAEs and SAEs for Cycle 1 through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and following the completion of Cycle 2 in patients with mBC will be summarized after all biopsies have been completed. Following 28 days of neratinib monotherapy after the completion of the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and Cycle 2 in patients with mBC through 28 calendar days after the last administration of neratinib, only SAE data will be collected and summarized.

AEs will be coded using the Medical Dictionary for Regulatory Activities MedDRA coding system and all AEs will be graded by the Investigator according to the NCI-CTCAE version 4.0.

Incidence of AEs will be summarized by system organ class (SOC) and preferred term (PT), and will be summarized by grade. A patient who experiences the same AE more than once within a SOC or preferred term category will be counted only once, using the worst toxicity grade for that event. SAEs will be summarized.

Serious AE and deaths will be provided in a listing. All AEs resulting in discontinuation of neratinib in Cycle 1 through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and following the completion of Cycle 2 in patients with mBC, dose modification, dosing interruption, and/or treatment delay of investigational product will also be listed and tabulated by PT.

Laboratory test results will be collected at screening and on Day 1/Cycle 1 and Cycle 2. On-study laboratory test abnormalities reported during screening, Cycle 1 and Cycle 2 will be summarized. In subsequent visits only liver function tests will be collected.

12.3.1. Primary Endpoint

The primary endpoint is change from baseline in pathological findings in colon biopsies after the first 28 days of neratinib monotherapy. The primary analysis of pathology findings will be conducted after all patients have completed 2 colonoscopies with associated biopsies.

12.3.2. Secondary Endpoints

The secondary endpoints are the incidence and severity of diarrhea summarized according to the NCI-CTCAE version 4.0 in the first 28-day cycle of neratinib treatment and change from baseline at the time of the first colonoscopy (prior to initiation of therapy with neratinib) to the second study colonoscopy procedure in serological and fecal inflammatory markers. The primary analysis of the incidence and severity of diarrhea and inflammatory markers will be conducted after all patients have completed 2 colonoscopies and all samples have been collected and analyzed.

12.4. Final Analysis

The final analysis will be conducted when all patients with stage 1 to 3c disease have completed 1 year of study treatment or have met other specified withdrawal criteria and patients with mBC have completed study treatment, discontinued treatment or met other specified withdrawal criterion.

12.5. Determination of Sample Size

Based on feasibility, 3-5 patients are to be enrolled in this study.

13. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

All observed or volunteered AEs regardless of treatment group or causal relationship to investigational product will be recorded on the AE page(s) of the CRF.

13.1. Definitions

13.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product (definition per International Conference on Harmonisation [ICH] E2A and E6 R1).

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology on the AE CRF page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see Section 13.3 on SAEs) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AE.

13.1.2. Abnormal Laboratory Results

The criteria for determining whether an abnormal laboratory test result should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or,
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting an AE), and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Test result leads to any of the outcomes included in the definition of a SAE, and/or
- Test result is considered to be an AE by the Investigator or by the Sponsor

Any abnormal test result that is determined to be an error does not require reporting as an AE, even if it did meet one of the above criteria except for when the test result leads to any of the outcomes included in the definition of a SAE. Clinically significant laboratory results must be recorded in the patient's CRF.

13.1.3. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose (ICH E2A and E6 R2):

- Results in death
- Is life-threatening
  This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the SAE definition.

13.1.4. Hospitalization

Any inpatient hospital admission that includes a minimum of an overnight stay to a healthcare facility meets the criteria for 'hospitalization'. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

The following are <u>not</u> considered to be hospitalization:

- Rehabilitation facilities
- Hospice facilities
- Respite care (eg, caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient /same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality)
- Social admission (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly physical examination)
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation and/or for the individual patient
- Admission exclusively for the administration of blood products

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

13.1.5. Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are events which are serious as per the above criteria, the nature or severity of which is not consistent with the applicable product information (eg, IB) and are judged by the Investigator or by the Sponsor to be related to investigational product. For a non-Sponsored investigational product (eg, a comparator product) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/SmPC.

13.1.6. Severity Assessment

Adverse events will be graded by the Investigator according to the NCI CTCAE v.4.0 (Publish Date: May 28, 2009, http://ctep.cancer.gov/reporting/ctc.html), according to the following general categories:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious adverse event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it meets one of the criteria for SAEs, listed above.

13.1.7. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF and report such an assessment in accordance with the serious adverse reporting requirements, if applicable.
A suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 13.2). If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (eg, investigational product or other illness). The relationship of the AE to the study treatment (investigational product, comparator or placebo [as applicable]) will be assessed following the definitions below:

- 'No' (unrelated): Any event that does not follow a reasonable temporal sequence from administration of investigational product AND is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- 'Yes' (related): Any reaction that follows a reasonable temporal sequence from administration of investigational product AND follows a known response pattern to the suspected investigational product AND recurs with re-challenge, AND/OR is improved by stopping the investigational product or reducing the dose.

In addition, if the Investigator determines an AE is associated with study procedures, the Investigator must record this causal relationship on the AE CRF page and report such an assessment in accordance with the SAE reporting requirements, if applicable.

13.1.8. Special Reporting Situations

Safety events of interest on the Sponsor's investigational product that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of an investigational product
- Suspected abuse/misuse of an investigational product
- Inadvertent or accidental exposure to an investigational product
- Medication error that may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength
- Suspected transmission via an investigational product of an infectious agent

Special reporting situations should be recorded on the AE CRF page. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE form and reported as required (see Section 13.3).

13.2. Reporting Adverse Events

For serious and non-serious AEs, the reporting period to the Sponsor (or its designated representative) begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through 28 calendar days after the last administration of the investigational product.

For all AEs with causal relationship to the investigational product, follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at the level acceptable to the Investigator, and the Sponsor concurs with that assessment.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

13.3. Reporting Serious Adverse Events

All SAEs, irrespective of relationship to investigational product, must be reported within 24 hours of discovery or notification of the event to the Sponsor or designated representative using the SAE form. The SAE form must be signed by the Investigator. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to follow-up information on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases. For SAE reporting information, please refer to the Study Contact List which is provided as a separate document.

Relevant medical records should be provided to the Sponsor or its designated representative as soon as they become available; autopsy reports should be provided for deaths if available.

Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to neratinib administration, it should be promptly reported.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

13.4. Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate Exposure In Utero (EIU) form.

For investigational products and for marketed products used as investigational product in neratinib studies, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed (eg, environmental exposure) to the investigational product, or the female becomes or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure) for 28 days after last dose of or exposure to neratinib.
- A male partner of a pregnant female has been exposed to the investigational product, either due to treatment or environmental exposure, within 3 months prior to the time of conception and/or is exposed during his partner’s pregnancy (paternal exposure).

If any study patient or study patient’s partner becomes or is found to be pregnant during the study patient’s treatment with the investigational product or exposure as defined above, the Investigator must submit this information on an EIU form to the Sponsor (or its designated representative). In addition, the Investigator must submit information regarding environmental exposure to an investigational product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see following information related to induce termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify the Sponsor or

its designated representative of the outcome as a follow-up to the initial EIU form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [including that in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant's death as related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

13.5. Sponsor Reporting Requirements to Health Authorities and IRB/IEC

The Sponsor assumes responsibility for reporting of AEs including SUSARs according to local and international regulations, as appropriate. The Investigator (or the Sponsor where required) must report these events to the appropriate IRB/IEC that approved the protocol unless otherwise required and documented by the IRB/IEC.

14. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

The Sponsor of this study may delegate some administrative aspects of this study to a duly authorized representative including, but not limited to, study initiation, monitoring, and management of SAE reports.

14.1. Data Collection, Processing, and Monitoring

14.1.1. Case Report Forms and Source Documentation

All data captured for the study is planned to be electronic using the Electronic Data Capture system.

eCRFs will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided by the Sponsor or designated representative.

The Investigator is responsible for maintaining adequate and accurate eCRFs which have been designed to record all observations and other data pertinent to the clinical investigation. Visit data should be entered into the eCRFs within 5 business days. Each eCRF should be completed by the Investigator or delegate as stated in the Site Delegation List.

The site will perform data entry of all eCRFs as per source documents. Completion Instructions for eCRFs will be provided for the Study Coordinator's use. Once the site monitor has verified the contents of the completed eCRF pages against the source data, queries may be raised if the data are unclear or contradictory. These queries must be addressed by the Investigator and verified by the clinical research associate (CRA). After all the data issues are resolved, these eCRFs may be locked to prevent any further data changes. At the end of the study or prior to the site closeout visit, the Investigator will review and approve the data for completeness and accuracy.

14.1.2. Study Monitoring and Access to Source Documentation

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), other national authorities (eg, the United Kingdom Medicines and Healthcare products Regulatory Agency, the German Federal Institute for Drugs and Medical Devices, and local health authorities as applicable, the Sponsor and representatives, and the IRB/IEC for each study site. The Investigator will permit authorized representatives of the Sponsor, the respective national or local health authorities, and auditors to inspect facilities and records relevant to this study.

The Sponsor or representative's monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. Source data to be reviewed during this study will include, but is not restricted to: patient's medical file, patient's diary cards (if applicable), and original laboratory test, histology, and pathology reports. All key data must be recorded in the patient's hospital notes.

Auditors, IRB/IEC and/or regulatory inspectors will also have access to the CRFs and source documents. The ICF will include a statement by which the patient allows the

monitor/auditor/inspector from the IRB/IEC or regulatory authority access to source data (eg, patient's medical file, appointment books, original laboratory test reports, X-rays, etc.) that substantiate information in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal drug information.

14.1.3. Data Quality Assurance

During and/or after completion of the study, quality assurance auditor(s) named by the Sponsor or the regulatory authorities may wish to perform on-site audits. The Investigators will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor's representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6 Good Clinical Practice (GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6), US Investigational Drugs (21 CFR§50, §54, §56, and §312), EU Clinical Studies Directive (Directive 2001/20/EC), and applicable regional regulatory requirements.

14.1.4. Data Processing

All data will be entered by site personnel into the electronic data capture system/CRF (as detailed in Section 14.1.1).

The data-review and data-handling document will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors.

The data management plan will include specifications for data review and data consistency. Outstanding query reports will be sent to the study monitors for resolution by site personnel.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The versions of the coding dictionaries will be provided in the Clinical Study Report (CSR).

14.1.5. Retention of Data and Study Records

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, ICFs, laboratory test results, and drug inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or

at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by agreement with the Sponsor. The Investigator should obtain written permission from the Sponsor prior to the destruction of any study document.

These records should be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with 21 CFR §312.68 or other National Regulatory Authorities.

14.2. Ethical Aspects

14.2.1. Good Clinical Practice and Ethical Conduct of the Study

This protocol accords with the principles of the World Medical Association Declaration of Helsinki as set forth at the 18th General Assembly (World Medical Association Declaration of Helsinki, Helsinki, Finland, 1964) and amendments thereto. The most current amended version will be in effect.

The procedures set out in this study protocol are also designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, the Directives of the European Union, and in keeping with local legal requirements.

The study will not commence without the prior written approval of a properly constituted IRB/IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

14.2.2. Informed Consent Responsibilities

It is the responsibility of the Investigator to obtain written informed consent from the patient or patient's legal representative. If informed consent has not been obtained, then no protocol required procedures are to be performed on the patient and no patient data are to be transferred to the Sponsor. Documentation of informed consent must be recorded in the source documents for each patient.

The study will be discussed with the patient, and the patient will receive written information and an explanation of what the study involves, i.e., the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. If applicable, the information will be provided in a certified translation of the local language.

A signed, IRB/IEC approved ICF must be obtained from patient before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record. Signed ICFs must remain in each patient's study file and must be available for verification by study monitors at any time. A copy of the fully signed ICFs will be given to the patient.

If the IRB/IEC requires modification of this form, the documentation supporting this requirement must be provided to the Sponsor, along with the new version. The Sponsor reserves the right to reject these modifications, should they not cover the minimum information required by ICH GCP.

A patient wishing to participate must also provide Authorization for Use and Release of Health and Research Study Information prior to any study-related procedures or change in treatment.

If a patient is not physically or mentally competent to understand and to give their informed consent to participate in the study (eg, is blind or illiterate), a legally acceptable representative or impartial witness as applicable, may sign the ICF on behalf of the patient. It remains the responsibility of the principal Investigator to assure that the patient is suitable for inclusion in this study and will be able to adhere to all study procedures throughout the course of the study.

The explicit wish of a minor, or mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be respected by the Investigator.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB/IEC, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

14.2.3. Confidentiality of Data

Any personal data of the sponsor, principal investigator, site, subject and / or any other individual collected and/or used in connection with the clinical trial, especially including the informed consent forms, will comply with the General Data Protection Regulation (EU) 2016/679 and other applicable data privacy laws and regulations with regard to the processing and transfer of such personal data.

All data used in the study will be anonymized and analysis will be performed on a deidentified patient-level dataset. The data system will be maintained and secured as requested by the local patient privacy regulations of each country participating in the study. Processes assuring data security will be employed during data extraction, storage and back-up. The data and all study documents will be kept until written notification that records may be destroyed.

Computer files will be password protected on computers which are stored in offices locked and accessible to study staff. Only the members of the study staff will have access to the passwords. All parties will ensure protection of subject's personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. All local privacy laws will be followed to ensure confidentiality of data is maintained.

14.3. Other Study Administrative Aspects

14.3.1. Protocol Approval and Protocol Amendment

The protocol (approved by the Sponsor or its representative) will be submitted to the IRB/IEC for review and it must be approved before the study is initiated. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

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 patients. A protocol change intended to eliminate an apparent immediate hazard to patients 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, by the Sponsor and the Investigator.

14.3.2. Investigator Responsibilities

The Investigator undertakes to perform the study in compliance with the protocol, ICH Guidelines per GCP and the applicable regulatory requirements. A copy of the guidelines will be available in the Investigator Site File.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The Investigator should also be able to demonstrate a potential for recruiting the required number of suitable patient within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to the Sponsor (or its representative) before starting the study.

If the patient has a primary physician, the Investigator should, with the patient's consent, inform the primary physician of the patient's participation in the study.

Agreement with the final CSR will be documented by the signed and dated signature of the principal or coordinating Investigator (Lead Investigator of the study) in compliance with ICH E3.

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator agreement to confirm acceptance and willingness to comply with the study protocol.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study. In particular, the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/IEC must be informed of study completion.

It is the responsibility of the Investigator to submit this protocol, the final approved informed consent document (approved by the Sponsor or its representative), relevant supporting information, all types of patient recruitment or advertisement information (approved by the Sponsor or its representative), and any other written information to be provided to the patient to the IRB/IEC for review and these must be approved before the study is initiated. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

On the approval letter, the study (title, protocol number and version), the documents reviewed (protocol, informed consent material, amendments) and the date of review should be clearly stated.

Investigational product supplies will not be released and the patient recruitment will not begin until this written approval has been received by the Sponsor or its designee.

The Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, and at least once a year. The Investigator must also keep the IRB/IEC informed of any serious and significant AEs.

14.3.3. Patient Responsibilities

Data collected during this study may be used to support the development, registration or marketing of neratinib. All data collected during the study will be controlled by the Sponsor (or designee) and the Sponsor will abide by all relevant data protection laws.

After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor and/or the company organizing the research on the Sponsor's behalf to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may additionally be reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number. The results of this study may be used in other countries throughout the world that have ensured an adequate level of protection for personal data.

Written authorization (United States [US] sites only) or written informed consent in accordance with current data protection regulations (EU sites only) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), General Data Protection Regulation (EU) 2016/679("GDPR") and any other state privacy requirements). If the patient is under the legal age of consent, the Authorization must be signed by the legally authorized representative in accordance with the applicable privacy requirements and other state privacy requirements.

14.3.4. Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in neratinib; any significant equity interest in the Sponsor, as defined in the US Code of Federal Regulations (21 CFR §54.2(b)).

In consideration of participation in the study, the Sponsor will pay the Investigator, study site or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

14.3.5. Publication Policy

The Sponsor encourages publication of results derived from the clinical research it sponsors. Publications include a paper in a peer reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting, or making results public by some other means. The Sponsor will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-chairs/Principal Investigator(s) are permitted to publish/present the results of the study, in part or in their entirety, without the written

authorization of the Sponsor. The review is aimed at protecting the Sponsor's pre-existing propriety information and commercial interests.

First Publication

The results of the entire multicenter study shall be presented in a first publication upon completion of the entire multicenter study (data lock), with authorship being determined by the Sponsor and Study Investigators using the criteria defined by the International Committee of Medical Journal Editors. At least two Sponsor representatives will also be included as coauthors on the first publication of the results of the entire multicenter study to allow recognition of the Sponsor's involvement in the design and execution of the study.

Subsequent Publications

Results from data subsets should not be published in advance of the first publication, and must make reference to it. Publications must include at least 2 Sponsor authors to allow recognition of the Sponsor's involvement.

In all publications, the study is to be identified as PUMA-NER-6203. The Study Principal Investigator(s) shall be free to publish or present, subject to the timing described in the Clinical Study Agreement.

15. REFERENCES

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16. SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Officer

Title of Study: An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

Study Number: PUMA-NER-6203

I have read and approve this protocol. 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, regulations, and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

_____
Signature

[redacted] _____
Name (Printed) Date

__[redacted]_____
Title

Declaration of Principal Investigator

Title of Study: An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

Study Number: PUMA-NER-6203

I have read and approve this protocol. 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, regulations, and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

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

_____
Signature

__[redacted]_____ _____
Name (Printed) Date

_____ Univ South Alabama College of Medicine
Title Institution (block letters) and site number

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17. APPENDICES

APPENDIX 1. SCHEDULE OF PROCEDURES

Table A1.1. Schedule of Study Procedures – Neratinib Monotherapy in the Extended Adjuvant Setting

Study Procedures	Screening[a]	Active Treatment[b] Cycle / Day (C/D)				Safety Follow-up Visit
	Days -28 to -1	C1/D1 (28-day cycle)	Colonoscopy 2	Post-second colonoscopy Visit 1-2-3	EOT Visit	28 Days After Last Dose
Study visit window in Days	0	-3[b]	+/-3	Every 3 months ±10	±5	+5
Informed consent[c]	X					
Medical/Cancer history/Demography[d]	X					
ERBB2 status documentation[e]	X					
ECOG performance status	X					
Serum or urine β-hCG[f]	X	X				
Physical examination[g]	X	X	X	X	X	
Vital signs[h]	X	X			X	
CBC plus differential[i]	X	X				
Serum chemistry[j]	X	X				
Liver function tests[k]	X	X		X		
INR	X					
ESR and CRP[l]		X	X			
MUGA or ECHO[m]	X					
ECG (12-lead)	X					
Colonoscopy[n]		X	X			
Fecal calprotein and fecal elastase		X	X			
Concomitant medications or treatments[o]	X	X	X	X		
Neratinib administration[p]		Continuous once-daily dosing (pill count at each visit)				
Loperamide administration[q]		Loperamide dosing during C1	As needed			
Adverse events[r]		X	X----------X			X

Abbreviations: β-hCG=beta-human chorionic gonadotropin; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=cycle; CBC=complete blood count; CRP = C-reactive protein; D=day; ECG= electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Collaborative Oncology Group; eCRF=electronic case report form; EOT = end of treatment; ESR = erythrocyte sedimentation rate; FISH =

fluorescence in situ hybridization ; Hb=hemoglobin; Hct=hematocrit; IHC=immunohistochemistry; INR = International Normalized Ratio; LFT=liver function test; LDH=lactate dehydrogenase; MUGA=multiple-gated acquisition scan; NP=nurse practioner; PA=physician's assistant; RBC=red blood cell; SAE=serious adverse event; TEAE=treatment-emergent adverse event; WBC=white blood cell.

[a] Screening procedures and enrollment may occur on one day, however, enrollment must not be done before all screening procedures have been completed and results confirming eligibility have been reviewed.

[b] Cycle 1 is defined as 28 days. The EOT Visit will be performed as soon as possible, but no later than 5 business days after the last dose and before start of new anticancer regimen. If patient discontinues neratinib for reasons of toxicity or disease progression, all activities indicated for the EOT Visit should be conducted within 5 business days of last dose of neratinib. All visit dates are calculated from the date of first dose. If a visit occurs before or after a scheduled visit date, the next visit is still expected to occur on the date initially calculated for this visit, and is not shifted due to an earlier or later prior visit.

[c] Informed consent must be obtained before any protocol required assessments are performed. Certain procedures done prior to informed consent as part of the standard work-up are acceptable, as long as they have been performed within 28 days from the date of enrollment. Acceptable procedures are: CBC (with differential), serum chemistry, MUGA/ECHO, and ECGs. When obtaining the patient's informed consent, the Investigator must review with the patient the Patient Instructions for the management of diarrhea and the Patient Diary for the patient's daily recording of neratinib dose, any adverse reactions, number of loose stools and use of loperamide and/or other antidiarrheals (adverse reactions, stools, and antidiarrheals are to be documented only for the first cycle [28 days]). Both the patient and the Investigator must sign the patient instructions for the management of diarrhea. Copies of both documents are handed to the patient before she leaves the site with neratinib and loperamide on Cycle 1/Day 1. The Investigator must also complete and sign the Investigator Checklist by Cycle 1/Day 1.

[d] Collect presence of chronic conditions and/or medical history of significance; include review of history of cardiac, pulmonary, and gastrointestinal disease including assessment of bowel movements experienced during the previous 28 days as well as those ongoing at the time of screening, any medical conditions that require medication, and therapies such as chemotherapy/biotherapy/immunotherapy.

[e] Documentation of locally assessed ERBB2-amplified status by FISH (>2.2) or ERBB2 overexpression by IHC (3+) by a validated approved method must be confirmed.

[f] For women of childbearing potential, serum or urine β-hCG test to be performed both at screening and repeated within 72 hours prior to Cycle 1/Day 1. bleeding.

[g] Physical examination may be delegated and performed by a properly trained NP, PA or equivalent. During treatment, brief symptom-guided physical examinations including worsening of medical history conditions will be done approximately every 3 months. As per Section 12.3 beginning with Cycle 3 through the end of the study and during visits scheduled per standard of care, only SAEs will be reported.

[h] Vital signs will be measured after resting in a seated position for 5 minutes, prior to dosing, and will include: blood pressure (systolic and diastolic; mmHg), resting heart rate (beats per minute), body temperature (°C), respiration rate, weight (kg), height (screening only).

[i] CBC to include Hct, Hb, platelet count, RBC and WBC count plus differential. CBCs must be tested at screening and on Day 1 of Cycle 1 (-3 days), and as clinically indicated. The Cycle 1/Day 1 tests do not need to be performed, if the screening tests were done within 72 hours of enrollment.

[j] Serum chemistry tests include sodium, potassium, chloride, calcium, magnesium, BUN or urea, serum creatinine, albumin, LDH, phosphorus, and glucose (non-fasting). The Cycle 1/Day 1 tests do not need to be performed, if the screening tests were done within 72 hours of enrollment.

[k] LFTs must include total bilirubin, ALT, ALP, and AST. LFTs must be tested at screening, on Day 1 of Cycle 1,and approximately every 3 months, and as clinically indicated. Visits for LFT testing should be aligned with CBC testing and other routine study visits when possible. LFTs should also be tested in patients experiencing Grade 3 or higher diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia. During the evaluation of potential hepatotoxicity, bilirubin should be fractionated and prothrombin time should be measured. Also, liver imaging should be obtained for patients with any signs or symptoms of hepatotoxicity and/or Grade 3 or higher LFT elevations, or as clinically indicated. Refer to the guidelines for the management of LFT changes in the main section of the protocol.

[l] ESR and CRP must be collected at the time of the Baseline colonoscopy or prior to initiation of neratinib in Cycle 1 and at the time of the second study colonoscopy procedure after the first 28-day cycle, i.e., Day 1 of Cycle 2 (+ 5 days). If Screening is to be performed within 72 hours of enrollment and the first colonoscopy, ESR and CRP testing may be performed at the time of screening.

[m] During trial participation, ECHO or MUGA will be performed at Screening, and as clinically indicated. It is strongly recommended to use the same method of measurement for the same patient throughout the duration of the study.

[n] Colonoscopy will be performed after eligibility has been confirmed, but prior to administration of the first dose of neratinib on Day 1 of Cycle 1, Andon Day 30 (± 3 days). Oral medications, including the morning dose of neratinib, will be withheld on the day of the colonoscopy as per local standard of care. In addition, biopsies will be collected as described in Section 8.2.2.

[o] Concomitant medications and concomitant nonpharmacological treatments/therapies are recorded at screening from 28 days before signing of the informed consent form, on Day 1 of Cycle 1, on the day before and day of the second study colonoscopy procedure, and on Day 1 of Cycle 3.

[p] Neratinib is to be self-administered as per instructions in Section 6.1.

[q] Loperamide is to be self-administered as per instructions in Section Section 6.4.2. Patients are asked to document administration of neratinib and loperamide in a diary on a daily basis during the first cycle (28 days) of the study, and to return this diary to the site at appropriate visit. Individual patient dosing compliance should be reviewed by study site staff. Investigators must ensure that patients have loperamide on hand when starting to take neratinib. Neratinib will be dispensed directly by the study sites on or before Cycle 1/Day 1 and during subsequent visits as needed. Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is used, the reason must be documented in the source documents. Acceptable reasons are non-tolerance of loperamide or lack of efficacy.

[r] From the signing of the informed consent form through 28 days of neratinib monotherapy following the second study colonoscopy procedure in patients with stage 1 to 3c breast cancer treated in the extended adjuvant setting, and in and Cycle 2 in patients with mBC, TEAEs and SAEs will be monitored continuously and recorded in the eCRF. Patients must use the diary to document any episodes of diarrhea for the first cycle (28 days) of the study.

[r] After the completion of Cycle 2 through 28 calendar days after the last administration of neratinib, only SAE data will be collected. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to administration of neratinib, it should be promptly reported. All SAEs must be reported within 24 hours of awareness of the event using the SAE Report Form.

Table A1.2. Schedule of Study Procedures – Neratinib In Combination with Capecitabine in Metastatic Breast Cancer

Study Procedures	Screening[b]	Active Treatment[a] Cycle / Day (C/D)				Treatment Discontinuation	Safety Follow-up Contact
	Days -28 to -1	C1/D1 (28-day)	C2/D1 (21-day)	Colonoscopy 2	C3+ (21-day)[q,r]	0-3 Days After Last Dose	28 Days After Last Dose
Study visit window in Days	0	-3[b]	±5		±5		±5
Informed consent[c]	X						
Medical/Cancer history/Demography[d]	X						
ERBB2 status documentation[e]	X						
ECOG performance status	X						
Serum or urine β-hCG[f]	X	X					
Physical examination	X	X[g]	X[g]		X[g]	X[g]	
Vital signs[h]	X	X	X		X	X	
CBC plus differential[i]	X	X			X	X	
Serum chemistry[j]	X	X			X	X	
Liver function tests[k]	X	X	X		X	X	
INR	X						
ESR and CRP[l]		X		X			
MUGA or ECHO[m]	X				X		
ECG (12-lead)[n]	X				X	X	
Colonoscopy[o]		X		X			
Fecal calprotein and fecal elastase		X		X			
Concomitant medications or treatments[p]	X	X	X	X	X		
Neratinib administration[q]		Continuous once-daily dosing (pill count at each visit)					
Capecitabine[r]			X		X		

Study Procedures	Screening[b]	Active Treatment[a] Cycle / Day (C/D)				Treatment Discontinuation	Safety Follow-up Contact
	Days -28 to -1	C1/D1 (28-day)	C2/D1 (21-day)	Colonoscopy 2	C3+ (21-day)[q,r]	0-3 Days After Last Dose	28 Days After Last Dose
Study visit window in Days	0	-3[b]	±5		±5		±5
Loperamide administration[q]		Loperamide dosing during C1	As needed				
Adverse events[s,t]		X[s]	X[t]----------X				

Abbreviations: β-hCG=beta-human chorionic gonadotropin; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=cycle; CBC=complete blood count; CRP = C-reactive protein; D=day; ECG= electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Collaborative Oncology Group; eCRF=electronic case report form; EOT = end of treatment; ESR = erythrocyte sedimentation rate; FISH= fluorescence in situ hybridization; Hb=hemoglobin; Hct=hematocrit; IHC=immunohistochemistry; INR = International Normalized Ratio; LFT=liver function test; LDH=lactate dehydrogenase; MUGA=multiple-gated acquisition scan; NP=nurse practioner; PA=physician's assistant; RBC=red blood cell; SAE=serious adverse event; TEAE=treatment-emergent adverse event; WBC=white blood cell.

[a] Cycle 1, neratinib monotherapy, is defined as 28 days. Cycle 2 and all subsequent cycles are defined as 21 days. Cycle 2 will begin after the completion of the second study colonoscopy procedure. The Treatment Discontinuation Visit will be performed as soon as possible, but no later than 3 business days after the last dose and before start of new anticancer regimen. All visit dates are calculated from the date of first dose of neratinib. If a visit occurs before or after a scheduled visit date, the next visit is still expected to occur on the date initially calculated for this visit, and is not shifted due to an earlier or later prior visit.

[b] Screening procedures and enrollment may occur on one day, however, enrollment must not be done before all screening procedures have been completed and results confirming eligibility have been reviewed.

[c] Informed consent must be obtained before any protocol required assessments are performed. Certain procedures done prior to informed consent as part of the standard work-up are acceptable, as long as they have been performed within 28 days from the date of enrollment. Acceptable procedures are: CBC (with differential), serum chemistry, MUGA/ECHO, and ECGs. When obtaining the patient's informed consent, the Investigator must review with the patient the Patient Instructions for the management of diarrhea and the Patient Diary for the patient's daily recording of neratinib dose, any adverse reactions, number of loose stools and use of loperamide and/or other antidiarrheals (adverse reactions, stools, and antidiarrheals are to be documented only for the first cycle [21 days]). Both the patient and the Investigator must sign the patient instructions for the management of diarrhea. Copies of both documents are handed to the patient before she leaves the site with neratinib and loperamide on Cycle 1/Day 1. The Investigator must also complete and sign the Investigator Checklist by Cycle 1/Day 1.

[d] Collect presence of chronic conditions and/or medical history of significance (include review of history of cardiac, pulmonary, and gastrointestinal disease experienced during the previous 28 days as well as those ongoing at the time of screening, any medical conditions that require medication, and therapies such as chemotherapy/biotherapy/immunotherapy.

[e] Documentation of locally assessed ERBB2-amplified status by FISH (>2.2) or ERBB2 overexpression by IHC (3+) by a validated approved method must be confirmed.

[f] For women of childbearing potential, serum or urine β-hCG test to be performed both at screening and repeated within 72 hours prior to Cycle 1/Day 1. bleeding.

[g] Physical examination may be delegated and performed by a properly trained NP, PA or equivalent. During treatment, brief symptom-guided physical examinations including worsening of medical history conditions will be done on Day 1 of each cycle. As per Section 12.3 beginning with Cycle 3 through the end of the study and during visits scheduled per standard of care, only SAEs will be reported.

[h] Vital signs will be measured after resting in a seated position for 5 minutes, prior to dosing, and will include: blood pressure (systolic and diastolic; mmHg), resting heart rate (beats per minute), body temperature (°C), respiration rate, weight (kg), and height (screening only).

[i] CBC to include Hct, Hb, platelet count, RBC and WBC count plus differential. CBCs must be tested at screening and on Day 1 of Cycle 1 (-3 days), and as clinically indicated. Visits for CBC testing should be aligned with LFT testing and other routine study visits when possible. The Cycle 1/Day 1 tests do not need to be performed, if the screening tests were done within 72 hours of enrollment.

[j] Serum chemistry tests include sodium, potassium, chloride, calcium, magnesium, BUN or urea, serum creatinine, albumin, LDH, phosphorus, and glucose (non-fasting). The Cycle 1/Day 1 tests do not need to be performed, if the screening tests were done within 72 hours of enrollment.

[k] LFTs must include total bilirubin, ALT, ALP, and AST, as well as serum lipase and serum amylase. LFTs must be tested at screening, on Day 1 of each treatment cycle, and as clinically indicated. Visits for LFT testing should be aligned with CBC testing and other routine study visits when possible. LFTs should also be tested in patients experiencing Grade 3 or higher diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia. During the evaluation of potential hepatotoxicity, bilirubin should be fractionated and prothrombin time should be measured. Also, liver imaging should be obtained for patients with any signs or symptoms of hepatotoxicity and/or Grade 3 or higher LFT elevations, or as clinically indicated. Refer to the guidelines for the management of LFT changes in the main section of the protocol. Patients receiving neratinib and capecitabine on study should be monitored for signs or symptoms related to pancreatitis, including abdominal pain, especially epigastric pain radiating to the back and elevations in serum lipase and serum amylase. Severe pancreatitis can also be accompanied by ecchymotic discoloration of the periumbilical or flank regions, fever, hypotension, and hypoxemia. Serum lipase and (pancreatic) amylase should be measured at baseline and subsequently at any time if pancreatitis is suspected. If pancreatic enzymes are elevated, imaging should be performed in accordance with standard institutional protocols for investigation of acute pancreatitis.

[l] ESR and CRP must be collected at the time of the Baseline colonoscopy or prior to initiation of neratinib in Cycle 1 and at the time of the second study colonoscopy procedure after the first 28-day cycle, ie, Day 1 of Cycle 2 (+ 5 days). If Screening is to be performed within 72 hours of enrollment and the first colonoscopy, ESR and CRP testing may be performed at the time of screening.

[m] During trial participation, ECHO or MUGA will be performed at Screening, and should be repeated at Cycle 3/Day 1, Cycle 6/Day 1, Day 1 of every 6th subsequent cycle, as clinically indicated. It is strongly recommended to use the same method of measurement for the same patient throughout the duration of the study.

[n] ECGs should be performed at Screening, and should be repeated at Cycle 3/Day 1, Cycle 6/Day 1, every 6th subsequent cycle during the active treatment phase, and as clinically indicated. ECG should also be performed at Treatment Discontinuation if not done during the previous 12 weeks. Patients using drugs known to cause QT/QTc prolongation should be monitored closed with serial ECGs at the Investigator's discretion. Refer to Appendix 6 for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing Torsade's de Pointes.

[o] Colonoscopy will be performed after eligibility has been confirmed, but prior to administration of the first dose of neratinib on Day 1 of Cycle 1, and after the first 28-day cycle, i.e., Day 1 of Cycle 2 (+ 5 days). Oral medications, including the morning dose of neratinib on the day of the Day 1/Cycle 2 colonoscopy, will be withheld on the day of the colonoscopy as per local standard of care. In addition, biopsies will be collected as described in Section 8.2.2.

[p] Concomitant medications and concomitant nonpharmacological treatments/therapies are recorded at screening from 28 days before signing of the informed consent form, on Day 1 of Cycle 1, on Day 1 of Cycle 2, on the day before and day of the second study colonoscopy procedure, and on Day 1 of Cycle 3.

[q] Loperamide is to be administered as per instructions in Section 6.2. Patients are asked to document administration of neratinib and loperamide in a diary on a daily basis during the first cycle (28 days) of the study, and to return this diary to the site at appropriate visit. Individual patient dosing compliance should be reviewed by study site staff. Investigators must ensure that patients have loperamide on hand when starting to take neratinib. Neratinib will be dispensed directly by the study sites on or before Cycle 1/Day 1 and during subsequent visits as needed. Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is used, the reason must be documented in the source documents. Acceptable reasons are non-tolerance of loperamide or lack of efficacy.

[r] Capecitabine therapy will begin following the completion of the second study colonoscopy procedure and will be administered on Day 1-14 of each cycle. **Note: capecitabine cannot be administered until after the second study colonoscopy procedure is completed.**

[s] From the signing of the informed consent form through the end of Cycle 2 TEAEs and SAEs will be monitored continuously and recorded in the eCRF. Patients must use the diary to document any episodes of diarrhea for the first cycle (28 days) of the study.

[t] After the completion of Cycle 2 through 28 calendar days after the last administration of neratinib, only SAE data will be collected. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to administration of neratinib, it should be promptly reported. All SAEs must be reported within 24 hours of awareness of the event using the SAE Report Form.

APPENDIX 2. INVESTIGATIONAL PRODUCT DOSE ADJUSTMENT FOR TOXICITY

1. Dose adjustment levels

Recommended dose reductions for the -1 and -2 dose levels of **neratinib** and **capecitabine** are listed in Table 3 in Section 6.1.1 and in Table 6 in Section 6.3.1.

2. Toxicities Requiring Investigational Product Dose Adjustments

General Toxicities:

The guidelines for dose adjustments of **neratinib** and **capecitabine** for general toxicities due to the combination of **neratinib** plus **capecitabine** are shown in Table A2.1.

Table A2.1. General Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE v.4.0	Action
Grade 2 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at the starting dose level.
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 3rd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 4th appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 3rd appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** and **capecitabine** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** and **capecitabine** until resolved to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID). • If the event occurs again despite one dose reduction, permanently discontinued **neratinib.**

Abbreviations: BID: twice daily; NCI CTCAE v4.0, National Cancer Institute Common Terminology for Adverse Events Version 4.0.

Gastrointestinal Toxicity:

Guidelines for adjusting doses of **neratinib** and **capecitabine** in the event of gastrointestinal toxicity diarrhea are shown in Table A2.2.

Table A2.2. Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE V4.0	Action
• **Grade 1 Diarrhea** [Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.] OR • **Grade 2 Diarrhea** [Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline;] lasting <5 days OR • **Grade 3 Diarrhea** [Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline limiting self-care activities of daily living (ADL)] **lasting ≤2 days**	• Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 6.2 and Section 7.2). • Continue **neratinib** and **capecitabine** at full dose. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea (refer to Section 7.2). • Fluid intake of ~2L should be maintained to avoid dehydration. • Once the event resolved to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.
• Persisting and intolerable **Grade 2 Diarrhea** lasting ≥5 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia** OR • **Grade 3 Diarrhea** 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** [Life-threatening consequences; urgent intervention indicated]	• Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 6.2 and Section 7.2). • Hold **neratinib** and **capecitabine** until recovery to ≤ Grade 1 or baseline. • Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea. • Fluid intake of ~2L should be maintained, intravenously if needed. • If recovery occurs: o ≤1 week after withholding treatment, resume same dose of **neratinib** and **capecitabine**. o Within 1-4 weeks after withholding treatment, reduce **neratinib** dose to the next lower dose level and maintain the same dose of **capecitabine**. • If event occurs a 2nd time and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to the next lower dose level and maintain the same dose of **capecitabine**. If neratinib dose has already been reduced, the reduce the dose of capecitabine to 1100 mg/m^{2a} (550 mg/m^2 BID) (maintain same dose of neratinib) • If subsequent events occur, reduce the dose of **neratinib** or **capecitabine** to the next lower dose level in an alternate fashion (i.e., reduce **capecitabine** to 750 mg /m^2 (375 mg/m^2 BID) if **neratinib** was previously reduced, or reduce **neratinib** to 120 mg if **capecitabine** was previously reduced.. • Once the event resolved to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Abbreviations: BID: twice daily; IV: intravenous; L: liter; NCI CTCAE v4.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface are is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Pulmonary Toxicity:

Guidelines for adjusting doses of **neratinib** in the event of pulmonary toxicities are shown in Table A2.3. Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target EGFR ±HER2 (*ERBB2*), including lapatinib, gefitinib, and erlotinib. Rare cases of pneumonitis (0.6%) and lung infiltration (0.4%) have been reported in patients treated with **neratinib** monotherapy, and considered drug-related. Patients receiving **neratinib** should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough, and fever and treated appropriately.

Table A2.3. Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.0	Action
• **Grade 2 Pneumonitis/Interstitial Lung Disease** [Symptomatic; medical intervention indicated; limiting instrumental ADL]	• Hold **neratinib** until recovery to ≤ Grade 1 or baseline. • Reduce **neratinib** to 160 mg or discontinue **neratinib** as per Investigator's best medical judgment.
• **Grade ≥3 Pneumonitis/Interstitial Lung Disease** [Severe symptoms; limiting self-care ADL; oxygen indicated]	• Discontinue **neratinib** permanently.

Abbreviations: NCI CTCAE v4.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Liver Toxicity:

Guidelines for adjustment of **neratinib** and **capecitabine** in the event of liver toxicity are shown in Table A2.4.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

Patients who experience ≥Grade 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time must also be collected during hepatotoxicity evaluation.

Table A2.4. Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.0	Action
Grade 3 ALT (>5 – 20x ULN) **OR** **Grade 3 bilirubin** (>3-10x ULN)	• Hold **neratinib** and **capecitabine** until recovery to ≤ Grade 1 for patients with ALT ≤ Grade 1 at baseline OR ≤ Grade 2 for patients with Grade 2 ALT at baseline. • Evaluate alternative causes. • For patients with ALT ≤ Grade 1 at baseline: Resume **neratinib** at the next lower dose level (160 mg) and **capecitabine** at the next lower dose level (1100 mg/m^2 [550 mg/m^2 BID])[a] if recovery to ≤Grade 1 occurs within 4 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue **neratinib** and **capecitabine**.
Grade 4 ALT (>20x ULN) **OR** **Grade 4 Bilirubin** (>10x ULN)	• Permanently discontinue **neratinib** and **capecitabine**. • Evaluate alternative causes.
ALT >3x ULN AND **Total bilirubin** >2x ULN AND **Alkaline phospatase <**2x ULN (potential Hy's law indicators of drug-induced liver damage)	• Hold **neratinib** and **capecitabine**. The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasm (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, total bilirubin, direct bilirubin, PT and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, concomitant medications, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned above (i.e., ALT > 3 x ULN associated with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN), with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. • Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product. • **These events must be reported as SAEs.**

Abbreviations; ALT=alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; PT: prothrombin time; SAE: serious adverse event; ULN: upper limit of normal.
NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, prothrombin time must be measured, and liver imaging should be considered.

[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface are is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m2 dosing.

Left Ventricular Ejection Fraction Toxicity

Guidelines for dose adjustments of neratinib in the event of abnormalities in LVEF are shown in Table A2.5. LVEF assessments will be performed according to the Schedule of Procedures (Appendix 1). It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each time point for each patient.

Table A2.5: Left Ventricular Ejection Fraction (LVEF) Results Requiring Dose Adjustments of Neratinib

EVENT ON DAY OF SCHEDULED TREATMENT	Action
Asymptomatic absolute decline of LVEF ≥15% from baseline OR absolute decline of LVEF ≥10% ad below the lower limit of normal of 50%	A) If LVEF is 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 every 12 weeks and consider cardiac support with input from cardiologist B) If LVEF is between 40% to 50%: continue **neratinib** with caution and surveillance. Initiate monthly monitoring of LVEF. • If while monitoring, LVEF falls to <40%: Follow bullet point A instructions described above. • If while monitoring, LVEF remains ≥40%: continue **neratinib**, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.
Symptomatic cardiac failure	• **Neratinib** should be discontinued.

Abbreviations: LVEF: left ventricular ejection fraction.

If a patient has a second episode of asymptomatic decline in LVEF that meets either of the above criteria, permanently discontinue **neratinib**, repeat LVEF in 3-4 weeks and consider cardiology consult.

Note that, for AEs other than symptomatic LVEF decline, if **neratinib** is held for >28 days, the patient should be withdrawn from the active treatment phase of the study (see Section 10.1). In case of asymptomatic LVEF decline, patients may resume **neratinib** within 1 week after LVEF recovery is documented as above, even if the timeframe exceeds 3 weeks. If a site does not provide normal ranges for ECHO or MUGA, a lower limit of normal of 50% should be used.

Hematologic Toxicity

Patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with **capecitabine**. If unscheduled laboratory assessments

during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with **capecitabine** should be held.

Guidelines for dose adjustments of capecitabine for hematologic toxicity due to combination of neratinib plus capecitabine are shown in **Table A2.6**.

Table A2.6: Hematologic Abnormalities Requiring Dose Adjustment of Capecitabine (When Administered in Combination with Neratinib)

NCI CTCAE v 4.0	Action
Grade 3 Neutrophil: <1000-500/mm^3; <1-0.5 x 10^9/L Platelet: <50,000-25,000/mm^3; <50-25 x 10^9/L Hemoglobin decreased: <8 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• **Neratinib** should be continued at the same dose • Hold **capecitabine** until event resolves or decreases to Grade 1 or Grade 2 • Reduce next **capecitabine** dose to 1100 mg/m^2 (550 mg/m^2 BID) • If the event recurs a 2nd time, hold **capecitabine** until event resolves or decreases to Grade 1 or Grade 2 • Reduce next **capecitabine** dose of 750 mg/m^2 (375 mg/m^2 BID) • If the event recurs/persists, discontinue **capecitabine** permanently.
Grade 4 Neutrophil: <500/mm^3; <0.5 x 10^9/L Platelet: <25,000/mm^3; <25 x 10^9/L Hemoglobin decreased: life-threatening consequences; urgent intervention indicated	• **Neratinib** should be continued at the same dose. • **Capecitabine** should be discontinued permanently OR if the Investigator deems it to be in the patient's best interest to continue, hold **capecitabine** until resolved to Grade ≤1 • If the Investigator decides to resume **capecitabine**, reduce the dose to 750 mg/m^2 (375 mg/m^2 BID) • If the event recurs/persists, discontinue **capecitabine** permanently

Abbreviations: BID: twice daily; L=liter; NCI CTCAE v 4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Hand and Foot Syndrome

Guidelines for dose adjustments of neratinib and capecitabine for toxicity of Hand and Foot Syndrome (Palmar-Plantar Erythrodysesthesia syndrome) due to combination of neratinib plus capecitabine are show in Table A2.7.

Table A2.7: Hand and Foot Syndrome (Palmar-Plantar Erythrodysesthesia Syndrome) Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE v4.0	Action
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	• Continue **neratinib** and **capecitabine** at starting dose

NCI CTCAE v4.0	Action
Grade 2: Skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain, limiting instrumental ADL. PI: painful erythema and swelling of the hands and/or feet and/or discomfort affecting ADL.	• Continue neratinib at starting dose level and hold capecitabine until recovery or to ≤grade 1, then resume at starting dose. • If the event recurs/persists, continue neratinib at starting dose level and reduce capecitabine dose to 1100 mg/m^2 (550 mg/m^2 BID)

Table A2.7: Hand and Foot Syndrome (Palmar-Plantar Erythrodysesthesia Syndrome) Requiring Dose Adjustment of Neratinib and Capecitabine (Continued)

NCI CTCAE v4.0	Action
Grade 3: Severe skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain, limiting self-case ADL. PI: moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or sever discomfort limiting self-care ADL	• Continue neratinib at starting dose level and hold capecitabine until recovery or to grade ≤1, then reduce dose to 1100 mg/m^2 (550 mg/m^2 BID) • If the event recurs/persists, continue neratinib at starting dose level and capecitabine dose of 750 mg/m^2 (375 mg/m^2 BID)

Abbreviations: ADL: activities of daily living; BID: twice daily; NCI CTCAE v 4.0 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Pancreatitis

Guidelines for dose adjustments of neratinib and capecitabine for pancreatitis due to combination of neratinib plus capecitabine are show in Table A2.8.

Table A2.8: Recommendations for Dose Adjustment of Neratinib and Capecitabine and Management of Patients with Pancreatitis

NCI CTCAE v.4.0	Action
Grade 2 Pancreatitis: Enzyme elevation or radiologic findings OR **Grade 3 Pancreatitis:** Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	• Temporarily suspend (i.e., hold) **neratinib** and **capecitabine** • Evaluate for any possible alternative causes • If no alternative cause for pancreatitis is identified, discontinue **neratinib** and **capecitabine** permanently. • If an alternative cause is identified (e.g., gallstones) or enzyme levels return to baseline within 3 weeks with clinical recovery, re-start treatment with reduced doses of **neratinib** 160 mg and **capecitabine** 1100 mg/m^2 (550 mg/m^2 BID). • If the event occurs a second time, discontinue **neratinib** and **capecitabine** permanently.
Grade 4 Pancreatitis: Life-threatening consequences; urgent intervention indicated	• Discontinue **neratinib** and **capecitabine** permanently.

Abbreviations: BID: twice daily; NCI CTCAE v 4.0 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

APPENDIX 4. INHIBITORS AND INDUCERS OF THE CYTOCHROME P450 ISOENZYMES

CYP3A4 Inducers		
Carbamazepine	Macrolide antibiotics	Rifabutin
Efavirenz	Phenobarbital	Rifampin
Glucocorticoids:	Phenylbutazone	Rifapentine
Dexamethasone	Phenytoin	St. John's Wort
Prednisone	Primidone	Sulfinpyrazone
CYP3A4 Inhibitors		
Amprenavir	Grapefruit juice	Paroxetine
Anastrozole	Indinavir	Propranolol
Cimetidine	Itraconazole	Quinidine
Clarithromycin	Ketoconazole	Quinine
Clotrimazole	Mibefradil	Ranitidine
Danazol	Miconazole	Ritonavir
Delavirdine	Mirtazapine (weak)	Saquinavir
Diethyldithiocarbamate	Nefazodone	Sertraline
Diltiazem	Nelfinavir	Sildenafil (weak)
Erythromycin	Nevirapine	Troglitazone
Fluconazole	Norfloxacin	Troleandomycin
Fluoxetine	Norfluoxetine	Zafirlukast
Fluvoxamine		
CYP3A5-7 Inducers		
Phenobarbital	Primidone	Rifampin
Phenytoin		

Source: Tatro,2012.

APPENDIX 5. SUBSTRATES AND INHIBITORS OF P-GLYCOPROTEIN (P-GP)

P-glycoprotein Substrates		
Amiodarone (eg, Cordarone)	Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)
Chlorpromazine (eg, Thorazine)	Hydrocortisone (eg, Cortef)	Promethazine (eg, Phenergan)
Clarithromycin (eg, Biaxin)	Indinavir (Crixivan)	Quinidine
Cyclosporine (eg, Neoral)	Itraconazole (eg, Sporanox)	Reserpine
Dactinomycin (Cosmegen)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Daunorubicin (eg, Cerubidine)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Dexamethasone (eg, Decadron)	Loperamide (eg, Imodium)	Sirolimus (Rapamune)
Digoxin (eg, Lanoxin)	Lovastatin (eg, Mevacor)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Mifepristone (Mifeprex)	Tamoxifen (eg, Nolvadex)
Doxorubicin (eg, Adriamycin)	Mitoxantrone (Novantrone)	Teniposide (Vumon)
Erythromycin (eg, Ery-Tab)	Nelfinavir (Viracept)	Testosterone Delatestryl)
Estradiol (eg, Estrace)	Nicardapine (eg, Cardene)	Trifluoperazine
Etoposide (eg, Vepesid)	Nifedipine (eg, Procardia)	Verapamil (eg, Calan)
Felodipine (Plendil)	Ondansetron (Zofran)	Vinblastine (eg, Velban)
Fexofenadine (Allegra)	Paclitaxel (eg, Taxol)	Vincristine (eg, Vincasar PFS)
P-glycoprotein Inhibitors		
Amiodarone (eg, Cordarone)	Indinavir (Crixivan)	Quinidine
Atorvastatin (Lipitor)	Itraconazole (eg, Sporanox)	Reserpine
Chlorpromazine (eg, Thorazine)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Clarithromycin (eg, Biaxin)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Cyclosporine (eg, Neoral)	Mifepristone (Mifeprex)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Nelfinavir (Viracept)	Tamoxifen (eg, Nolvadex)
Erythromycin (eg, Ery-Tab)	Nicardipine (eg, Cardene)	Testosterone (Delatestryl)
Felodipine (Plendil)	Nifedipine (eg, Procardia)	Trifluoperazine
Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)	Verapamil (eg, Calan
Hydrocortisone (eg, Cortef)	Propranolol (eg, Inderal)	

Source: Tatro, 2012.

APPENDIX 6. DRUGS ASSOCIATED WITH RISK OF QT/QTC PROLONGATION LEADING TO TORSADE DE POINTES

Drugs Reported to Prolong QT Interval		
Analgesics		
Celecoxib (Celebrex)	Methadone (eg, Dolophine, Methadose)	
Anesthetic agents		
Enflurane (eg, Ethrane)	Halothane	
Isoflurane (eg, Forane)		
Antiarrhythmic agents		
Class IA	Class III	
Disopyramide (eg, Norpace)*	Amiodarone (eg, Cordarone)*[b]	
Procainamide (eg, Procanbid)*	Bretylium*	
Quinidine*	Dofetilide (Tikosyn)*[b]	
Class IC	Ibutilide (Corvert)*[b]	
Flecainide (eg, Tambocor)*[a]	Sotalol (eg, Betapace)*[b]	
Propafenone (eg, Rythmol)*[b]		
Anticonvulsants		
Felbamate (Felbatol)*	Fosphenytoin (Cerebyx)	
Antiemetics		
Dolasetron (Anzemet)[b]	Droperidol (eg, Inapsine)*[b]	Ondansetron (Zofran)
Antihistamines		
Desloratadine (Clarinex)[b] (overdose)	Fexofenadine (Allegra)	
Diphenhydramine (eg, Benadryl)	Hydroxyzine (Atarax)	
Anti-infectives		
Amantadine (eg, Symmetrel)*	Macrolides and related antibiotics	
Antimalarials	Azithromycin (eg, Zithromax)	
Mefloquine (eg, Lariam)[b]	Clarithromycin (eg, Biaxin)*[b]	
Quinine*	Erythromycin (eg, Ery-Tab, EES)*[b]	
Antivirals	Telithromycin (Ketek)[b]	
Efavirenz (Sustiva)*	Troleandomycin	
Azole antifungal agents	Pentamidine (eg, Pentam 300, Nebupent)*	
Fluconazole (eg, Diflucan)*[b]	Quinolones	
Itraconazole (eg, Sporanox)	Gatifloxacin (eg, Tequin)*[b]	

Drugs Reported to Prolong QT Interval		
Ketoconazole (eg, Nizoral)	Levofloxacin (eg, Levaquin)*[a, b]	
Voriconazole (Vfend)[b]	Moxifloxacin (eg, Avelox)[b]	
Chloroquine (eg, Aralen)*	Ofloxacin (eg, Floxin)*[b]	
Clindamycin (eg, Cleocin)	Sparfloxacin (Zagam)[b]	
Foscarnet (Foscavir)	Trimethoprim/sulfamethoxazole (eg, Bactrim)*	
Antineoplastics		
Arsenic trioxide (Trixenox)*[b]	Doxorubicin (eg, Adriamycin)	Tamoxifen (eg, Nolvadex)
Bronchodilators		
Albuterol (eg, Proventil)[b]	Salmeterol (Serevent)[b]	
Formoterol (Foradil)[b]	Terbutaline (eg, Brethine)[b]	
Isoproterenol (eg, Isuprel)		
Calcium channel blockers		
Isradipine (DynaCirc)	Nicardipine (eg, Cardene)	
Contrast media		
Ionic contrast media*	Non-ionic contrast media: Iohexol (Omnipaque)	
Corticosteroids		
Prednisolone (eg, Prelone)	Prednisone (eg, Deltasone)*	
Diuretics		
Furosemide (eg, Lasix)	Indapamide (eg, Lozol)	
Gastrointestinal agents		
Cisapride (Propulsid)*[b,]	Famotidine (eg, Pepcid)*	
Immunosuppressants		
Tacrolimus (Protopic)*[b] (postmarketing)		
Miscellaneous		
Levomethadyl	Papaverine (eg, Pavaden three times daily [TID])*	
Moexipril/Hydrochlorothiazide (Uniretic)	Probucol (Lorelco)*	
Octreotide (Sandostatin)[b]	Vasopressin (eg, Pitressin)*	
Oxytocin (eg, Pitocin; intravenous bolus)		
Psychotropics		
Droperidol (eg, Inapsine)*	Primozide (Orap)*[b,]	Trazodone (eg, Desyrel)
Haloperidol (eg, Haldol)*	Quetiapine (Seroquel)[b]	Tricyclic antidepressants
Lithium (eg, Eskalith)*	Risperidone (Risperdal)[b] (overdose)	Amitriptyline*

Drugs Reported to Prolong QT Interval		
Maprotiline*	Serotonin Reuptake Inhibitors (SRIs)	Clomipramine (eg, Anafranil)
Phenothiazines	Citalopram (eg, Celexa)*	Desipramine (eg, Norpramin)*
Chrlorpromazine (eg, Thorazine)*	Fluoxetine (eg, Prozac)*[a]	Doxepin (eg, Sinequan)*
Fluphenazine (eg, Prolixin)*	Paroxetine (eg, Paxil)*	Imipramine (eg, Tofranil)*
Perphenazine	Sertraline (Zoloft)*[a, b] (postmarketing)	Nortriptyline (eg, Pamelor)
Thioridazine (Mellaril)*[b]	Venlafaxine (Effexor)[b] (postmarketing)	
Trifluopherazine		
Serotonin 5-HT[1] agonists		
Naratriptan (Amerge)	Sumatriptan (Imitrex)[b]	Zolmitriptan (Zomig)[b]
Skeletal muscle relaxants		
Tizanidine (eg, Zanaflex)[b] (animals)		

* Drugs for which Torsades de Pointes has also been reported.
[a] Association unclear
[b] QT, QTc, and/or Torsades de Pointes association listed in FDA-approved product labeling
Source: Tatro, 2012.

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