An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide

NCT02400476

Study Protocol – Amendment 7.1

25-Jul-2019

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Study Protocol Number:	PUMA-NER-6201	
Disease Condition:	HER2-Positive Breast Cancer	
Sponsor's Investigational Product Name/Formulation:	Neratinib Tablets	
US IND Number	066783	
EudraCT Number	2015-004374-15	
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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 Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide

Condition or Disease: HER2-positive Breast Cancer

Approximate Values

Number of Patients	Approximately 750	**Duration of Patient Participation**	1 year
Number of Centers	Approximately 74	**Duration of Study**	7 years

Objectives:

Primary: The primary objective of this study is to characterize the incidence and severity of diarrhea in patients with early-stage HER2 overexpressed/amplified (HER2+) breast cancer treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab.

Secondary: The secondary objectives of this study are:

- To assess the incidence of serious adverse events (SAEs) and other adverse events of special interest (AESI).
- To assess the incidence and severity of diarrhea after the administration of an anti-inflammatory agent (for patients enrolled under Amendment 3), a bile acid sequestrant (for patients enrolled under Amendment 4 and Amendment 5), or following 2 different dose-escalation regimens of neratinib (for patients enrolled under Amendment 6/6.1 and for patients enrolled starting with Amendment 7, respectively).

Exploratory:

Exploratory objectives include:

- For patients enrolled starting with Amendment 2:
  - To assess patient-reported health outcomes using the EuroQol 5D-5L (EQ-5D-5L) and the Functional Assessment of Cancer Therapy Breast (FACT-B) questionnaires.
  - To collect biomarkers of disease from cell-free DNA (cfDNA) to evaluate their relationship to clinical recurrence of disease.
- For patients enrolled starting with Amendment 6:
  - Evaluation of stool bacterial diversity (microbiome)
- For patients enrolled starting with Amendment 6.1:
  - To assess patient-reported health outcomes using the Rotterdam Symptom Checklist (RSCL)

Study Design:

This is an open-label, Phase 2 study that will investigate the incidence of diarrhea in HER2+ breast cancer patients receiving neratinib with intensive loperamide diarrhea prophylaxis, alone and in combination with an anti-inflammatory treatment or a bile acid sequestrant treatment, who have previously undergone a course of trastuzumab therapy in the adjuvant setting.

Patients will receive:

- Neratinib 240 mg orally once daily for thirteen (13) 28-day cycles.
- Loperamide daily for two (2) 28-day cycles and then as needed.

- For patients enrolled under Amendment 3, an anti-inflammatory treatment for 1 cycle and loperamide to be administered daily for two (2) 28-day cycles and then as needed, thereafter;
- For patients enrolled under Amendment 4, colestipol for 1 cycle and loperamide to be administered 1 cycle and then as needed, thereafter;
- For patients enrolled under Amendment 5, colestipol for 1 cycle and loperamide to be administered on an as-needed basis only.
- For patients enrolled under Amendment 6/6.1, 120 mg neratinib for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib for Week 3 and thereafter (C1D15 to End-of-treatment [EOT]). Loperamide will be administered on an as-needed basis only.
- For patients enrolled starting with Amendment 7, 160 mg neratinib for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib thereafter (C2D1 to End-of-treatment [EOT]). Loperamide will be administered on an as-needed basis only.

Patients will receive neratinib for 13 cycles (364 days) or until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.

The effect of the anti-inflammatory treatment budesonide and the bile acid sequestrant, colestipol, on the incidence, severity, and duration of diarrhea will be investigated in sequential patient cohorts using a sample size of approximately 64 patients per cohort. The anti-inflammatory cohort added in Amendment 3 will be assigned to receive budesonide 9 mg once daily with or without food for 28 days along with neratinib 240 mg /day (13 cycles) and intensive loperamide prophylaxis that will continue through the first 2 cycles (total 56 days), and then on an as-needed basis thereafter.

Following the completion of enrollment of the patients receiving budesonide, neratinib, and intensive loperamide prophylaxis, the next cohort will be evaluated after receiving colestipol 2 g twice daily with or without food for 28 days, to be taken at least 2 hours after, but at least 4 hours before, neratinib 240 mg /day (13 cycles) and intensive loperamide prophylaxis. For this cohort, intensive loperamide prophylaxis will continue through the first cycle (total 28 days); for Cycle 2 and beyond, loperamide may be administered as needed (PRN).

Following complete enrollment of the cohort treated with colestipol + intensive loperamide prophylaxis, all patients in the next cohort will be evaluated after receiving colestipol and neratinib with loperamide administered on a PRN basis only.

Following complete enrollment of the cohort receiving neratinib + colestipol + loperamide PRN, all patients in the next cohort will be evaluated after receiving neratinib administered according to the following dose-escalation scheme: 120 mg neratinib for 1 week (C1D1 – C1D7), followed by 160 mg neratinib for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib for Week 3 and thereafter (C1D15 to EOT). Loperamide is to be administered on a PRN basis only.

Following complete enrollment of all patients in the 120 mg/160 mg/240 mg dose-escalation scheme, patients enrolled in the next cohort will be evaluated after receiving neratinib administered according to a second dose escalation scheme: 160 mg neratinib to be taken for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib to be taken for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib daily dose taken thereafter (C2D1 to EOT). Loperamide is to be administered on a PRN basis only.

The Sponsor will regularly review accumulating safety data (by individual subject and in aggregate). Early termination of a cohort or the study may be permitted if data indicate that anti-diarrheal treatment is ineffective.

Patients in all treatment groups will continue to complete the remaining 12 treatment cycles.

The final analysis will be conducted after all patients have completed 13 cycles of study treatment or have met other specified withdrawal criterion (see Section 10).

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

Study Endpoints:

- The primary endpoint of the study is the incidence of Grade 3 or higher diarrhea.
- Secondary endpoints include the frequency distribution of the maximum grade incidence of diarrhea, the incidence and severity of diarrhea with and without anti-inflammatory agents, with and without a bile acid sequestrant, the effect of lower starting doses and dose escalation of neratinib on the incidence and severity of diarrhea; and the incidence of SAEs and AESIs.
- The exploratory endpoint of patient-reported health outcomes will be assessed by the EuroQol EQ-5D-5L, the FACT-B questionnaires (for patients enrolled starting with Amendment 2), and the RSCL (for patients enrolled starting with Amendment 6.1).
- The exploratory endpoint of disease biomarkers will consist of the biomarkers of disease recurrence (for patients enrolled starting with Amendment 2).
- The exploratory endpoint of evaluation of stool bacterial diversity, i.e., microbiome (for patients enrolled starting with Amendment 6/6.1).

Neratinib, Loperamide, Anti-inflammatory, and Bile Acid Sequestrant Treatments, Dose, and Administration:

- Neratinib: Six (6) 40 mg tablets (total dose 240 mg) orally, once daily with food, preferably in the morning, continuously for 13 cycles (364 days), except for patients enrolled under Amendment 6/6.1 who will receive neratinib in the dose escalation scheme detailed above (ie, total dose 120 mg daily for the first week, 160 mg daily for Week 2, and 240 mg daily for Week 3 and thereafter, until EOT), and except for patients enrolled under Amendment 7/7.1 who will receive neratinib in a second dose escalation scheme (ie, total dose 160 mg daily for the first 2 weeks, 200 mg daily for the following 2 weeks, and 240 mg daily thereafter until EOT)..
- Loperamide:
  - For patients enrolled under the Original Protocol:
    - Initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 2 mg (1 tablet/capsule) every 4 hours for the first 3 days. After the first 3 days, loperamide 2 mg every 6 to 8 hours through the first 2 cycles of therapy (56 days) from start of neratinib.
  - For patients enrolled under Amendment 1 – Amendment 3:
    - For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
    - After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first 2 cycles of therapy (Day 56) from start of neratinib dosing
  - For patients enrolled under Amendment 4:
    - For the first 14 days. The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib, followed by loperamide 4 mg (2 tablets/capsules) self-administered orally by patients 3 times a day (total 12 mg a day).
    - After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day), for 1 cycle [28 days], and then as needed (PRN) (not to exceed 16 mg per day).
  - For patients enrolled under Amendment 5, Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1:
    - Loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients on a PRN basis only, from the start of neratinib dosing (not to exceed 16 mg per day).

- Budesonide
  - For patients enrolled under Amendment 3 and who participate in the evaluation of budesonide, patients will self-administer oral budesonide at a dose of 9 mg once daily for the first treatment cycle, to be taken with neratinib and intensive loperamide prophylaxis.
- Colestipol
  - For patients enrolled under Amendment 4 and Amendment 5 and who participate in the evaluation of colestipol, patients will self-administer colestipol at a dose of 2 g twice daily for the first treatment cycle, to be taken at least 2 hours after, but at least 4 hours before neratinib and intensive loperamide prophylaxis (Amendment 4) or loperamide PRN (Amendment 5). Colestipol is a bile acid sequestrant anion resin that has the potential to interact with co-administered medication. Precaution should be taken around the timing of administration to avoid drug-drug interaction. Please refer to Section 7.6 and Appendix 10 of the protocol for additional specific recommendations regarding the administration of concomitant medication including neratinib and loperamide, the investigation products in this protocol.

Patients must use a diary to record their intake of medicinal product as supplied by sponsor.

Diagnosis and Main Criteria for Inclusion:

Study Population:

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 3c 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 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. The last dose of trastuzumab must have been given >2 weeks and ≤1 year (365 days) from enrollment.
6. Physician assessment confirming that the patient is negative for local or regional recurrence of disease or metastatic disease at the time of study entry, including:
   a. Per standard of care, bone scan or positron emission tomography (PET) scan; required only if alkaline phosphatase (ALP) is ≥2 x upper limit of normal (ULN) and/or there are symptoms of metastatic bone disease. A confirmatory imaging study is required if the results from the bone scan are questionable.
   b. Per standard of care, computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound of the abdomen and chest; required only if aspartate aminotransferase (AST)/alanine aminotransferase (ALT) or ALP is ≥2 x ULN.

      Other radiologic assessments may be performed to rule out underlying breast cancer recurrence if indicated and as per standard of care (for patients enrolled starting with Amendment 6.1).
7. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
8. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
9. 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.]

10. Women of childbearing potential must agree and commit to the use of a highly effective non-hormonal method of contraception, ie, 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. Man (male patient) with 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 (ie, 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.
11. Recovery (ie, to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).
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. Clinical or radiologic evidence of local or regional recurrence of disease or metastatic disease prior to or at the time of study entry.
2. Currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.
3. Major surgery within <30 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.
4. 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.
5. QTc interval >0.450 seconds (males) or >0.470 (females), or known history of QTc prolongation or Torsade de Pointes (TdP).
6. 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	≤100,000/µl (≤100 x 10^9/L)
Hemoglobin	≤9 g/dL
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
Creatinine	Creatinine clearance <30 mL/min (as calculated by Cockcroft-Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])

a. Cockcroft and Gault, 1976.
b. Levey et al, 1999.

7. Active, unresolved infections.
8. 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.

9. Currently pregnant or breast-feeding.
10. 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).
11. Clinically active infection with hepatitis B or hepatitis C virus.
12. 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.
13. Known hypersensitivity to any component of the investigational products; known allergies to any of the medications or components of medications used in the trial.
14. Unable or unwilling to swallow tablets.

Safety Assessments:

The primary endpoint is the incidence of Grade 3 or higher diarrhea. AEs and AESIs will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE), version 4.0. SAEs and AESIs will be reported through 28 days after the last dose of investigational product and 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 neratinib's administration, it should be promptly reported. Safety will also be assessed based on medical history, vital sign measurements, physical examination findings, electrocardiogram results, MUGA or ECHO, and laboratory assessments.

Other Assessments:

Patient Reported Health Outcomes Assessments

The following questionnaires will be used to collect patient-reported health outcomes data:

1) EQ-5D-5L Health Questionnaire (for patients enrolled starting with Amendment 2)
2) FACT-B (for patients enrolled starting with Amendment 2)
3) RSCL (for patients enrolled starting with Amendment 6.1)

Patient-reported outcomes assessments will be performed at C1D1, C2D1, C4D1, C7D1, C10D1, and C13D28/EOT.

Biomarkers (for patients enrolled starting with Amendment 2)

cfDNA will be obtained from plasma samples collected at Screening, C7D1, C13D28 and/or at time of treatment discontinuation, and at disease recurrence; cfDNA will undergo molecular profiling to identify biomarkers of disease recurrence.

Microbiome Evaluation (for patients enrolled starting with Amendment 6)

At select study centers, a stool swab will be collected at Screening, C2D1, and C4D1 and/or at time of treatment discontinuation if earlier than C4D1 for possible future assessments of microbiome to assess the effect that neratinib has on the microbiome (currently in US only).

Disease Recurrence

Clinical documentation of recurrence, including recurrence site, radiographic, and/or pathologic procedures will be collected at end-of -treatment (EOT).

Statistical Methods:

Sample Size:

The first 120 patients will be under the Original Protocol, Amendment 1, and Amendment 2. The incidence of Grade 3 or higher diarrhea is assumed to be 15% in this study. A sample size of 120 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 18.5%. For example, if 18 out of the 120 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CIs will be 15.0% (9.1%, 22.7%) where the width of the CI is 13.5%.

In addition to the analyses of the overall safety population, anti-diarrheal prophylaxis regimen-specific subgroup analyses will be performed as needed. Precision of the estimated 95% CIs for the regimen-specific subgroup(s) will be lower than what is provided above for the overall safety population.

To further investigate treatments, cohorts were added. For patients enrolled under Amendment 3, the effect of budesonide + mandatory loperamide prophylaxis on the incidence, severity, and duration of diarrhea will be assessed. For patients enrolled under Amendment 4 and Amendment 5, the effect of colestipol + mandatory loperamide prophylaxis (Amendment 4) and colestipol + PRN loperamide (Amendment 5) will be assessed; for patients enrolled under Amendment 6/6.1 and under Amendment 7/7.1, the effect of the dose escalation regimen of neratinib will be assessed. The incidence of Grade 3 or higher diarrhea will be evaluated. A sample size of 64 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 26%. For example, if 7 out of the 64 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CI will be 10.9% (4.5–21.2%) where the width of the CI is 17%.

For each additional cohort, a sample size of 100 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 21%. For example, if 15 out of the 100 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CI will be 15.0% (8.7–23.5%) where the width of the CI is 15%.

Cohorts will continue to enroll without interruption, in sequence. Thus enrollment may exceed initial projections.

Statistical Analysis:

The primary endpoint is the incidence of Grade 3 or higher diarrhea. The accompanying 2-sided 95% Clopper-Pearson CIs will be computed.

Safety:

All patients who receive a dose of neratinib will be analyzed for safety. Treatment emergent AEs, SAEs, and AESIs, as well as select laboratory tests will be summarized. Deaths and discontinuation from study treatment will also be summarized.

Exploratory:

Patient-related outcomes data (scores from the EQ-5D-5L, FACT-B, and RSCL questionnaires) will be summarized and plotted over time. Changes from baseline will be provided with both point estimates and CIs.

Exploratory analyses will be conducted to evaluate the relationship between disease biomarkers identified from molecular profiling and indications of clinical disease recurrence.

Microbiome evaluation from participating sites will be summarized at baseline, C2D1, C4D1, and/or at time of treatment discontinuation. No formal statistical analyses are planned of the microbiome data.

All analyses of exploratory endpoints are descriptive and no formal testing is planned.

Interim Analysis:

An interim analysis is planned when approximately 120 patients enrolled under the Original protocol, Amendment 1, and Amendment 2, have completed at least 2 cycles (56 days) of neratinib with loperamide prophylaxis. The interim analysis will only include those 120 patients enrolled under the Original Protocol, Amendment 1, and Amendment 2. Other additional analyses by cohort, in addition to the interim analysis, may be carried out as required.

Final Analysis:

The final analysis is planned when all patients have completed 13 cycles (364 days) of neratinib therapy or have discontinued the study.

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
Akt	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
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
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
D	Day
DM1	Emtansine
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 (formerly EMEA)
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol 5D-5L
ERBB	epidermal growth factor family of trans-membrane receptors (also known as HER)
ERBB2 V-erb-b2	avian erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian), HER2
EU	European Union
FACT-B	Functional Assessment of Cancer Therapy Breast Cancer
FDA	Food and Drug Administration (United States)

GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
Hb	Hemoglobin
hCG	β-human chorionic gonadotropin
Hct	Hematocrit
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2 (neu [N ethyl nitrosourea stimulated] gene product); also known as c erB2, ERBB2, or p185
HIPAA	Health Insurance Portability and Accountability Act
HR	hormone receptor
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)
IRB	Institutional Review Board
IV	intravenous(ly)
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters mercury
MRI	magnetic resonance imaging
MUGA	multiple-gated accession scan
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OS	overall survival
PB-272	Neratinib
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PO	by mouth
PT	preferred term
PRN	Pro re nata (as needed)
QOL	Quality of Life
QTc	QT interval, corrected for heart rate
RBC	red blood cell

RSCL	Rotterdam Symptom Checklist
SAE	serious adverse event
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T-DM1	trastuzumab emtansine
TdP	Torsade de Pointes
TID	three times daily
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 the leading cause of cancer mortality in women worldwide. Breast cancer accounted for approximately 522,000 deaths worldwide in 2012, and the global incidence of new cases in women was approximately 1.67 million (International Agency for Research on Cancer, GLOBOCAN 2012).

2.2. ERBB2 Gene and Cancer

2.2.1. The Epidermal Growth Factor Receptor Family (ERBB)

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, 1989). 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. Current Therapies Targeting ERBB Receptors

2.3.1. Trastuzumab

Trastuzumab (Herceptin® Package Insert, Herceptin Summary of Product Characteristics [SmPC], Herceptin Product Monograph), the first agent approved for treatment of HER2+ breast cancer, is a monoclonal antibody that binds to the juxtamembrane portion of the HER2/neu receptor, resulting in inhibition of tumor proliferation (Goldenberg, 1999). While the exact mechanism of action is uncertain, Junttila et al (2009) reported that trastuzumab induced dissociation of ligand independent HER2-HER3 heterodimers resulting in dephosphorylation of HER3 and inhibition of downstream signaling, and Park et al (2010) reported that the antitumor effects of trastuzumab also involved antibody-dependent, cell-mediated cytotoxicity.

2.3.2. Pertuzumab

Pertuzumab (Perjeta® Package Insert) is a humanized monoclonal antibody that binds HER2 at a different epitope of the HER2 extracellular domain (subdomain II) than trastuzumab (Baselga et al, 2012) thereby preventing HER2 from dimerizing with other ligand-activated HER receptors, most notably HER3 (Baselga and Swain, 2009; Agus et al, 2002). The HER2-HER3 heterodimer is considered to be the most potent signaling pair (Agus et al, 2002), driving cell proliferation in HER2+ cancer (Lee-Hoeflich et al, 2008; Hsieh and Moasser, 2007). In recent studies, the addition of pertuzumab to combination therapy has led to improvements in PFS in patients with HER2+ metastatic breast cancer (MBC) and higher response rates in the preoperative setting (Murphy and Morris, 2012).

2.3.3. Pertuzumab in Combination with Trastuzumab

Although treatment with trastuzumab in addition to chemotherapy (as compared with chemotherapy alone) significantly improves PFS and OS among patients with HER2+ MBC, in most patients, the disease progresses (Nahta and Esteva, 2007).

Because pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action, the combination of these two agents, provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity than either agent alone in

HER2+ tumor models (Lee-Hoeflich et al, 2008; Scheuer et al, 2009). In Phase 2 studies, a pertuzumab plus trastuzumab regimen showed activity in patients with HER2+ MBC (Baselga et al, 2010; Portera et al, 2008) and in patients with early breast cancer (Gianni et al, 2010).

The Clinical Evaluation of pertuzumab and trastuzumab (CLEOPATRA) study assessed the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel (control group), as first-line treatment for patients with HER2+ MBC who had not received chemotherapy or biologic therapy for their metastatic disease (Baselga et al, 2012). At the final analysis (median follow-up of 50 months), treatment with pertuzumab plus trastuzumab plus docetaxel resulted in significant improvement in PFS and OS with an unprecedented increase of 15.7 months in median OS, compared with the control group (Swain et al, 2014). CLEOPATRA findings suggest that targeting HER2+ tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action results in a more comprehensive blockade of HER2 and highlights the clinical importance of preventing the ligand-dependent formation of HER2 dimers in order to silence HER2 signaling to the greatest extent possible (Baselga and Swain, 2009; Yarden and Sliwkowski, 2001).

Pertuzumab received approval in the US in 2012 for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ MBC who have not received prior anti HER2 therapy or chemotherapy for metastatic disease. In 2013, pertuzumab received approval for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

2.3.4. Ado-trastuzumab Emtansine

Ado-trastuzumab emtansine (T-DM1, Kadcyla® Package Insert) is an antibody-drug conjugate that combines HER2-targeted delivery of the potent microtubule polymerization inhibitor emtansine (DM1), a derivative of maytansine, with the antitumor activity of trastuzumab (Lewis Phillips et al, 2008; Remillard et al, 1975; Cassady et al, 2004; Widdison et al, 2006; Junttila et al, 2011). In T-DM1, trastuzumab and DM1 are covalently linked via a stable thioether linker (*N*-maleimidomethyl) cyclohexane-1-carboxylate, which is thought to limit the exposure of normal tissue to DM1 (Krop et al, 2010; Burris et al, 2011). Antitumor activity was established in a proof of concept Phase 2 study of single-agent T-DM1 in patients with HER2+ MBC, who had progressed while receiving HER2-directed therapy (Burris et al, 2011). Furthermore, in a single-arm Phase 2 study, T-DM1 demonstrated efficacy in patients with HER2+ MBC who previously received all standard HER2-directed therapies (trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine) (Krop et al, 2012).

Primary results from the EMILIA study (a Phase 3, randomized, multicenter study of T-DM1 compared with lapatinib plus capecitabine in patients with HER2+ locally advanced or MBC previously treated with a trastuzumab-based regimen and a taxane) showed a significant and clinically meaningful improvement with T-DM1 in PFS compared with lapatinib plus capecitabine (Verma et al, 2012). Other end points supported T-DM1 as an active and well-tolerated novel therapy for HER2+ advanced breast cancer. T-DM1 is approved in the US for patients with HER2-positive MBC who have previously received trastuzumab and a taxane separately or in combination.

2.3.5. Other HER2-targeted Therapies

Other HER2-targeted agents include lapatinib, a small molecule tyrosine kinase inhibitor that targets the tyrosine kinase domains of both EGFR and HER2 (Rusnak and Gilmer, 2011). Trastuzumab and lapatinib have received approval from the United States (US) Food and Drug Administration (FDA) for the treatment of patients with advanced or metastatic HER2-overexpressing breast cancer who have previously been treated with an anthracycline, a taxane, and trastuzumab.

2.4. Neratinib

Neratinib (PB-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 will have antitumor activity in ERBB1- and/or ERBB2-expressing carcinoma cell lines, with cellular IC_{50} <100 nM (Rabindran et al, 2004).

Neratinib may have advantages over other HER2 inhibitors due to its ability to irreversibly inhibit both HER1 and HER2. Breast cancer cells may become resistant to trastuzumab 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+ breast cancer are provided in the neratinib Investigator's Brochure (IB).

2.4.1. 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 IB Version 5.0 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.

2.4.2. Diarrhea Prophylaxis in Neratinib Clinical Studies

Although patients in studies 3144A1-201-WW, 3144A2-3003-WW, I-SPY2 and early cohorts of 10-005 received standard-of-care diarrhea management on occurrence of diarrhea, the studies did not mandate concomitant treatment with loperamide or other anti-diarrheal agents at the outset of

neratinib therapy for prevention of neratinib-related diarrhea. In these studies, 28-39% of patients experienced Grade 3 or Grade 4 diarrhea Table 1).

In ongoing neratinib clinical studies that are currently enrolling patients with solid tumors, prophylactic use of antidiarrheal medication is mandatory. Data for ongoing study PUMA-NER-4201 and the later cohorts of 10-005 are shown in Table 2. Among patients receiving prophylactic antidiarrheal medication in these studies, 12-16% of patients experienced Grade 3 or Grade 4 diarrhea.

Table 1 illustrates diarrhea incidence in neratinib studies without loperamide prophylaxis. Table 2 illustrates diarrhea incidence in neratinib studies that use intensive loperamide prophylaxis.

Table 1: Neratinib Diarrhea Incidence Without Loperamide Prophylaxis

Study	Patients	Investigational Product	Patients N	Grade 3-4 Diarrhea n (%)
3144A1-201-WW[a]	Locally advanced or HER2+ MBC	neratinib 240 mg	66[b]	21 (32%)
3144A2-3003-WW[a]	Locally advanced or HER2+ MBC	neratinib 240 mg (monotherapy arm)	116	33 (28%)
3144A2-3004-WW	Early stage HER2+ breast cancer	neratinib 240 mg (monotherapy arm)	1408	562 (39.9%)
10-005[c]	Triple-negative or HER2+ MBC	neratinib (240 mg) + temsirolimus IV (once per week)	35	10 (29%)
I-SPY2[d]	HER2+/HR- Breast Cancer	neratinib (240 mg) + paclitaxel (once per week)	116	45 (39%)

HER = human epidermal growth factor receptor; HR = hormone receptor; IV = intravenously; MBC = metastatic breast cancer
[a] Data from 3144A1-201-WW CSR and 3144A2-3003-WW interim CSR.
[b] Includes patients in Arm A with prior adjuvant trastuzumab therapy.
[c] Patients without diarrhea prophylaxis; data cut-off 22-AUG-2014.
[d] AACR Annual Meeting, Park et al, 2014.

Table 2: Neratinib Diarrhea Incidence Using Loperamide Prophylaxis

Study	Patients	Investigational Product	Patients N	Grade 3-4 Diarrhea n (%)
PUMA-NER-4201[a]	Advanced or metastatic HER2-mutant NSCLC	neratinib (240 mg)	17	2 (12%)[b]
		neratinib (240 mg) + temsirolimus[c]	28	4 (14%)[b]
10-005[a]	Triple-negative or HER2+ MBC	neratinib (240 mg) + temsirolimus[c]	51	8 (16%)[d]

Data cut-off 22-AUG-2014
HER = human epidermal growth factor receptor; IV = intravenously; MBC = metastatic breast cancer; NSCLC = non-small cell lung cancer
[a] To be compliant, patients with intensive diarrhea prophylaxis were to receive loperamide 4 mg with first dose of neratinib followed by loperamide 2 mg every 4 hours for the first 3 days. Thereafter, loperamide 2 mg every 6 to 8 hours until the end of the first cycle of therapy.
[b] One (1) patient in each arm had Grade 3 diarrhea during Cycle 1; both patients were non-compliant with loperamide prophylaxis.
[c] Temsirolimus 8 or 15 mg IV once per week.
[d] Five (5) patients had Grade 3 diarrhea during Cycle 1; three (3) of these patients were non-compliant with loperamide prophylaxis.

Refer to the neratinib IB Version 5.0 for more detailed information.

2.4.3. Preliminary 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 randomized Phase 3 ExteNET trial (Extended Adjuvant Treatment with Neratinib [3144A2-3004-WW], Chan et. al., 2015) 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.

2.5. Study Rationale

The results shown in Table 1 and Table 2 suggest that the implementation of the intensive diarrhea management has resulted in a lower incidence of Grade 3 diarrhea. The rationale of this study is to collect safety data in patients with early-stage HER2-positive breast cancer who have completed a prior course of adjuvant trastuzumab in order to expand the safety profile of

neratinib when given concomitantly with intensive antidiarrheal prophylaxis for 2 cycles. As of Amendment 4, starting with the group receiving colestipol, intensive loperamide prophylaxis is to be administered for 1 cycle (28 days), and then as needed (PRN) during Cycle 2 and thereafter. The duration for the administration of intensive loperamide prophylaxis was changed from 2 cycles to 1 cycle (28 days) in Amendment 4 since review of data for the incidence of new diarrhea indicated that the majority of episodes occur within the first 28 days of starting neratinib treatment.

In Amendment 5, the study will investigate a bile acid sequestrant (colestipol) given in addition to the antidiarrheal medication loperamide, administered on a PRN basis, that may be effective in further lowering the incidence of Grade 3 diarrhea. The results will guide how to better manage neratinib-related diarrhea in this patient population.

2.5.1. Neratinib Dose Escalation Rationale

Amendments 6 and 6.1, will investigate the effect on the incidence and severity of diarrhea of a lower dose of neratinib starting at 120 mg/day with a dose-escalation regimen. This dose escalation scheme is based on (1) a logistic regression model using ExteNET data that suggests the odds of having Grade 2 or higher diarrhea increase with increasing average daily dose of neratinib; and (2) the observation that Grade 3 diarrhea occurs most frequently in the first month after neratinib initiation, suggesting intestinal adaptation to neratinib exposure. By starting administration of neratinib at the lower dose of 120 mg in the first week (C1D1 to C1D7), followed by 160 mg in Week 2 (C1D8 to C1D14), reaching full treatment dose of 240 mg at Week 3 and then thereafter (C1D15 to EOT), patients may experience less early and severe episodes of neratinib-associated diarrhea and thereby achieve increased tolerability and adherence to neratinib treatment. Starting with Amendment 7, the study will investigate the effects of an alternate neratinib dose escalation regimen, starting with the introduction of 160 mg neratinib for the first two weeks of treatment. Subsequently, 200 mg neratinib will start for the next two weeks, allowing a stepwise approach that leads to reaching full dose neratinib 240 mg. By having a longer duration of 2 weeks at each dose level patients have the opportunity to acclimate to neratinib, which may increase tolerability and optimize the management of adverse effects. Accumulating data from PUMA-NER-6201 suggest that many patients who remain on neratinib therapy through the first month are able to remain on neratinib for the complete one year treatment course. Gut bacterial biodiversity will be evaluated from a stool swab at Screening, C2D1, and C4D1 and/or at time of treatment discontinuation to assess the effect that neratinib has on the microbiome.

2.5.2. Results of Preclinical Investigations

A rat model to investigate neratinib-associated diarrhea was developed and histopathology showed infiltration of polymorphonuclear cells and lymphocytes in the ileum and colon (unpublished data on file). This may suggest an inflammatory process that could be ameliorated with anti-inflammatory agents. Ongoing investigations into several interventions are proceeding in the rat model.

2.5.3. Rationale for use of an Anti-inflammatory Agent

Budesonide will be investigated in the first pilot cohort as a proof-of-principle for the anti-inflammatory effect. Budesonide has a high glucocorticosteriod (GCS) activity and substantial

first-pass elimination (Package Insert-Uceris® (budesonide) tablets, Santarus, Inc.). The formulation contains budesonide in an extended release tablet core. The tablet core is enteric coated to protect dissolution in gastric juice which delays budesonide release until exposure to a pH ≥ 7 in the small intestine. Upon disintegration of the coating, the core matrix provides extended release of budesonide in a time dependent manner. Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect.

2.5.4. Rationale for Use of a Bile Acid Sequestrant

The bile acid sequestrant colestipol is a lipid lowering agent for oral use, that binds bile acids in the intestine forming a complex that is excreted in the feces (Package Insert-Colestid® [colestipol], Pfizer). This non-systemic action results in a partial removal of bile acids from enterohepatic circulation, preventing their reabsorption. The formation of this complex may counteract neratinib induced diarrhea by slowing gastrointestinal transit time and by attenuating the possible irritant effect of bile acids on inflamed gastrointestinal lumen. Constipation is the major single adverse effect of colestipol and most instances are mild and transient. In animal model studies investigating neratinib induced diarrhea, initial observations suggest that there is a reduction in severe diarrhea when rats were administered a bile acid sequestrant during neratinib administration.

2.5.5. Enrollment

The projected numbers for enrollment have increased as of Amendment 5. The planned number had been 40 patients per additional cohort. Amendment 3 over-enrolled patients due to plans for continued investigation to a total of 64 patients. Amendment 4 over-enrolled, exceeding 40 patients to finally include a total of 136 patients. Amendment 5 though originally planned to include 64 patients enrolled 104 patients. Amendment 6 and Amendment 6.1 are currently enrolling patients and are projected to enroll approximately 64 patients. Amendment 7 and Amendment 7.1 are planned to enroll approximately 100 additional patients. Cohorts will continue to enroll without interruption, in sequence. Thus enrollment may exceed initial projections.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to characterize the incidence and severity of diarrhea in patients with early-stage HER2 overexpressed/amplified (HER2+) breast cancer treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the incidence of serious adverse events (SAEs) and other adverse events of special interest (AESI).
- To assess the incidence and severity of diarrhea after the administration of an anti-inflammatory agent (for patients enrolled under Amendment 3), a bile acid sequestrant (for patients enrolled under Amendment 4 and Amendment 5), or following 2 different dose escalation regimens of neratinib (for patients enrolled under Amendment 6 and for patients enrolled starting with Amendment 7, respectively).

3.3. Exploratory Objectives

The exploratory objectives of this study are to evaluate:

For patients enrolled starting with Amendment 2:

- To assess patient reported outcomes using the EQ-5D-5L Health Questionnaire (EQ-5D-5L) and the Functional Assessment of Cancer Therapy Breast (FACT-B) questionnaires.
- To collect plasma biomarkers to evaluate their relationship to clinical recurrence of disease.

For patients enrolled starting with Amendment 6:

- Evaluation of stool bacterial diversity (microbiome)

For patients enrolled starting with Amendment 6.1:

- To assess patient-reported outcomes using the RSCL (for patients enrolled starting with Amendment 6.1)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, Phase 2 study that will investigate the incidence of diarrhea in HER2+ breast cancer patients receiving neratinib with intensive loperamide diarrhea prophylaxis, with and without an anti-inflammatory treatment or a bile acid sequestrant treatment and who have previously completed trastuzumab therapy in the adjuvant setting.

Patients will receive:

- Neratinib 240 mg orally once daily with food for thirteen (13) 28-day cycles.
- Loperamide daily for two (2) 28-day cycles and then as needed.
- For patients enrolled under Amendment 3, an anti-inflammatory treatment for 1 cycle and loperamide to be administered daily for two (2) 28-day cycles and then as needed, thereafter;
- For patients enrolled under Amendment 4, colestipol for 1 cycle and loperamide to be administered 1 cycle and then as needed, thereafter;
- For patients enrolled under Amendment 5, colestipol for 1 cycle and loperamide to be administered on an as-needed basis only.
- For patients enrolled under Amendments 6 and 6.1, 120 mg neratinib for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib starting for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib starting at Week 3 and thereafter (C1D15 to EOT). Loperamide will be administered on an as-needed basis only.
- For patients enrolled starting with Amendment 7, 160 mg neratinib for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib thereafter (C2D1 to End-of-treatment [EOT]). Loperamide will be administered on an as-needed basis only.

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 thirteen (13) 28-day treatment cycles (Section 9.2). Neratinib and loperamide will be administered orally by patients as described in Section 6. Neratinib is to be taken continuously, in 28-day cycles, with no rest between cycles.

The effect of the anti-inflammatory treatment, budesonide and the bile acid sequestrant colestipol on the incidence, severity, and duration of diarrhea will be investigated in sequential patient cohorts using a sample size of approximately 64 patients per cohort (Figure 1). The anti-inflammatory cohort added in Amendment 3 will be assigned to receive budesonide tablets 9 mg once daily with or without food for 28 days along with neratinib 240 mg/day (13 cycles) and intensive loperamide prophylaxis that will continue through the first 2 cycles (total 56 days), and on an as-needed basis thereafter.

Following the planned completion of enrollment of the 40 patients receiving budesonide, neratinib, and intensive loperamide prophylaxis (final enrollment was 64 patients), the next

cohort will be evaluated after receiving colestipol 2 g twice daily with or without food for 28 days, to be given at least 2 hours after, but at least 4 hours before, neratinib 240 mg/day (13 cycles) and intensive loperamide prophylaxis. For this cohort, intensive loperamide prophylaxis will continue only through the first cycle (28 days); for Cycle 2 and beyond, loperamide may be administered as needed (PRN).

Following complete enrollment of the cohort treated with colestipol and intensive loperamide prophylaxis, all patients in the next cohort (approximately 64) will be evaluated after receiving colestipol and neratinib with loperamide administered on a PRN basis only. (Note: For Amendment 5 and Amendment 6, enrollment into the budesonide cohort and the first colestipol cohort is complete and the administration of mandatory loperamide prophylaxis is now also complete).

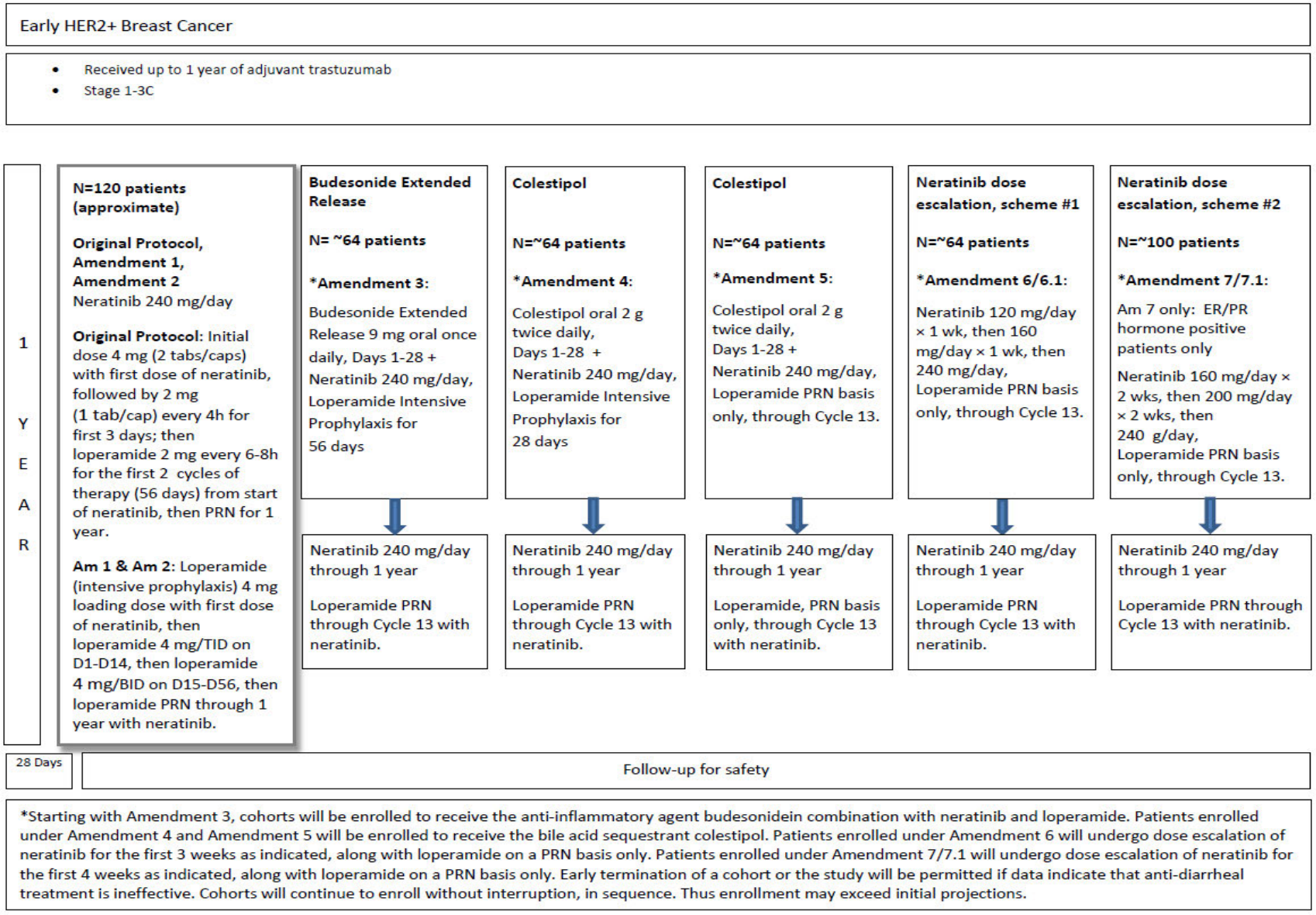
Patients enrolled under Amendment 6/6.1 will be evaluated after receiving neratinib administered according to the following dose-escalation scheme: 120 mg neratinib for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib starting at Week 2 (C1D8 – C1D14), followed by 240 mg neratinib starting at Week 3 and thereafter (C1D15 to EOT). Loperamide is to be administered on a PRN basis only.

Following complete enrollment of all patients in the 120 mg/160 mg/240 mg dose-escalation scheme, patients enrolled under Amendment 7/7.1 will be evaluated after receiving neratinib administered according to a second dose escalation scheme: 160 mg neratinib to be taken for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib to be taken for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib daily dose taken thereafter (C2D1 to EOT). Loperamide is to be administered on a PRN basis only.

The Sponsor will regularly review accumulating safety data (by individual subject and in aggregate). Early termination of a cohort or the study may be permitted if data indicate that anti-diarrheal treatment is ineffective.

Patients in all treatment groups will continue to complete the remaining 12 treatment cycles. Analyses are further described in Section 12.4.1. Cohorts will continue to enroll without interruption, in sequence. Thus enrollment may exceed initial projections.

Figure 1: Study Design (Starting with Amendment 7)



Clinic visits during the active treatment phase are planned on Day 1 of Cycle 1, 2, 3, 4, 7, and Cycle 10. End of Treatment (EOT) Visit is planned on Day 28 of Cycle 13, followed by Safety Follow-up Visit 28 days after the last dose of neratinib. Assessments required throughout the study are summarized in the Schedule of 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 the incidence of Grade 3 or higher diarrhea. Secondary endpoints include the frequency distribution of the maximum grade incidence of diarrhea over time, the incidence and severity of diarrhea by anti-diarrheal treatment exposure; and the incidence of SAEs and AESIs. Additional exploratory endpoints consisting of patient-reported health outcomes and biomarkers of disease recurrence will be evaluated (for patients enrolled starting with Amendment 2).

An interim analysis is planned when approximately 120 enrolled under the Original Protocol, Amendment 1, and Amendment 2 have completed at least 2 cycles (56 days) of neratinib with loperamide prophylaxis. The analysis will only include those 120 patients enrolled under the Original Protocol, Amendment 1, and Amendment 2. Other additional analyses by cohort may be carried out as required (Section 12.5). The final analysis is planned when all patients have either completed 13 cycles (364 days) of neratinib therapy or have discontinued from the study.

For the Original protocol, Amendment 1, and Amendment 2, approximately 120 patients were to be enrolled at approximately 35-45 centers. See Section 12.7 for a discussion of sample size.

For the 5 cohorts evaluating additional treatments added in Amendment 3 (budesonide), Amendment 4 and Amendment 5 (colestipol), Amendment 6/6.1 (neratinib dose escalation from 120 mg/day), and Amendment 7/7.1 (neratinib dose escalation from 160 mg/day), approximately 450 additional patients will be enrolled at approximately 74 centers. The approximate total enrollment will be 750 patients total.

Patients 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, and safety follow-up visit 28 days after the last dose of neratinib. 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).

4.2. Study Duration and Termination of Study

The approximate duration of the study is 7 years.

Patients receive neratinib for 13 cycles (364 days) or until disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.

The final analysis will be conducted after all patients have completed 13 cycles of study treatment or have met other specified withdrawal criterion (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 the 1-year course of treatment either through a treatment extension study or through a managed access program.

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 3c 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 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. The last dose of trastuzumab must have been given >2 weeks and ≤1 year (365 days) from enrollment.
6. Physician assessment that the patient is negative for local or regional recurrence of disease or metastatic disease at the time of study entry, including
   - Per standard of care, bone scan or positron emission tomography (PET) scan; required only if ALP is ≥2 x upper limit of normal (ULN) and/or there are symptoms of metastatic bone disease. A confirmatory imaging study is required if the results from the bone scan are questionable.
   - Per standard of care computed tomography (CT), MRI or ultrasound of the abdomen and chest; required only if aspartate aminotransferase (AST)/alanine aminotransferase (ALT) or ALP is ≥2 x ULN.
   - Other radiologic assessments may be performed to rule out underlying breast cancer recurrence if indicated and as per standard of care (for patients enrolled starting with Amendment 6.1).
7. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) ECHO.
8. ECOG status of 0 to 1.
9. Negative 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].
10. Women of childbearing potential must agree and commit to the use of a highly effective non-hormonal method of contraception, ie, 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. Man (male patient) with 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 (ie, 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.

11. Recovery (ie, to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).
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. Clinical or radiologic evidence of local or regional recurrence of disease or metastatic disease prior to or at the time of study entry.
2. Currently receiving chemotherapy, radiation therapy, immunotherapy, or biotherapy for breast cancer.
3. Major surgery within <30 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.
4. 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.
5. QTc interval >0.450 seconds (males) or >0.470 (females), or known history of QTc prolongation or Torsade de Pointes (TdP).
6. 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	≤100,000/µl (≤100 x 10^9/L)
Hemoglobin	≤9 g/dL
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
Creatinine	Creatinine clearance <30 mL/min (as calculated by Cockcroft-Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])

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

7. Active, unresolved infections.
8. 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.
9. Currently pregnant or breast-feeding.
10. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] CTCAE v.4.0 diarrhea of any etiology at baseline).
11. Clinically active infection with hepatitis B or hepatitis C virus.
12. 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.
13. Known hypersensitivity to any component of the investigational products; known hypersensitivity to salicylates; known allergies to any of the medications or components of medications used in the trial.
14. 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, LOPERAMIDE, ANTI-INFLAMMATORY, AND BILE ACID SEQUESTRANT 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; however, neratinib may be taken in the evening. Neratinib will be given continuously for one year (364 days) in thirteen (13) 28-day cycles, with no rest between cycles. Patients enrolled under Amendment 6 and Amendment 6.1 will receive neratinib at a starting dose of 120 mg/day with dose escalation (ie, total dose 120 mg daily for Week 1, 160 mg daily for the Week 2, and 240 mg daily for Week 3 and thereafter, until EOT). Patients enrolled starting with Amendment 7 will receive neratinib 160 mg neratinib for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib thereafter (C2D1 to EOT). Daily dosing should continue until a criterion for treatment withdrawal is met (see Section 10).

For patients starting with Amendment 7, patients must use a diary to record intake of neratinib for every cycle (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.

For patients enrolled under the dose-escalation schemes of Amendment 6/6.1, Amendment 7/7.1, during the dose escalation phase (<240 mg neratinib), for any patient who experiences Grade ≥ 2 AE(s) leading to neratinib dose interruption which do not resolve to Grade ≤ 1, a review of the patient and the patient's adverse event profile must occur with the Sponsor's Medical Monitor to determine whether the patient should be allowed to continue in the study.

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
Starting Dose	240 mg
-1	160 mg
-2	120 mg

mg = milligrams
Note: Dose reduction applies following completion of dose escalation to 240 mg (after C1D15) for patients enrolled starting with Amendment 6.

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 (ie, 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

- For patients enrolled under the Original Protocol:
  - Initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 2 mg (1 tablet/capsule) every 4 hours for the first 3 days. After the first 3 days, loperamide 2 mg every 6 to 8 hours through the first 2 cycles of therapy (56 days) from start of neratinib.
- For patients enrolled under Amendment 1 – Amendment 3:
- For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
- After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first 2 cycles of therapy (Day 56) from start of neratinib dosing
- For patients enrolled under Amendment 4:
  - For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
- After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) with the first dose of neratinib, for 1 cycle [28 days], and then as needed (not to exceed 16 mg per day).

- For patients enrolled under Amendment 5, Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1:
  - Loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients on a PRN basis, from the start of neratinib dosing with a goal of titrating to 1-2 bowel movements a day (not to exceed 16 mg per day).

Patients enrolled under the Original Protocol can maintain the loperamide prophylaxis dose already initiated with a goal of titrating to 1-2 bowel movements a day.

Recommended loperamide dosing by amendment is listed below in Table 4.

Table 4: Loperamide Dosing

Day	Loperamide Dose
Amendment 1 – Amendment 3	
1-14	Daily dose of 12 mg in 3 divided doses of 4 mg
15-56	Daily dose of 8 mg in 2 divided doses of 4 mg
57+	Daily dose as needed (not to exceed 16 mg per day)
Amendment 4	
Colestipol + loperamide intensive prophylaxis cohort :	
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)
Amendment 5	
Colestipol + loperamide PRN	
All cycles	Loperamide 4 mg PRN
Amendment 6, Amendment 6.1, Amendment 7, Amendment 7.1	
Neratinib dose escalation + loperamide PRN	
All cycles	Initial dose 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 (≤16 mg/day); continue loperamide at this frequency until diarrhea-free for 12 hours. Then titrate loperamide (4 mg PRN) to keep diarrhea controlled (1-2 bowel movements/day).

For patients starting with Amendment 6.1, patients must use a diary to record intake of loperamide for the first 2 cycles (56 days) of the study. Loperamide pill counts will be conducted only during the first 2 cycles (56 days) of therapy (only during the first cycle [28 days], starting with the colestipol cohort under Amendment 4).

6.2.1. Loperamide Dose Adjustment

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose with the goal of titrating to 1-2 bowel movements a day.

- For patients who develop diarrhea during Cycles 1-2, loperamide should be increased up to a maximum of 16 mg a day (or during Cycle 1 or after, for patients enrolled under Amendment 4; thereafter, loperamide may be administered up to 16 mg per day, as described above in Section 6.2).
- 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

6.3. Budesonide

For patients enrolled under Amendment 3 and who participate in the initial cohort that will evaluate budesonide, patients will self-administer oral budesonide at a dose of 9 mg once daily with or without food, for the first treatment cycle (28 days), to be taken with neratinib and intensive loperamide prophylaxis (Table 6). If a patient experiences an intolerable Grade 2 or higher AE deemed related to budesonide, dosing of budesonide should be held until the AE resolves to Grade 1 or lower and then restarting dosing will be considered. Neratinib and loperamide should be continued while budesonide dosing is being held. If the intolerable AE recurs, budesonide dosing should be discontinued and neratinib and loperamide continued.

Table 6: Budesonide Dosing

	Suggested Dosing Time		
	7 a.m	**3 p.m**	**9 p.m.**
Treatment Cohort (budesonide)	Budesonide[a] 9 mg		
C1D1 through 28 days			
	Neratinib 240 mg with food		
	Loperamide 4 mg[b]	Loperamide 4 mg[b]	Loperamide 4 mg[b]

[a] Budesonide tablets 9 mg should be swallowed whole with water and not chewed, crushed, or broken. Patients should be advised to avoid the consumption of grapefruit juice for the duration of their budesonide therapy. The total daily dosage is 9 mg tablet taken orally in the morning.
[b] Amendment 1 – Amendment 3: For the first 14 days, loperamide 4 mg is to be self-administered 3 times a day. After the first 14 days, loperamide 4 mg is to be self-administered twice a day through the first 2 cycles of therapy (Day 56). Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day). Amendment 4: After the first 14 days, loperamide 4 mg is to be self-administered twice a day through the first cycle only of therapy (Day 28). Amendment 5: loperamide is to be self-administered on an as-needed basis only from the beginning of neratinib treatment

6.4. Colestipol

- For patients who participate in the evaluation of colestipol, patients will self-administer colestipol at a dose of 2 g twice daily for the first treatment cycle, to be taken at least 2 hours after, but at least 4 hours before, neratinib and intensive loperamide prophylaxis (Table 7). Colestipol is a bile acid sequestrant anion resin that has the potential to interact with co-administered medication. Precaution should be taken around the timing of administration to avoid drug-drug interaction. Please refer to Section 7.6 and Appendix 10 of the protocol for specific recommendations regarding the administration of concomitant medication.

If a patient experiences an AE leading to dose interruption of any study treatment, all study treatments should be held until the AE resolves to Grade 1 or lower.

Table 7: Colestipol Dosing

	Suggested Dosing Times				
	7 a.m.	**9 a.m.**	**2 p.m.**	**5 p.m.**	**9p.m.**
Treatment Cohort (colestipol) C1D1 through 28 days		Colestipol[a] 2 g		Colestipol[a] 2 g	
	Neratinib 240 mg with food				
	Loperamide 4 mg[b]		Loperamide 4 mg[b]		Loperamide 4 mg[b]

[a] Colestipol tablets two (2) 1 g tablets should be taken orally twice daily for a total daily dose of 4 g. Important precautions are provided in Appendix 10.
[b] Amendment 1 – Amendment 3: Loperamide intensive prophylaxis is to be given during Cycle 1, during the initial 14-day dosing period. After Day 14, loperamide 4 mg twice daily, intensive prophylaxis is to be given during the balance of Cycle 1. For Cycle 2, loperamide may be administered PRN. Amendment 4: After the first 14 days, loperamide 4 mg is to be self-administered twice a day through the first cycle only of therapy (Day 28). Amendment 5: loperamide is to be self-administered on an as-needed basis only from the beginning of neratinib treatment.

6.5. Packaging, Labeling, and Storage

6.5.1. 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.

6.5.2. Loperamide

Commercially available loperamide will be provided to study sites by the Sponsor. Loperamide will be relabeled by the Sponsor, “For investigational use.”

6.5.3. Budesonide

Commercially available budesonide will be provided to study sites by the Sponsor. Budesonide will be relabeled by the Sponsor, “For investigational use.”

6.5.4. Colestipol

Commercially available colestipol will be provided to study sites by the Sponsor. Colestipol will be relabeled by the Sponsor, "For investigational use."

6.6. Drug Accountability and Treatment Compliance*

The study site must maintain accurate records documenting dates and quantities of investigational product: neratinib, loperamide, budesonide, and colestipol received from the Sponsor. Records must also be maintained documenting dates and quantities (ie, pill counts) of neratinib, loperamide, budesonide and colestipol 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 products, neratinib, loperamide, anti-inflammatory, or bile acid sequestrant treatments accidentally or deliberately destroyed must also be documented.

Throughout the study, reconciliation will be made between the amounts of investigational product: neratinib, loperamide, anti-inflammatory, and bile acid sequestrant treatments supplied, dispensed, returned, and subsequently destroyed or returned to the Sponsor. All investigational products, neratinib, loperamide, anti-inflammatory, and bile acid sequestrant treatments 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).

*reference to loperamide, budesonide and colestipol investigational product accountability and treatment compliance are related to the specific protocol amendment cohorts.

7. CONCOMITANT MEDICATIONS

All concomitant medications and concomitant nonpharmacological treatments/therapies will be recorded from 30 days prior to the signing of the informed consent form (ICF) until the Safety Follow-up Visit occurring 28 days after the last dose of neratinib. 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 30 days, which medications are ongoing at the time of screening, any medical conditions that require medication, and all prior cancer therapies. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

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 7.5), or drugs with potential for drug-drug interactions (Section 7.6), or in the associated Appendices (Appendix 4, Appendix 5, Appendix 6, Appendix 9, and Appendix 10), 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.

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). Prior to Amendment 5, primary prophylactic use of antidiarrheal medication was **mandatory** for all enrolled patients taking neratinib; starting with Amendment 5, and continuing in Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1 primary prophylactic use of loperamide is no longer required.

As noted in Section 6.2, loperamide is the recommended standard therapy to treat diarrhea in this study, and it is provided to the sites by the Sponsor. 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 and adjunctive therapies (eg, octreotide [SANDOSTATIN®] (or equivalent as approved by the Sponsor) are also recommended for use when appropriate.

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 2

cycles (56 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.

Intensive Prophylactic dosing instructions (patients enrolled in Amendment 1 to Amendment 4)

- Inform patients that they will experience diarrhea while taking neratinib.
- Administer loperamide:
  - For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients three times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
  - After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first 2 cycles of therapy (Day 56) from start of neratinib dosing.
    - For patients in the treatment group receiving colestipol under Amendment 4, this regimen would be for the rest of the first cycle of therapy [Day 28], from the start of neratinib dosing.
  - Patients enrolled under the Original Protocol can maintain the loperamide prophylaxis dose already initiated with a goal of titrating to 1-2 bowel movements a day.
  - Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day) (during Cycle 2 and beyond for patients in the treatment group receiving colestipol under Amendment 4).

- For patients who develop diarrhea during Cycles 1-2, loperamide should be increased up to a maximum of 16 mg a day (or during Cycle 1 or after, for patients enrolled under Amendment 4).
- 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 Cycle 1 or Cycle 2 (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection 3 times a day, 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.

PRN dosing instructions (patients enrolled in Amendment 5, Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1)

- 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 (1-2 bowel movements/day).

Other instructions (all protocol versions)

- The sites must contact the patient by phone at 1 day, 2 days, and 3 days after the first dose of neratinib:

1. to inquire about any diarrhea and about potential AEs;
2. to provide guidance to the patients for immediate and appropriate management of AEs, including diarrhea as specified in this protocol;
3. to confirm that the patients have loperamide available
4. to inquire about the first date of neratinib dosing; the Investigator/research staff must update the electronic CRF (eCRF) within 3 days of receipt of this information.

These phone calls are mandatory and must be recorded in the study chart together with response from the patient and action taken.

- 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

For Cycle 3 and beyond for patients enrolled prior to Amendment 4; for Cycle 2 and beyond for the treatment group receiving colestipol under Amendment 4; after the start of dosing for the treatment group receiving colestipol under Amendment 5, and for treatment groups under Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1:

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.
- 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 Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneously (SC) three times daily (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 patients enrolled starting with Amendment 6, other measures to consider for Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy) should include:
  - Budesonide 9 mg orally (PO) once daily (QD) for 14 to 28 days.
  - Colestipol 2 g twice daily (PO, BID) for 14 to 28 days.

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 twice daily (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. Colonoscopy with biopsy should be strongly considered for patients who have significant diarrhea. Results for appearance, histology, pathology, and cultures 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. Anti-inflammatory Treatment

For patients enrolled under Amendment 3, the effect of an anti-inflammatory treatment, specifically budesonide, will be tested to determine the effect on the incidence, severity, and duration of diarrhea.

Following the completion of Cycle 1 by the first approximately 64 patients in the first treatment cohort who receive neratinib and intensive loperamide prophylaxis plus budesonide anti-inflammatory treatment, the treatment cohort will be evaluated. The Sponsor will regularly review accumulating safety data (by individual subject and in aggregate). Early termination of a treatment cohort or the study may be permitted if data indicate that anti-inflammatory treatment is ineffective. Once enrollment in the cohort testing budesonide is complete, the next cohort will begin enrollment, to evaluate the bile acid sequestrant colestipol.

The Patient Diary will be used by patients to record the daily use of budesonide treatment. Also, the daily dose of the anti-inflammatory treatment noted on the diary will be reviewed and recorded on the CRF.

Budesonide (along with neratinib and loperamide) 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 budesonide concomitantly with the first dose of neratinib and loperamide to minimize the occurrence and severity of diarrhea.

Anti-inflammatory dosing instructions:

- Budesonide
  - For the first treatment cycle, budesonide will be self-administered orally by patients at a dose of 9 mg once daily either with or without food, for the first treatment cycle, and to be taken with neratinib and loperamide on the intensive prophylaxis schedule. Budesonide should be swallowed whole and not chewed, crushed or broken.

7.4. Colestipol (Amendment 4 and Amendment 5)

For patients enrolled under Amendment 4 and Amendment 5, the effect of the bile acid sequestrant, colestipol, on the incidence, severity, and duration of diarrhea will be investigated in a treatment cohort of 40 patients.

Following the completion of Cycle 1 by the first approximately 40 patients in the first cohort who receive neratinib and intensive loperamide prophylaxis plus budesonide, patients in the next cohort will receive colestipol 2 g, twice daily, for 28 days. The Sponsor will regularly review accumulating safety data (by individual patient and in aggregate). Early termination of a cohort or the study may be permitted if data indicate that bile acid sequestrant treatment is ineffective for the treatment of diarrhea.

The Patient Diary will be used by patients to record daily the use of colestipol. Also, the daily dose of colestipol noted on the diary will be reviewed and recorded onto the CRF.

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

7.5. 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.
- Systemic steroid use, by oral or parenteral route.

7.6. Potential for Drug-Drug Interactions

7.6.1. Potential Drug-Drug Interactions with Neratinib

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 Torsades 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 coumarin-derivative anticoagulants (ie, 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), 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.

7.6.2. Potential for Drug-Drug Interactions with Budesonide

For patients participating in Amendment 3, when taking budesonide with neratinib and loperamide during the first 28 days (Cycle 1) there should be close monitoring during the concomitant administration with ketoconazole (and itraconazole, ritonavir, saquinavir, or erythromycin), or any other CYP3A4 inhibitor for increased signs and/or symptoms of hypercorticism. Refer to Appendix 9 for contraindications, warnings, and precautions for budesonide.

Avoid grapefruit juice, which is a known CYP3A4 inhibitor.

Since the dissolution of the coating of budesonide is pH dependent, the release properties and uptake of the compound may be altered when budesonide is used after treatment with gastric acid reducing agents (PPI's, H2-receptor antagonists and antacids).

7.6.3. Potential for Drug-Drug Interactions with Colestipol

For patients participating in Amendment 4, when taking colestipol with neratinib and lopermide during the first 28 days (Cycle 1), there should be attention to the time interval between the administration of colestipol tablets and any other medication. The interval for colestipol administration should be as long as possible from other concomitant medication. Patients should take other drugs at least one hour before or four hours after colestipol to avoid impeding their administration. Since colestipol is an anion exchange resin, this effect may be related to a strong affinity for anions other than the bile acids. In vitro studies have indicated that colestipol binds a number of drugs.

Repeated doses of colestipol given prior to a single dose of propranolol in human trials have been reported to decrease propranolol absorption. Patients on propranolol and possibly other beta-blockers should be monitored when colestipol is added or deleted from the therapeutic regimen. Effects of the absorption of other beta-blockers have not been determined.

Studies in humans show that the absorption of chorothiazide as reflected in urinary excretion is markedly decreased even when administered one hour before colestipol. The absorption of tetracycline, furosemide, penicillin G, hydrochlorothiazide, and gemfibrozil was significantly decreased when given simultaneously with colestipol. These drugs were not tested to determine the effect of administration one hour before colestipol.

No lowering effect on blood levels in humans was noted when colestipol was administered with any of the following drugs: aspirin, clindamycin, clofibrate, methyldopa, nicotinic acid (niacin), tolbutamide, phenytoin or warfarin. Particular caution should be observed with digoxin preparations since ther are conflicting results for the effect of colestipol on the availability of digoxin and digitoxin. The potential for binding of these drugs if given concomitantly is present. Discontinuing colestipol could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking colestipol.

Bile acid bind resins such as coletipol may also interfere with the absorption of oral phosphate supplements and hydrocortisone.

A study has shown that cholestyramine binds bile acids and reduces mycophenolic acid exposure. As colestipol also binds bile acids, colestipol may reduce mycophenolic acid exposure and potentially reduce efficacy of mycophenolate mofetil.

Refer to Appendix 10 for contraindications, warnings, and precautions for colestipol.

7.7. Treatment Compliance

Refer to Section 6.6.

8. STUDY ASSESSMENTS

8.1. Efficacy Assessment

Not applicable for this study.

8.2. Safety Assessments

8.2.1. Clinical Endpoints and Definitions

Safety Endpoints:

- The primary endpoint of the study is the incidence of Grade 3 diarrhea in patients with early-stage HER2+ breast cancer.
- Secondary safety endpoints include the frequency distribution of the maximum grade incidence of diarrhea, the incidence and severity of diarrhea by loperamide exposure, with and without anti-inflammatory treatment; and the incidence of SAEs and AESIs.

Refer to the Schedule of Procedures (Appendix 1) for time points. The following safety endpoints will be assessed: medical history, AEs, vital signs, detailed/brief (symptom-guided) physical examinations, 12-lead ECGs, LVEF (ECHO or MUGA), and laboratory evaluations.

AEs and AESIs will be graded according to the NCI CTCAE, version 4.0. Serious AEs and AESIs will be reported until 28 days after the last dose of the investigational product and will be followed until resolution. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to neratinib's administration, it should be promptly reported. More details on AEs can be found in Section 13.

For patients starting with Amendment 6.1, the diary used for recording of investigational product intake will also be used by patients to document any other study treatment for the first 2 cycles (56 days) of the study (see Section 8.5.2). 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. Laboratory Assessments

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

The institutional laboratory will analyze all hematology and routine blood chemistry samples collected. Samples will be analyzed at a facility meeting Good Laboratory Practice (GLP) requirements and using methods documented in a methods validation report.

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

The following laboratory endpoints will be determined, as summarized in Table 8.

Table 8: 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 or urine pregnancy test	In women of child-bearing capacity (at screening and within 72 hours prior to C1D1, and monthly, including at the End-of-Treatment Visit and at the Safety Follow-up Visit).	

For Amendment 4 and Amendment 5 patients who will be receiving colestipol, a baseline (occurring at Screen or C1D1) and C2D1 fasting lipid panel is required to assess total cholesterol, HDL-C, and triglycerides.

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 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 approximately 40 mL, corresponding to approximately 10 mL blood during screening and 5 mL blood at subsequent visits.

8.2.3. 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.

8.2.4. Physical Examination

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

The brief (symptom-guided) physical examination will evaluate any clinically significant abnormalities; including worsening of medical history conditions.

8.2.5. 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.

8.2.6. 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), ie, within 4 weeks before Day 1 of Cycle 1 and at EOT, Cycle 13/Day 28. 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

Assessments for health outcomes and biomarkers will only be collected for patients enrolled starting with Amendment 2.

8.3.1. Health Outcomes Assessments

The exploratory endpoint of patient-reported health outcomes will be assessed by the EuroQol EQ-5D-5L and by the FACT-B questionnaires (for patients enrolled starting with Amendment 2) and the RSCL (for patients enrolled starting with Amendment 6.1).

Health outcomes will be assessed by patient-reported responses to the EQ-5D-5L multi-dimensional health status questionnaire (Appendix 7) and by the FACT-B (Appendix 8), and by the RSCL (Appendix 11). These assessments will be administered in accordance with the Schedule of Procedures (Appendix 1).

The patient-reported assessments are for the purpose of exploring the subject's own perceptions about their symptoms and health-related quality of life and thus a proxy (ie, a caregiver or study personnel) should not complete the questionnaires. Additionally, the investigator must not influence the subject's assessments. Every effort should be made to maintain an unbiased assessment. Questionnaires should be administered before any other study procedures on the day of the study visit. If questionnaires can only be completed after the study visit, they should be administered no later than 5 days from the visit. Both assessments need to be completed on the same day. On the day of treatment discontinuation, it is acceptable for questionnaires to be

performed after study procedures. If assessments were completed within the previous 7 days at a regularly scheduled visit, assessments do not need to be administered at the EOT visit.

EQ-5D-5L:

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

FACT-B:

The FACT-B (version 4) is a 37-item questionnaire with 5 subscales assessing physical, social, emotional, and functional well-being and additional concerns more specific to women with breast cancer. Subjects will be asked to indicate how true a statement had been for them over the past 7 days using a 5-point scale as follows: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All items receive equal weighting.

Rotterdam Symptom Checklist:

The RSCL measures both physical and psychological aspects of quality of life (QOL) in cancer patients. The instrument assesses symptom-related distress among patients for physical symptoms, psychological symptoms, and activities of daily living. The 3 domains are assessed in a 4-point scale (not at all, a little, quite a bit, very much) for 38 items. Patients are asked to indicate the degree to which they have been bothered by the indicated symptoms in the past week.

8.3.2. Biomarkers

The exploratory endpoint of disease biomarkers will consist of biomarkers of disease recurrence (for patients enrolled starting with Amendment 2).

cfDNA will be obtained from plasma samples collected several times during the study and at disease recurrence (if applicable), in accordance with the Schedule of Procedures (Appendix 1). cfDNA will undergo molecular profiling to identify biomarkers of disease recurrence

8.3.3. Disease Recurrence

Clinical documentation of recurrence, including recurrence site, radiographic, and/or pathologic procedures will be collected at end-of-treatment.

8.3.4. Microbiome Evaluation (for patients enrolled starting with Amendment 6)

At select study centers, a stool swab will be collected at Screening, C2D1, and C4D1 and/or at time of treatment discontinuation if earlier than C4D1 for possible future assessments of microbiome to assess the effect that neratinib has on the microbiome.

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 patient diary will be provided by the Investigator for the patient to record daily study medication intake for every cycle. The number of stools per day and the use of antidiarrheal treatment will also be required to be recorded in the patient diary during the first 2 treatment cycles.

Individual patient dosing compliance should be reviewed 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.

For the first 2 cycles, eDiaries will be implemented, either hand-held or web-based, to collect the number of daily bowel movements, neratinib self-administration (number of tablets taken), and anti-diarrheal intake (number of loperamide capsules or tablets, and as applicable, the number of doses of other anti-diarrheal medications). If the use of an eDiary, either hand-held or web-based, is not feasible, the alternative of a paper diary will be considered on a case-by-case basis.

After 2 cycles, the hand-held or web-based diary will continue to be available to patients, or alternatively, they may switch to a paper diary to be completed on a daily basis and returned to the clinic (site) for review and evaluation at scheduled study visits.

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 9 in Section 5.1), which should be performed, both, at screening and within 72 hours prior to Cycle 1/Day 1.

Documented HER2 overexpression or gene-amplified tumor by a validated approved method (Wolff et al, 2013) must be retrieved.

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.
  - Cancer history, including but not limited to, date of first diagnosis, nodal status (based on pathologic assessment of nodes at the time of surgery, either before adjuvant chemotherapy or after completion of neoadjuvant chemotherapy), histology, tumor stage at diagnosis, previous chemotherapy/biotherapy/immunotherapy, previous adjuvant therapy, drug names, start and stop dates, reason for treatment discontinuation, previous radiation, and prior cancer related surgical therapies.
  - Other previous and concomitant medication will be documented, as described in Section 7.
- Demography: date of birth, sex, ethnicity, and race (Asian, Black or African American, White, Other).
- Physical examination. Refer to Section 8.2.4.
- Vital signs, including height and weight. Refer to Section 8.2.3.
- ECG. Refer to Section 8.2.5.
- LVEF. Refer to Section 8.2.6.
- Laboratory tests. Refer to Section 8.2.2.
- Health outcomes assessments. Refer to Section 8.3.1

- Biomarkers. Refer to Section 8.3.2.
- Microbiome evaluation. Refer to Section 8.3.4.
- Per standard of care, bone scan or positron emission tomography (PET) scan performed within 28 days prior to the date of enrollment; only required if ALP is ≥2x upper limit of normal (ULN) and/or there are symptoms of metastatic bone disease. A confirmatory imaging study is required if the results from the bone scan are questionable (see Section 5.1)
- Per standard of care, computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound of the abdomen and chest performed within 28 days prior to the date of enrollment; only required if aspartate aminotransferase (AST)/ALT or ALP is ≥2x ULN (see Section 5.1)
- Other radiologic assessments may be performed within 28 days prior to the date of enrollment, unless a CT scan has already been performed, to rule out underlying breast cancer recurrence if indicated and as per standard of care (for patients enrolled starting with Amendment 6.1).
- ECOG status will be assessed in accordance with the Schedule of Procedures (Appendix 1). The ECOG categories are summarized in Appendix 3.

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.

For patients enrolled under Amendment 3, the anti-inflammatory treatment budesonide will be administered for 1 cycle during Cycle 1 for patients in this treatment cohort. For patients enrolled under Amendment 4, colestipol will be administered for 1 cycle during Cycle 1 (colestipol + intensive loperamide prophylaxis), and colestipol will also be administered for patients enrolled under Amendment 5 (colestipol + PRN loperamide). All patients enrolled under Amendment 6 and Amendment 6.1 will be evaluated after receiving neratinib administered according to the following dose-escalation scheme: 120 mg neratinib for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib for Week 3 and thereafter (C1D15 to EOS). All patients enrolled under Amendment 7 and Amendment 7.1 will be evaluated after receiving neratinib administered according to a second dose escalation scheme: 160 mg neratinib to be taken for the first 2 weeks (C1D1 – C1D14), followed by 200 mg neratinib to be taken for the next 2 weeks (C1D15 – C1D28), followed by 240 mg neratinib daily dose taken thereafter (C2D1 to EOT). Loperamide is to be administered on a PRN basis only. For both dose escalation regimens, the Investigator or research staff must call patients at the end of the first and second weeks of treatment (ie, Day 7 or Day 8, and Day 14 or Day 15) to confirm that the patient has increased the dose of neratinib from 120 mg to 160 mg, and from 160 mg to 240 mg, respectively.

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

- AE assessment. Refer to Section 13.

- Monthly serum or urine pregnancy testing. Refer to Inclusion Criterion 9 in Section 5.1 and Section 8.2.2. The Investigator or designee must contact patients on months that do not have a scheduled visit to confirm that the patient has performed the pregnancy test, is not pregnant, and this is noted in the clinical progress notes.
- Concomitant medication assessment. Refer to Section 7.
- Brief symptom-guided physical examination. Refer to Section 8.2.4.
- Vital signs, including weight. Refer to Section 8.2.3.
- ECG. Refer to Section 8.2.5.
- Laboratory tests. Refer to Section 8.2.2.
- Health outcomes assessments. Refer to Section 8.3.1.
- Biomarkers. Refer to Section 8.3.2.
- Microbiome evaluation. Refer to Section 8.3.4.
- Treatment compliance assessment. Refer to Section 6.6.
- Collect Patient Diary at C2D1 and at C3D1 visits, and at clinic visits when applicable.

9.3. Treatment Discontinuation or End-of-Treatment Assessments

The EOT visit will occur within 5 business days of Cycle 13/Day 28. 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.
- Serum or urine pregnancy test. Refer to Inclusion Criterion 9 in Section 5.1.
- Concomitant medication assessment. Refer to Section 7.
- Physical examination. Refer to Section 8.2.4.
- Vital signs, including weight. Refer to Section 8.2.3.
- ECG. Refer to Section 8.2.5.
- LVEF. Refer to Section 8.2.6.
- Laboratory tests (hematology, chemistry, LFT). Refer to Section 8.2.2.
- Health outcomes assessments. Refer to Section 8.3.1 .
- Biomarkers. Refer to Section 8.3.2.
- Microbiome evaluation. Refer to Section 8.3.4.
- Disease recurrence as applicable. Refer to Section 8.3.3.
- Collect Patient Diary for treatment compliance assessment.

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 AESIs/SAEs and to obtain a serum or urine pregnancy test.

9.5. Long-term Follow-up

Not applicable for this study.

9.6. End of Study

The 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 end of study (EOS) is declared earlier, patients will be offered the opportunity to complete the 1-year course of treatment either through a treatment extension study or through a managed access program.

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 a AESIs/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 (ie, 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.

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 at least one week of study therapy 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 the 1-year course of 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. Before database lock, a separate statistical analysis plan will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

12.1. General Considerations

12.1.1. Subgroups/Cohorts

Unless otherwise specified, all analyses will be done by the following cohorts: (1) the Original Protocol, (2) Amendment 1 or Amendment 2, (3) Amendment 3, (4) Amendment 4, (5) Amendment 5, (6) Amendment 6 and Amendment 6.1, or (7) Amendment 7 and Amendment 7.1 by treatment cohort.

12.2. Study Patients

12.2.1. Disposition of Patients

The number and percentage of patients entering and completing the study will be presented. Reasons for withdrawal will also be summarized.

12.2.2. Demographic Data, Medical History, Baseline Characteristics, and Concomitant Medications

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.

12.2.3. Treatment Compliance

Duration of treatment will be summarized. In addition, the cumulative dose, dose intensity (quantity per time unit) and the relative dose intensity (dose intensity/scheduled dose per time unit) will be summarized. The number of patients with dose holds or dose reductions will be tabulated.

12.3. Efficacy Analyses

Not applicable for this study.

12.4. Safety Analysis

All patients who receive a dose of neratinib will be analyzed for safety.

12.4.1. Statistical Methods

The primary endpoint is the incidence of Grade 3 or higher diarrhea. The accompanying Clopper-Pearson 2-sided 95% CIs will be computed. The primary endpoint will be estimated for the overall safety population and, if needed, for subgroups of patients with specific anti-diarrheal prophylaxis regimens per protocol.

12.4.2. Adverse Events

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 and AESIs will also be summarized.

Serious AE and deaths will be provided in a listing. All AEs resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of investigational product will also be listed and tabulated by PT.

12.4.3. Laboratory Results

Laboratory test results will be collected pretreatment through 28 days after the last dose of investigational product. Standard reference ranges will be used for missing or discrepant normal ranges.

Mean change from baseline in laboratory test values at each visit will be provided. On-study laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be summarized.

12.5. Exploratory Endpoints Analyses

Exploratory analyses will be conducted on all patients in the safety population who were enrolled starting under Amendment 2.

12.5.1. Health Outcomes Assessments

Patient-reported health outcomes data (scores on the EQ-5D-5L, FACT-B, and RSCL questionnaires) will be summarized and plotted over time. Analyses will be descriptive only; changes from baseline will be provided with both point estimates and CIs.

12.5.2. Biomarkers Analyses

Exploratory analyses will be conducted to evaluate the relationship between disease biomarkers identified from molecular profiling and indications of clinical disease recurrence. No formal statistical analyses are planned, however, of biomarker data.

12.5.3. Microbiome Analyses

Results of microbiome evaluation from participating sites, if available, will be summarized at baseline, C2D1, C4D1, and/or at time of treatment discontinuation if earlier than C4D1. No formal statistical analyses are planned of the microbiome data.

12.6. Interim Analysis

An interim analysis is planned when approximately 120 patients enrolled under the Original protocol, Amendment 1, and Amendment 2, all patients have completed at least 2 cycles (56 days) of neratinib with loperamide prophylaxis. The interim analysis will only include those 120 patients enrolled under the Original Protocol, Amendment 1, and Amendment 2. Other additional analyses by cohort may be carried out as required.

12.7. Determination of Sample Size

The first 120 patients will be under the Original Protocol, Amendment 1, and Amendment 2. The incidence of Grade 3 or higher diarrhea is assumed to be 15% in this study. A sample size of 120 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 18.5%. For example, if 18 out of the 120 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CIs will be 15.0% (9.1%, 22.7%) where the width of the CI is 13.5%.

In addition to the analyses of the overall safety population, anti-diarrheal prophylaxis regimen-specific subgroup analyses will be performed as needed.

For patients enrolled under Amendment 3, the effect of anti-inflammatory treatment budesonide on the incidence, severity, and duration of diarrhea will be assessed. For patients enrolled under Amendment 4, the effect of a bile acid sequestrant colestipol was to be assessed, with either intensive loperamide prophylaxis, or loperamide given on a PRN basis (Amendment 5); for patients enrolled under Amendment 6/6.1, under Amendment 7/7.1, the effect of 2 different dose-escalation schemes of neratinib will be assessed. The incidence of Grade 3 or higher diarrhea will be evaluated. For each additional cohort, a sample size of 64 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 26%. For example, if 7 out of the 64 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CI will be 10.9% (4.5–21.2%) where the width of the CI is 17%.

For each additional cohort, a sample size of 100 patients will ensure that the width of the 95% Clopper-Pearson CI of the incidence of Grade 3 or higher diarrhea is no more than 21%. For example, if 15 out of the 100 patients are observed to have Grade 3 or higher diarrhea, the incidence and its 95% (2-sided) CI will be 15.0% (8.7–23.5%) where the width of the CI is 15%.

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 Version 5.0) 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, ie, 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's 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. However, if necessary and only if requested by the Sponsor, data capture may be performed using paper CRFs.

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. The data should be reviewed, signed and dated by the Investigator electronically for accuracy and completeness. 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.

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. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

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 and in keeping with local legal requirements.

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, ie, 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.

14.3. 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.

<u>First Publication</u>

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.

<u>Subsequent Publications</u>

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-6201. The Study Principal Investigator(s) shall be free to publish or present, subject to the timing described in the Clinical Study Agreement.

15. REFERENCE LIST

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16. SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Officer

Title of Study: An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide.

Study Number: PUMA-NER-6201

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

_____ _____
Name (Printed) Date

_____
Title

Declaration of Principal Investigator

Title of Study: An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide.

Study Number: PUMA-NER-6201

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

_____ _____
Name (Printed) Date

_____ _____
Title Institution (block letters) and site number

_____ _____
Address Phone number

17. APPENDICES

APPENDIX 1. SCHEDULE OF PROCEDURES

Table A1.1. Schedule of Study Procedures

Study Procedures	Screening	Active Treatment[a] Cycle / Day (C/D)							Safety Follow-up Visit
	Days -28 to -1	C1/D1	C2/D1	C3/D1	C4/D1	C7/D1	C10/D1	C13/D28 / End of Treatment Visit[a]	28 Days After Last Dose
Study visit window in Days	0	-3[b]	±5	±10	±10	±14	±14	±5	(+5)
Informed consent[c]	X								
Medical/Cancer history/Demography	X								
ERBB2 status documentation[d]	X								
ECOG performance status	X								
Serum or urine β-hCG[e]	X	X	X	X	X	X	X	X	X
Physical examination	X							X	
Targeted physical examination[f]		X	X	X	X	X	X		
Vital signs[g]	X	X	X	X	X	X	X	X	
Complete blood count plus differential[h]	X	X	X	X	X	X	X	X	
Serum chemistry[i]	X	X	X	X	X	X	X	X	
Liver function tests[j]	X	X	X	X	X	X	X	X	
Biomarkers[k]	X					X		X	
Stool swab for microbiome evaluation[l]	X		X		X				
MUGA or ECHO[m]	X							X	
ECG (12-lead)	X		X		X	X	X	X	
Bone scan or PET scan[n]	X								
CT scan or MRI or ultrasound of the abdomen and chest[o]	X								
Health outcomes assessments[p]		X	X		X	X	X	X	
Concomitant medications or treatments[q]	X	X	X	X	X	X	X	X	X
Neratinib administration[r]		Continuous once-daily dosing (pill count at each visit)							
Loperamide administration[r]		For loperamide dosing during C1 & C2, see Footnote "r" (pill count at each visit)	As needed						

Study Procedures	Screening	Active Treatment[a] Cycle / Day (C/D)							Safety Follow-up Visit
	Days -28 to -1	C1/D1	C2/D1	C3/D1	C4/D1	C7/D1	C10/D1	C13/D28 / End of Treatment Visit[a]	28 Days After Last Dose
Study visit window in Days	0	-3[b]	±5	±10	±10	±14	±14	±5	(+5)
Anti-inflammatory or colestipol administration[s]		X							
Adverse events[t]		X----------X							X
Phone calls to patient after first dose[u]		X							

Abbreviations: β-hCG=beta-human chorionic gonadotropin; C=cycle; CT = computed tomography; D=day; ECG= electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Collaborative Oncology Group; ERBB2=human epidermal growth factor receptor 2; MRI = magnetic resonance imaging; MUGA=multiple-gated acquisition scan; PET = positron emission tomography.

[a] A treatment cycle is defined as 28 days. The Cycle 13/Day 28 Visit (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 study treatment 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.

[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: complete blood count (with differential), serum chemistry, MUGA/ECHO, ECGs, CT scan/MRI/ultrasound of abdomen and chest, and bone scan or PET scan. 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, (for patients starting with Amendment 7, this will be for every cycle of the study), any adverse reactions, number of loose stools and use of loperamide and/or other antidiarrheals (for patients starting under Amendment 7, adverse reactions, stools, and antidiarrheals are to be documented only for the first 2 cycles [56 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] Documentation of locally assessed ERBB2-amplified status by fluorescence in situ hybridization (FISH) (>2.2) or ERBB2 overexpression by immunohistochemistry (IHC) (3+) must be retrieved.

[e] For women of childbearing potential; to be performed both at screening and within 72 hours prior to Cycle 1/Day 1, and monthly, including at the End-of-Treatment Visit and at the Safety Follow-up Visit. The Investigator or research staff must contact patients on months that do not have a scheduled visit to confirm that the patient has performed the pregnancy test. In addition, a pregnancy test may be done at any time during the study at the discretion of the investigator if a subject misses a period or has unusual menstrual bleeding.

[f] During treatment, brief symptom-guided physical examinations will be done on Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 7, and Cycle 10.

[g] 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).

[h] Complete blood count (CBC) to include hematocrit (Hct), hemoglobin (Hb), platelet count, red blood cell (RBC) count, and white blood cell (WBC) count plus differential. CBCs must be tested at screening and on Day 1 of Cycle 1 (-3 days), Cycle 2 (±5 days), Cycle 3 (±10 days), Cycle 4 (±10 days), Cycle 7 (±14 days), Cycle 10 (±14 days), as well as on Day 28 of Cycle 13/EOT Visit (±5 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.

[i] Serum chemistry tests include sodium, potassium, chloride, calcium, magnesium, blood urea nitrogen (BUN) or urea, serum creatinine, albumin, lactate dehydrogenase (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. For Amendment 4 and Amendment 5 patients who will be receiving colestipol, a baseline (occurring at Screen or C1D1) and C2D1 fasting lipid panel is required to assess total cholesterol, HDL-C, and triglycerides.

[j] Liver function tests (LFTs) must include total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST). LFTs must be tested at screening, and on Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 7, and Cycle 10, as well as on Day 28 of Cycle 13/EOT Visit (±5 days), 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 (see Appendix 2).

[k] For patients enrolled starting with Amendment 2 only: cfDNA will be obtained from plasma samples collected at screening, C7D1, C13D28, and/or at time of treatment discontinuation and at disease recurrence; cfDNA will undergo molecular profiling to identify biomarkers of disease recurrence.

[l] At selected centers, a small stool swab from toilet paper, inserted into a tube that is provided, will be collected by the patient at Screening, C2D1, and C4D1 or at time of treatment discontinuation if earlier than C4D1 for possible future assessments of microbiome. The tube is to be inserted into a bag then labeled for return in packaging.

[m] During trial participation, ECHO or MUGA will be performed at Screening and on Day 28 of Cycle 13/EOT Visit. It is strongly recommended to use the same method of measurement for the same patient throughout the duration of the study.

[n] Per standard of care, bone scan or positron emission tomography (PET) scan performed within 28 days prior to the date of enrollment; only required if alkaline phosphatase (ALP) is ≥2x upper limit of normal (ULN) and/or there are symptoms of metastatic bone disease. A confirmatory imaging study is required if the results from the bone scan are questionable (see Section 5.1).

[o] Per standard of care, computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound of the abdomen and chest performed within 28 days prior to the date of enrollment; only required if aspartate aminotransferase (AST)/alanine aminotransferase (ALT) or ALP is ≥2x ULN (see Section 5.1).

[p] For patients enrolled starting with Amendment 2 only: Health outcomes assessments consist of the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and the EQ-5D-5L questionnaires. For patients enrolled starting with Amendment 6.1: the Rotterdam Symptom Checklist (RSCL) will be added to the health outcomes questionnaires that the patient will complete. Questionnaires should be completed before any other study procedures on the day of the study visit. At the final or EOT visit, it is acceptable for questionnaires to be completed after study procedures. Questionnaires are to be completed by the patient at C1D1, C2D1, C4D1, C7D1, C10D1, and C13D28.

[q] Concomitant medications and concomitant nonpharmacologic treatments/therapies are recorded from 30 days before signing of the informed consent form until the Safety Follow-up Visit.

[r] Patients enrolled starting with Amendment 6 will receive neratinib at a starting dose of 120 mg/day with dose escalation (ie, total dose 120 mg daily for the first week, 160 mg daily for the Week 2, and 240 mg daily for Week 3 and thereafter, until EOT. For patients receiving budesonide, loperamide is to be administered daily for two (2) 28-day cycles and then as needed (PRN). For patients in Amendment 4, loperamide is to be administered for one 28-day cycle and then as needed (PRN) thereafter. For patients enrolled under Amendment 5, Amendment 6, Amendment 6.1, Amendment 7, and Amendment 7.1, loperamide is to be administered as needed (PRN) for the entire study. Patients are asked to document administration of neratinib and loperamide on a diary on a daily basis (for patients starting with Amendment 6.1, this will be for the first 2 cycles (56 days) of the study; for patients starting with Amendment 7, after 2 cycles only neratinib administration is to be recorded, until EOT), and to return this diary to the site at appropriate visits (for patients starting with Amendment 6.1, the diary will be collected at C3D1, or at EOT if earlier). Individual patient dosing compliance should be reviewed at each study visit by study site staff. Investigators must ensure that patients have loperamide on hand when starting to take neratinib. Loperamide and 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.

[s] The effect of anti-inflammatory treatment (for patients enrolled under Amendment 3 and a bile acid sequestrant, colestipol, (for patients enrolled under Amendment 4 and Amendment 5) on the incidence and severity of Grade 3 or higher diarrhea will be investigated in 3 sequential patient cohorts. The first treatment cohort will receive budesonide + intensive loperamide prophylaxis, the next cohort will receive colestipol + intensive loperamide prophylaxis, and the subsequent cohort will receive colestipol + loperamide on a PRN only basis.

[t] From the signing of the informed consent form to 28 days after the last dose, adverse events (AEs) and serious adverse events (SAEs) are monitored continuously and recorded in the electronic case report form (eCRF) at every visit. Patients must be instructed to contact the site to report and discuss the severity of diarrhea and the appropriate course of treatment. Patients must use the diary to document any episodes of diarrhea for the first 2 cycles (56 days) of the study. On this diary, patients also record the baseline number of stools per day, and in case of diarrhea, the number of loose stools per day and use of loperamide and/or other antidiarrheals, if applicable. Patients are asked to return this diary to the site at each visit. Patient instructions for the management of diarrhea are reviewed with the patients and handed to the patient at the time of enrollment. Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to neratinib's administration, it should be promptly reported.

[u] The Investigator or research staff must call the patients 1, 2, and 3 days after the first dose of neratinib (i) to inquire about potential adverse events, including diarrhea; (ii) to provide guidance to the patients for immediate and appropriate management of AEs, including diarrhea as specified in this protocol; (iii) to confirm that the patients have loperamide available, in case needed; (iv) to inquire about the first date of neratinib intake; the Investigator/research staff must update the eCRF within 3 days of receipt of this information. In addition, for patients enrolled under Amendment 6, the Investigator or research staff must call patients at the end of the first and second weeks of treatment (ie, Day 7 or Day 8, and Day 14 or Day 15) to confirm that the patient has increased the dose of neratinib from 120 mg to 160 mg, and from 160 mg to 240 mg, respectively, as required by the protocol. For patients enrolled under Amendment 7 and Amendment 7.1, the Investigator or research staff must call patients at the end of the first 2 weeks of treatment (ie, Day 14 or Day 15) and at the end of Cycle 1 (C1D28 or C2D1) to confirm that the patient has increased the dose of neratinib from 160 mg to 200 mg, and from 200 mg to 240 mg, respectively, as required by the protocol.These phone calls are mandatory and must be recorded in the study chart together with response from the patient and action taken (See Section 7.2).

APPENDIX 2. INVESTIGATIONAL PRODUCT DOSE ADJUSTMENT FOR TOXICITY

1. Dose adjustment levels

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

For patients enrolled starting with Amendment 6, during the dose escalation phase (<240 mg neratinib), for any patient who experiences Grade ≥2 AE(s) leading to neratinib dose interruption which do not resolve to Grade ≤ 1, a review of the patient and the patient's adverse event profile must occur with the Sponsor's Medical Monitor to determine whether the patient should be allowed to continue in the study.

2. Toxicities Requiring Investigational Product Dose Adjustments

General Toxicities:

The guidelines for general toxicities 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** until event resolves to Grade ≤1; then resume **neratinib** at the starting dose level.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 3rd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 4th appearance	• Discontinue **neratinib** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 3rd appearance	• Discontinue **neratinib** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** until resolved to Grade ≤1; then resume **neratinib** at 160 mg. • If the event occurs again despite one dose reduction, permanently discontinued **neratinib.**

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Gastrointestinal Toxicity:

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

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

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 Continue **neratinib** at full dose. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea. • 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.
	• Hold **neratinib** 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:
	  ○ ≤1 week after withholding treatment, resume same dose of neratinib.
	  ○ Within 1-4 weeks after withholding treatment, reduce neratinib dose to the next lower dose level.
	• If event occurs a 2nd time and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to the next lower dose level.
	• If subsequent events occur, reduce **neratinib** dose to the next lower dose level.
	• Once the event resolved to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

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.

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Liver Toxicity:

Guidelines for adjustment of neratinib 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** 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 if recovery to ≤Grade 1 occurs within 4 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue **neratinib**.
Grade 4 ALT (>20x ULN) **OR** **Grade 4 Bilirubin** (>10x ULN)	• Permanently discontinue **neratinib**. • 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**. 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.**

NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, prothrombin time must be measured, and liver imaging should be considered.

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, ie, 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 DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 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 DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 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	

Drugs Reported to Prolong QT Interval		
Itraconazole (eg, Sporanox)	Gatifloxacin (eg, Tequin)*[b]	
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

Drugs Reported to Prolong QT Interval		
Lithium (eg, Eskalith)*	Risperidone (Risperdal)[b] (overdose)	Amitriptyline*
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, DS. Drug-induced Prolongation of the QT Interval and Torsades de Pointes. Drug Interaction Facts. The Authority on Drug Interactions. Wolters Kluwer Health 2012.

APPENDIX 7. EUROQOL 5D-5L HEALTH QUESTIONNAIRE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

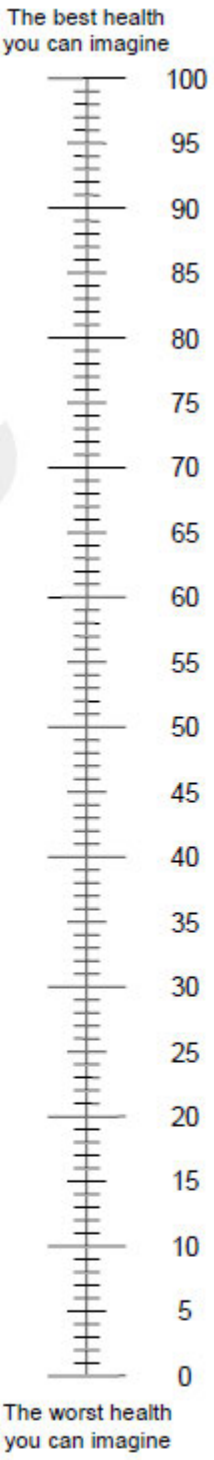
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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APPENDIX 8. FUNCTIONAL ASSESSMENT OF CANCER THERAPY – BREAST (FACT-B)

FACT-B (Version 4)

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

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

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
01	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GB1	I feel sad	0	1	2	3	4
GB2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GB3	I am losing hope in the fight against my illness	0	1	2	3	4
GB4	I feel nervous	0	1	2	3	4
GB5	I worry about dying	0	1	2	3	4
GB6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-B (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
B2	I have certain parts of my body where I experience significant pain	0	1	2	3	4

APPENDIX 9. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS FOR BUDESONIDE

Budesonide	Contraindications
	Known hypersensitivity to budesonide or any of the ingredients in budesonide tablets
	Warnings and Precautions
	Hypercorticism and adrenal suppression- since budesonide is a glucocorticosteroid, follow general warnings concerning glucocorticoids:
	When glucocorticoids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticoids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since budesonide is a glucocorticosteroid, general warnings concerning glucocorticosteroids should be followed.
	Transferring patients from systemic glucocorticoids: Risk of impaired adrenal function when transferring from glucocorticoid treatment with higher systemic effects to glucocorticoid treatment with lower systemic effects, such as budesonide. Taper patients slowly from systemic corticosteroids if transferring to budesonide.
	Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as budesonide, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously.
	Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.
	Patients who are on drugs that suppress the immune system are more susceptible to infection that healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure.
	How the dose, route, and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticoid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. See prescribing information for VZIG and IG. If chicken pox develops, treatment with antiviral agents may be considered.

Budesonide	Contraindications
	Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections.
	Replacement of systemic glucocorticosteroids with budesonide tablets may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by systemic drug.
	Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis.
	Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

APPENDIX 10. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS FOR COLESTIPOL

Colestipol	Contraindications
	Known hypersensitivity to micronized colestipol hydrochloride tablets or any of the ingredients in the tablets
	Warnings and Precautions
	Because it sequesters bile acids, colestipol hydrochloride may interfere with normal fat absorptions and thus may reduce absorption of folic acid and fat soluble vitamins such a, D, and K.
	Chronic use of colestipol hydrochloride may be associated with an increased bleeding tendency due to hypoprothrombinemia from vitamin K deficiency. This will usually respond promptly to parenteral vitamin K_1 and recurrences can be prevented by oral administration of vitamin K_1.
	Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm a favorable initial and adequate long-term response.
	Micronized colestipol hydrochloride tablets may produce or severely worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 2 grams once or twice a day. Increased fluid and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by a further 2 to 4 grams/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at 2 to 16 grams/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associate with micronized colestipol hydrochloride tablets may aggravate hemorrhoids.
	While there have been no reports of hypothyroidism induced in individuals with normal thyroid function, the theoretical possibility exists, particularly in patients with limited thyroid reserve.
	Since colestipol hydrochloride is a chloride form of an anion exchange resin, there is a possibility that prolonged use may lead to the development of hyperchloremic acidosis.
	Potential for Drug-drug Interactions
	Since colestipol is an anion exchange resin, this effect may be related to a strong affinity for anions other than the bile acids. In vitro studies have indicated that colestipol binds a number of drugs. Repeated doses of colestipol given prior to a single dose of propranolol in human trials have been reported to decrease propranolol absorption. Patients on propranolol and possibly other beta-blockers should be monitored when colestipol is added or deleted from

Colestipol	Contraindications
	the therapeutic regimen. Effects of the absorption of other beta-blockers have not been determined. Studies in humans show that the absorption of chorothiazide as reflected in urinary excretion is markedly decreased even when administered one hour before colestipol. The absorption of tetracycline, furosemide, penicillin G, hydrochlorothiazide, and gemfibrozil was significantly decreased when given simultaneously with colestipol. These drugs were not tested to determine the effect of administration one hour before colestipol. No lowering effect on blood levels in humans was noted when colestipol was administered with any of the following drugs: aspirin, clindamycin, clofibrate, methyldopa, nicotinic acid (niacin), tolbutamide, phenytoin or warfarin. Particular caution should be observed with digoxin preparations since ther are conflicting results for the effect of colestipol on the availability of digoxin and digitoxin. The potential for binding of these drugs if given concomitantly is present. Discontinuing colestipol could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking colestipol. Bile acid bind resins such as coletipol may also interfere with the absorption of oral phosphate supplements and hydrocortisone. A study has shown that cholestyramine binds bile acids and reduces mycophenolic acid exposure. As colestipol also binds bile acids, colestipol may reduce mycophenolic acid exposure and potentially reduce efficacy of mycophenolate mofetil.
	Information for Patients
	Micronized colestipol hydrochloride tablets may be larger than pills you have taken before. If you have had swallowing problems or choking with food, liquids or other tablets or capsules in the past, you should discuss this with your doctor before taking micronized colestipol hydrochloride tablets.
	It is important that you take micronized colestipol hydrochloride tablets correctly: • Always take on tablet at a time and swallow promptly • Swallow each tablet whole. Do not cut, crush, or chew the tablets • Micronized colestipol hydrochloride tablets much be taken with water or another liquid that you prefer. Swallowing the tablets will be easier if you drink plenty of liquid as you swallow each tablet.
	Difficulty swallowing and temporary obstruction of the esophagus (the tube between your mouth and stomach) have been rarely reported in patients taking micronized colestipol hydrochloride tablets. If a tablet does get stuck after you swallow it, you may notice pressure or discomfort. If this happens to you, you should contact your doctor. Do not take micronized colestipol hydrochloride tablets again without your doctor's advice.
	If you are taking other medications, you should take them at least one hour before or four hours after taking micronized colestipol hydrochloride tablets.
	Adverse Reactions
	Gastrointestinal
	The most common adverse reactions are confined to the gastrointestinal tract. Constipation is the major single complaint and at times is severe. Most instances of

Colestipol	Contraindications
	constipation are mild, transient, and controlled with standard treatment. Increased fluid intake and inclusion of additional dietary fiber should be the first step; a stool softener may be added if needed. Some patients require decreased dosage or discontinuation of therapy. Hemorrhoids may be aggravated.
	Other less frequent gastrointestinal complaints consist of abdominal discomfort (abdominal pain and cramping) intestinal gas (bloating and flatulence), indigestion and heartburn, diarrhea and loose stools, and nausea and vomiting. Bleeding hemorrhoids and blood in the stool have been infrequently reported. Peptic ulceration, cholecystitis, and cholelithiasis have been rarely reported in patients receiving colestipol hydrochloride granules, and are not necessarily drug related.
	Difficulty swallowing and transient esophageal obstruction have been rarely reported in patients taking micronized colestipol hydrochloride.
	Transient and modest elevations of aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) and alkaline phosphatase were observed on one or more occasions in various patients treated with colestipol hydrochloride.
	Cardiovascular
	Chest pain, angina, and tachycardia have been infrequently reports and are comparable to placebo rates in trials
	Hypersensitivity
	Rash has been infrequently reported. Urticaria and dermatitis have been rarely noted in patients receiving colestipol hydrochloride granules.
	Musculoskeletal
	Musculoskeletal pain, aches, and pains in the extremities, joint pain and arthritis, and backache have been reported.
	Neurologic
	Headache, migraine headache, and sinus headache have been reported. Other infrequently reported complaints include dizziness, light-headedness, and insomnia.
	Miscellaneous
	Anorexia, fatigue, weakness, shortness of breath, and swelling of the hands or feet, have been infrequently reported.

Source: Colestid (colestipol) US Package Insert.

APPENDIX 11. ROTTERDAM SYMPTOM CHECKLIST

Patient ID: |___|___|-|___|___|___|-|___|___|___|___|

Date: |___|___| / |___|___|___| / |___|___|___|___|
D D M M M Y Y Y Y

Rotterdam Checklist

A number of activities are listed below. We do not want to know whether you actually do these, but only whether you are able to perform them presently. Would you please circle the number per line that applies most to your condition of the past week?

	Activities	unable (1)	only with help (2)	without help, with difficulty (3)	without help (4)
R1	care for myself (wash etc.).....	1	2	3	4
R2	walk about the house.....	1	2	3	4
R3	light housework/household jobs.....	1	2	3	4
R4	climb stairs.....	1	2	3	4
R5	heavy housework/household jobs...	1	2	3	4
R6	walk out of doors.....	1	2	3	4
R7	go shopping.....	1	2	3	4
R8	go to work.....	1	2	3	4

R9	All things considered, how would you describe your quality of life during the past week?	1- excellent 2- good 3- moderately good 4- neither good nor bad 5- rather poor 6- poor 7- extremely poor

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