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

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Statistical Analysis Plan – Version 4.0

30-Aug-2019

STATISTICAL ANALYSIS PLAN

Protocol Title:	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 Protocol No.	PUMA-NER-6201
Disease Condition	HER2-Positive Breast Cancer
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LIST OF ABBREVIATIONS

Abbreviation	Term/Definition
AE	adverse event
AESI	adverse events of special interest
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CRF	case report form
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	estrogen receptor
EOS	end-of-study
EOT	end of treatment
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
IHC	Immunohistochemistry
IP	Investigational Product
ISH	in situ hybridization
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MUGA	multiple-gated accession scan
NCI	National Cancer Institute
PR	progesterone receptor
PT	preferred term
QOL	quality of life
QTc	QT interval, corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TDM-1	trastuzumab emtansine
TEAE	treatment emergent adverse event

1. PURPOSE OF ANALYSIS

The statistical analysis plan (SAP) outlines details of the statistical methods and analyses through Amendment 7.1 of the protocol "**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" (**PUMA-NER-6201), dated 25 July 2019.

The purpose of the SAP is to pre-specify analyses that are consistent with the protocol objectives to ensure appropriate interpretation of the data. It supplements the statistical section specified in the protocol with additional details and clarity related to the statistical analyses. The SAP must be finalized prior to database lock according to standard operating procedures. Deviations from this plan will be documented and described in the Clinical Study Report (CSR).

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objectives

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

2.1.2 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.

2.1.3 Exploratory Objectives

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 under 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)

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint is the incidence of Grade 3 or higher diarrhea.

2.2.2 Secondary Endpoints

Secondary endpoints include the incidence and severity of diarrhea and the incidence of SAEs and AESIs.

2.2.3 Exploratory Endpoints

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).

2.3 Overall Study Design and Plan

2.3.1 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.
- For patients enrolled Original Protocol, Amendment 1 or 2, 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 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.

Patients will participate in the active treatment phase, consisting of thirteen (13) 28-day treatment cycles. Neratinib and loperamide will be administered orally by patients. 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. 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 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 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 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 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 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. Cohorts will continue to enroll without interruption, in sequence. Thus enrollment may exceed initial projections.

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.

Patients may be discontinued from investigational product or from the study.

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 analysis by cohort may be carried out as required. 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.

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).

2.3.2 Neratinib Adjustments

Neratinib may be dose-adjusted/reduced due to neratinib-related toxicity from 240 mg down 160 mg or 120 mg. If doses of neratinib are held, study procedures for that cycle will proceed on schedule as planned, without delay. 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.

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.

2.3.3 Loperamide-Original Protocol

Under the original protocol, initial dose of loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 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. Thereafter, loperamide will be administered as needed. Patients are expected to take loperamide prophylaxis as directed and it is expected that all patients will comply with the initial 3-day loading dose of loperamide. Following the initial 3 days of loperamide, if a patient is unable to tolerate loperamide due to constipation, it should be held until the first bowel movement and then resumed at a dose reduced by one level. After a recurrent event, resume loperamide after the first bowel movement and reduce to the next lower dose level. At the third occurrence of constipation, hold loperamide and discuss subsequent loperamide dosing with the Medical Monitor. Neratinib dosing should continue if loperamide is held. Loperamide dose reduction levels for constipation are: Dose Level -1 (2mg every 12 hours or 2 tablets a day), Dose Level -2 (2mg once a day or 1 tablets a day).

2.3.4 Loperamide- Amendment 1 to Amendment 3

Starting from amendment 1, loperamide dosing was changed to improve effectiveness and compliance. The updated loperamide dosing schedule is as follows:

- 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.
- Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).

2.3.5 Loperamide- Amendment 4

With amendment 4, loperamide dosing was reduced to 1 cycle. The updated loperamide dosing schedule is as follows:

- 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 cycle (Day 28) from start of neratinib dosing.
- Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).

2.3.6 Loperamide- Amendment 5

Starting with amendment 5, loperamide dosing was changed to be given as prescribed. The updated loperamide dosing schedule is as follows:

- 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).

2.3.7 Loperamide- Amendments 6, 6.1, 7, and 7.1

With amendments 6 through 7.1, the updated loperamide dosing schedule is as follows:

- 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 0(≤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).

2.3.8 Loperamide Dose Adjustments-Amendments 1 through 7.1

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose (up to a maximum dose of 16 mg per day) 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). 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, loperamide should be held 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. Loperamide dose reduction levels for constipation are: Dose Level 0 (4mg TID or 6 tablets/capsules a day), Dose Level -1 (4 mg BID or 4 tablets/capsules a day), Dose Level -2 (2mg TID or 3 tablets/capsules a day), Dose Level -3 (2 mg BID or 2 tablets/capsules a day), or Dose Level -4 (2 mg once a day or 1 tablet/capsule a day). Neratinib dosing should continue if

loperamide is held.

2.3.9 Anti-inflammatory Treatment-Amendment 3

Under amendment 3, the use of anti-inflammatory agent was added to Cycle 1 of the neratinib-loperamide dosing regimen. The anti-inflammatory agent is as follows:

- Budesonide
  - For patients enrolled in 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.

2.3.10 Bile Acid Sequestrant-Amendments 4 and 5

Under amendments 4 and 5, the use of bile acid sequestrant was added to Cycle 1 of the neratinib-loperamide dosing regimen. The bile acid sequestrant is as follows:

- Colestipol
  - For patients enrolled in Amendments 4 and 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 with neratinib and intensive loperamide prophylaxis.

2.4 Sample Size Determination

A sample size of 120 patients was originally planned for the Loperamide Cohort. A sample size of 40 was originally planned for the Budesonide Cohort. A sample size of 64 was planned for the Colestipol, Colestipol+Loperamide PRN, and Neratinib Dose Escalation Cohorts. A sample size of 100 was planned for the Neratinib Dose Escalation Scheme 2 Cohort. For Grade 3 or higher treatment-emergent diarrhea, both incidence and exact confidence intervals are calculated (Clopper and Pearson, 1934). The below table presents several incidence and associated CI by planned sample sizes.

Incidence	CI for Sample Size N=120	CI for Sample Size N=40	CI for Sample Size N=64	CI for Sample Size N=100
15.0%	(9.1%, 22.7%)	(5.7%, 29.8%)	(7.3%, 26.1%)	(8.6%, 23.5%)
20.0%	(13.3%, 28.3%)	(9.1%, 35.7%)	(11.0%, 31.9%)	(12.7%, 29.2%)
25.0%	(17.5%, 33.7%)	(12.7%, 41.2%)	(15.0%, 37.4%)	(16.9%, 34.7%)
30.0%	(22.0%, 39.0%)	(16.6%, 46.5%)	(19.2%, 42.7%)	(21.2%, 40.0%)
35.0%	(26.5%, 44.2%)	(20.6%, 51.7%)	(23.5%, 47.9%)	(25.7%, 45.2%)
40.0%	(31.2%, 49.3%)	(24.9%, 56.7%)	(27.9%, 53.0%)	(30.3%, 50.3%)

3. DEFINITIONS

Baseline

The baseline value for a parameter of interest (e.g. labs) is the last measurement obtained prior to or on the date of the first dose of neratinib.

Cycle

A cycle in this protocol is 28 days.

Study Day 1

Study Day 1 is the date the first dose of neratinib is taken.

Treatment duration

Treatment duration in days = last dose date - first dose date + 1 (daily dosing)

Actual Dose Intensity

The actual dose intensity is defined as the cumulative actual dose divided by treatment duration.

Relative Actual Dose Intensity

The relative actual dose intensity is defined as the actual dose intensity divided by the planned dose intensity. For neratinib, the planned dose intensity is described in Section 6.8. For loperamide, it is described in Section 6.9.1.

Prescribed Dose Intensity

The prescribed dose intensity is defined as the cumulative prescribed dose divided by treatment duration.

Treatment-Emergent Adverse Event (TEAE)

A TEAE is defined as an AE that occurs or worsens on or after the first administration of neratinib and up to 28 days after the last administration of neratinib.

Investigational Product (IP)

Investigational product (IP) is used to reference neratinib.

Functional Assessment of Cancer Therapy- Breast Cancer (FACT-B)

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

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

(1) The general questionnaire on cancer (FACT-G), which includes the following 4 subscales:
    a. Physical well-being (PWB) consisting of 7 statements (GP1 – GP7)
    b. Social/Family well-being (SWB) consisting of 7 statements (GS1 – GS7)
    c. Emotional well-being (EWB) consisting of 6 statements (GE1 – GE6)
    d. Functional well-being (FWB) consisting of 7 statements (GF1 – GF7)

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

EQ-5D-5L

The EQ-5D-5L is a standardized instrument that provides a simple descriptive profile and index value for health status. The EQ-5D-5L consists of 6 items: 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score. Each dimension has 5 levels:

(1) No problems
(2) Slight problems
(3) Moderate problems
(4) Severe problems
(5) Extreme problems

and subjects are asked to select the level most descriptive of their current state of function or experience on each dimension.

Rotterdam Symptom Checklist (RSCL)

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.

(1) The 3 domains, which includes the following 3 subscales:

   a. Physical Symptom Distress (23 items) (not collected for this study)

   b. Psychological Distress (7 items) (not collected for this study)

   c. Activities of Daily Living (8 items)

(2) An additional single Overall Valuation of Life item consisting of 7 possible responses.

4. DATA SCREENING, ACCEPTANCE AND PROGRAMMING

4.1 General Principles

Clinical data are entered into the InForm database. Data cleaning and query resolution are performed according to the study specific data management plan. Prior to any formal analysis, a data cut-off date will be established by the clinical study team to ensure appropriate cleaning and query resolution of data up to the data cut-off date. Data extracts in SAS formats will be taken from a snapshot of the live database or a locked database will be used for the analyses.

The clinical study team will identify the criteria for important protocol deviations. Important protocol deviations will be summarized and listed in the clinical study report.

4.2 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified for investigation, and possible resolution, as part of the data cleaning. At the analysis time, missing data will be treated as missing, unless otherwise specified. Missing and incomplete dates for adverse events, concomitant medications, and historical data may be imputed for certain analyses.

Subjects missing baseline assessments for FACT-B, EQ-5D, or RSCL questionnaires will not be included in the analysis of these health outcomes assessments.

Partial dates will be defined as dates that are missing certain elements of the date field. This may include missing information for the month, day or year, or two of these elements, but not all three. If either month or year is missing or the date is completely missing then no data imputation will be implemented.

AEs with completely missing start dates will be considered as treatment-emergent adverse events unless there is clear evidence that the AEs start prior to the first dose.

4.3 Testing/Validation Plan

Statistical programming will be performed using SAS software, version 9.3 or higher, on a Windows Server OS. All SAS programs will be documented, QC'ed, written in accordance with department SOPs.

Analyses performed by statistical software other than SAS are permitted if the analyses cannot be readily performed in SAS. All statistical programming must follow commonly accepted practice including adequate comments within the program, code review, logic review, and check of program log. Key analysis results may require additional validation including but not limited to independent programming.

5. ANALYSIS POPULATIONS

5.1 Safety Population

The safety population is defined as all enrolled patients who have received at least one dose of neratinib. Unless otherwise specified, all analyses will be done by the following subgroups: (1) the Original Protocol, (2) Amendment 1 or Amendment 2, (3) Amendment 3 (Budesonide cohort), (4) Amendment 4 (Colestipol cohort), (5) Amendment 5 (Colestipol+Loperamide PRN cohort), (6) Amendment 6/6.1 (Neratinib Dose Escalation cohort), and (7) Amendment 7/7.1 (Neratinib Dose Escalation Scheme 2 cohort).Subgroups (1) and (2) may be combined into the Loperamide cohort.

5.2 Quality of Life (QOL) Analysis Population

The QOL analysis population is defined as all enrolled patients who are in the safety population and who also have a baseline QOL assessment as well as at least 1 post-baseline QOL assessment.

6. ANALYSIS METHODS

6.1 General Principles

For continuous endpoints, the sample size (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3) , minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Safety analyses will be performed by subgroups specified in section 5.2 when appropriate. Patient incidence will be provided for AEs, as specified in Section 6.10.2.

6.2 Disposition of Patients

Disposition of patients will be summarized into two general categories: Investigational Product Accounting and Study Completion Accounting. For each type of accounting, summaries will include the number of patients continuing either the treatment or study, and the number of patients who have discontinued treatment or study, along with the reasons for discontinuation of treatment or study. A listing will be provided for patient disposition.

6.3 Deviations

Protocol deviations will be classified and monitored during the study. All important deviations will be summarized and grouped into the following categories:

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who received an excluded concomitant treatment.

All important protocol deviations will be summarized and in addition listed by center.

6.4 Demographic and Baseline Characteristics

Demographic and baseline summaries will include:

- Age (years at enrollment)
- Age group (<=65, > 65),

- Sex
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or other Pacific Islander, White, Other)
- Height (cm)
- Weight (kg)
- Menopausal status
- Number of Baseline Bowel Movements
- BMI

Body mass index (BMI) will be calculated as:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)}/ (\text{Height(cm)} * 0.01)^2$$

A listing will be provided for demographics.

6.5 Medical History

Medical history will be summarized by system organ class and preferred terms.

6.6 Cancer History

6.6.1 Summary of Cancer History

ECOG performance status, breast tumor stage at diagnosis, histology, tumor stage at diagnosis, grade at diagnosis, cell type at diagnosis, and time from diagnosis to enrollment will be summarized. The number of patients who achieved pathological complete response will also be presented.

6.6.2 Prior Anti-cancer Therapy

Prior anti-cancer medication (yes/no), prior radiotherapy (yes/no), and prior cancer-related surgery (excluding diagnostic biopsies) will be summarized

For prior anticancer medication, the following summaries will be provided: number of patients who had prior neo-adjuvant therapy, the number of patients who had prior trastuzumab use in neo-adjuvant therapy and adjuvant therapy setting correspondingly, the number of patients who had prior anthracycline use, prior taxane use, prior pertuzumab use, and prior TDM-1 use. In addition, the duration of prior trastuzumab use, and the time from last prior trastuzumab use to enrolment will also be summarized.

6.7 Baseline Biomarkers

Biomarkers will be summarized: HER2 (ISH) type (FISH/CISH/SISH), HER2 (ISH) status, HER2 (IHC) status, ER status, PR status, will also be summarized. For each HER2 (ISH) type, the result (Amplified, Non-amplified, Unknown/not done) will be summarized.

6.8 Study Medication (Neratinib)

Exposure to neratinib during the study will be summarized by treatment duration in months, cumulative actual dose (mg), actual dose intensity (mg/day), relative actual dose intensity, cumulative prescribed dose, prescribed dose intensity, and compliance. The compliance for neratinib is calculated by using actual dose intensity divided by the prescribed dose intensity.

The number of dose reductions, the lowest dose reduction level, dose reduction due to AE (yes/no), will be summarized. In addition, the dose withheld due to AE (yes/no), and the number of dose withheld due to AE will be presented.

Refer to Section 3 for general endpoint definitions of dose intensities.

6.9 Concomitant Medications/ Therapy

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) category and preferred term. In addition, loperamide and anti-diarrhea medication exposure will be summarized for the first two cycles; and anti-inflammatory agents' exposure will be summarized for the first cycle.

6.9.1 Loperamide During the Mandatory Prophylactic Period

Exposure to loperamide during the first mandatory prophylactic period (first 2 cycles for Amendment 3 or earlier, first cycle for Amendment 4) will be summarized by treatment duration (days), cumulative actual dose (mg), actual dose intensity (mg/day) and relative actual dose intensity. In addition, the summary on the initial loading dose will also be provided.

The highest daily dose and lowest daily dose will be summarized. In addition, the following will also be summarized:

1. Dose reduction due to AE and the number of dose reduction due to AE
2. Dose increase due to AE and the number of dose increase due to AE
3. Dose hold due to AE and the number of dose hold due to AE.

For loperamide (original protocol) , for the first 3 days, the planned dose intensity is 12mg/day; for days 4 through 56, the planned dose intensity is 6-8 mg/day. For example, the planned dose intensity for loperamide for the first two cycle is (12mgx3days + 6mgx53days)/56 = 6.3mg/day.

For loperamide (amendment 1 to 3), for the first 14 days, the planned dose intensity is 12mg/day; for days 15 through 56, the planned dose intensity is 8 mg/day. For example, the planned dose intensity for loperamide for the first two cycle is (12mgx14days + 8mgx42days)/56 = 9mg/day.

For loperamide (amendment 4), for the first 14 days, the planned dose intensity is 12mg/day; for days 15 through 28, the planned dose intensity is 8 mg/day. For example, the planned dose intensity for loperamide for the first cycle is (12mgx14days + 8mgx14days)/28 = 10mg/day.

6.9.2 Anti-diarrheal Medications During the Mandatory Prophylactic Period

All anti-diarrhea medication (including loperamide and any other concomitant medication for diarrhea) during the mandatory prophylactic period, will be summarized by number of patients taking anti-diarrheal medication, the anti-diarrhea medication name, anti-diarrheal medication use duration.

6.9.3 Anti-inflammatory Agents During the First Cycle

Anti-inflammatory medication (budesonide) during the first cycle (28 days), will be summarized by treatment duration (days), cumulative actual dose (mg), actual dose intensity (mg/day), and relative actual dose intensity.

The highest daily dose and lowest daily dose will be summarized. In addition, the following will also be summarized:

1. Dose reduction due to AE and the number of dose reduction due to AE

2. Dose hold due to AE and the number of dose hold due to AE.

6.9.4 Bile Acid Sequestrant During the First Cycle

Bile acid sequestrant (colestipol) during the first cycle (28 days), will be summarized by treatment duration (days), cumulative actual dose (mg), actual dose intensity (mg/day), and relative actual dose intensity.

The highest daily dose and lowest daily dose will be summarized. In addition, the following will also be summarized:

1. Dose reduction due to AE and the number of dose reduction due to AE

2. Dose hold due to AE and the number of dose hold due to AE.

6.9.5 Concomitant Therapy

Concomitant therapy will be listed.

6.10 Adverse Events (AEs)

AEs are graded by the investigators according to the NCI CTCAE v.4.0. AEs will be coded using MedDRA v. 17.0 or later. Summaries will focus on treatment-emergent adverse events (TEAEs).

6.10.1 Treatment Emergent Diarrhea

The primary endpoint is the incidence of grade 3 or higher treatment-emergent diarrhea. The incidence of grade 3 or higher treatment-emergent diarrhea with accompanying Clopper-Pearson 2-sided 95% CI will be computed (Clopper and Pearson, 1934).

Additional summaries will be provided for incidence of diarrhea by worst grade, and incidences of serious, treatment-related, and serious treatment-related diarrhea, as well as the incidences of the action taken categories as a result of the diarrhea event, and the outcome of the last episode of diarrhea. The time to onset of first treatment-emergent diarrhea, duration of treatment-emergent diarrhea per episode and per patient, will be

summarized. Same summaries will be repeated for grade 2 or higher diarrhea and grade 3 or higher diarrhea. The incidence of dose interruption due to diarrhea, dose reduction due to diarrhea and the number of dose interruptions and time to the first dose reduction and interruption will also be summarized.

Diarrhea incidence by grade in each treatment cycle (28 days) will be plotted against the corresponding treatment cycle.

6.10.2 Treatment-Emergent Adverse Events (TEAEs)

A high-level summary of TEAE will be provided, including the incidence of any TEAE, any treatment-related TEAE, any Grade 3 or 4 TEAE, any serious TEAE, any serious treatment-related TEAE, any TEAE leading to treatment discontinuation, any TEAE leading to dose reduction, any TEAE leading to dose interruption, and fatal TEAE.

TEAEs will also be presented in incidence tables by system organ class (SOC), preferred term (PT), and grade for the following:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- Serious treatment-related TEAE
- Grade 3 or 4 TEAE
- Fatal TEAE
- TEAE leading to dose reduction
- TEAE leading to dose interruption
- TEAE leading to treatment discontinuation

Incidence tables of TEAEs in descending order of frequency by PT will be presented for any TEAE, TEAE>=10%, serious TEAE, Grade 3 or 4 TEAE, and fatal TEAE.

Listings will be provided for SAEs, TEAEs, and TEAEs leading to study drug discontinuation.

6.10.3 Adverse Events of Special Interest (AESI)

The AESI for neratinib will be based on SMQ or the complete list of the Sponsor-defined group of PTs. Tables will be provided with a summary of the incidence of all AESI by PT and Grade.

6.10.4 Death

Deaths will be summarized by number of deaths, number of on-study deaths (within 28 days after last dose of neratinib), and cause of death. A listing of deaths will be provided.

6.11 Clinical Laboratory Parameters

Laboratory data will be summarized combining all cohorts in the safety population. Descriptive statistics provided will include the actual values at baseline, last post-baseline, minimum post-baseline, maximum post-baseline, change for baseline to minimum, and change from baseline to maximum.

Shifts between baseline CTCAE grade and worst CTCAE grade post-treatment will be summarized for select lab parameters.

Listings of laboratory values for blood chemistry parameters, and hematology parameters will be provided.

In addition, abnormalities in liver function tests will be summarized for baseline assessments and any post-baseline assessments. A plot of liver function test abnormality results will also be provided.

6.12 Vital Signs

Vital sign measures (systolic and diastolic blood pressure, pulse, respiratory rate, oral temperature and weight) will be summarized for baseline, last post-baseline, minimum post-baseline, maximum post-baseline, change for baseline to minimum, and change from baseline to maximum, in addition to the incidence of abnormalities. Vital signs will be summarized combining all cohorts in the safety population.

6.13 ECG Abnormality

Electrocardiograms (ECGs) are measured after resting in a supine position for 5 minutes and include Heart rate, Rhythm pattern, RR interval PR interval, QRS interval, QT interval, QT_c interval-Bazett's, QTc interval-Fridericia's, QTc interval-Other.

Descriptive statistics of all the above ECG parameters will be summarized at baseline, and maximum post-baseline.

Additionally, the overall ECG evaluation will be summarized at baseline and worst post-baseline. ECG results will be summarized combining all cohorts in the safety population.

A listing of ECGs will be provided.

6.14 Left Ventricular Ejection Fraction (LVEF)

LVEF will be summarized descriptively for baseline, and worst (lowest) post-baseline. Descriptions will be by summary statistics and also by category cutoffs. LVEF and LVEF change from baseline will also be summarized by visit by summary statistics. Incidence of absolute decrease of LVEF>10% from baseline and below 50% will be provided. A plot of LVEF by visit will also be provided. A listing of ECHO/MUGA results will also be provided. LVEF results will be summarized combining all cohorts in the safety population.

6.15 Disease Recurrence

Disease recurrence will be summarized by type (ductal carcinoma in situ, invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, or invasive contralateral breast cancer). For distant recurrence, the disease recurrence site will be provided.

6.16 Health Outcome Assessments

Health outcomes in this study consist of the three questionnaires: FACT-B, EQ-5D-5L, and RSCL.

The FACT-B (version 4) is a 37-item questionnaire with 5 subscales, PWB, SWB, EWB, FWB and BCS. The overall total score is the sum of the 5 subscale scores based upon the following formulas*:

PWB = [(4-GP1)+(4-GP2)+(4-GP3)+ (4-GP4)+(4-GP5)+ (4-GP6)+(4-GP7)]×7/(# responses)

SWB = [GS1+GS2+GS3+GS4+GS5+GS6+GS7]×7/(# responses)

EWB = [(4-GE1)+GE2+(4-GE3)+ (4-GE4)+(4-GE5)+ (4-GE6)]×6/(# responses)

FWB = [GF1+GF2+GF3+GF4+GF5+GF6+GF7]×7/(# responses)

BCS = [(4-B1)+(4-B2)+(4-B3)+B4+(4-B5)+(4-B6)+(4-B7)+(4-B8)+B9]×9/(# responses)

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

These formulas account for missing responses via proration, ie, multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items responded to by the patient.

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

FACT-B = FACT-G + BCS = (PWB + SWB + EWB + FWB) + BCS.

The greater the FACT-B score, the better the breast cancer patient's quality of life.

The Trial Outcome Index formularies are:

TOI-PFB=PWB+FWB+BCS

TOI-ESB=EWB+SWB+BCS

The EQ-5D-5L consists of 6 items: 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score. Each of the 5 dimensions has 5 levels. The combination of 1 level from each of the 5 dimensions (e.g. 12234) will be used to obtain the health index score. The EQ-5D-5L cross-walk value set for UK will be used (Van Hout et al 2012) in the derivation of health index scores.

The RSCL is a 38-item questionnaire with 3 subscales Physical Symptom Distress (PSD), Psychological Distress (PD), and Activities of Daily Living (ADL), plus a single-item Overall Valuation of Life (OVL) question. Each distress subscale question has 4 responses (not at all, a little, quite a bit, very much), while each activity question has 4 responses (unable, only with help, without help/with difficulty, without help), and the valuation of life question has 7 responses (extremely poor, poor, rather poor, neither good nor bad, moderately good, good, and excellent).

PSD=S1+S3+S5+S7+S8+S10+S12+S13+S14+S15+S16+S18+S20+S21+S22+S23+S24+S25+S26+S27+S28+S29+S30 (not collected for this study)

PD=S2+S4+S6+S9+S11+S17+S19 (not collected for this study)

ADL=ACT1+ACT2+ACT3+ACT4+ACT5+ACT6+ACT7+ACT8

OVL=ALL1

For scoring consistency across subscales, the ADL score can be reversed based on the following formula: 32-SUM OF (ACT1 TO ACT8). After application of this reversal, for all 4 scales, the greater the RSCL score, the worse the breast cancer patient's quality of life.

In the case of missing questions, if at least 50% of the questions for a patient's subscale have been answered, then replace the missing questions with the subscale mean.

Physical Symptom Distress range is from 23 to 92.

Psychological Distress range is from 7 to 28.

Activity Level range is from 0 to 24.

Overall Valuation of Life= 1 to 7.

Finally, scores for RSCL can be standardized using the formula

[(RAW SUBSCALE SCORE – MINIMUM RAW SCORE)/(MAXIMUM SCORE – MINIMUM SCORE)] x 100

QOL completion rates for FACT-B, EQ-5D-5L, and RSCL will be summarized. Descriptive statistics (n, mean, std dev, median, minimum and maximum) will be presented for FACT-B subscales (PWB, SWB, EWB, FWB, and BCS) and total scores (FACT-G, FACT-B, TOI-PFB, and TOI-ESB),EQ-5D-5L health index and health state score at each visit, and RSCL-ADL and RSCL-OVL standardized scores at each visit, for both the raw scores and the change-from-baseline. These variables will also be summarized by plotting mean score versus visit.

6.17 Exploratory Biomarker Analysis

Biomarker analysis will follow the general analysis and reporting conventions described in Section 6.1. All analyses will be descriptive and no formal testing planned. Descriptive statistics (n, mean, std dev, median, minimum and maximum) will be presented for biomarker plasma cfDNA sample data at each visit for both the raw scores and the change-from-baseline.

6.18 Exploratory Microbiome Analysis

Results of microbiome evaluation from participating sites will be summarized at baseline, C2D1, C4D1, and/or at time of treatment discontinuation.

7. INTERIM ANALYSES

An interim analysis was originally planned when approximately 120 patients enrolled under the Original protocol, Amendment 1, and Amendment 2, have completed (or had the opportunity to complete) at least 2 cycles (56 days) of neratinib with loperamide prophylaxis. When this analysis was conducted, there were a total of 133 patients in the safety population and consisted of Original Protocol, Amendment 1, and Amendment 2. Additional analyses by cohort when the follow-up of a cohort is complete are considered planned analyses. Ad hoc analyses of data from ongoing cohort(s) may also be performed.

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9. REFERENCES

Agresti, A. Categorical Data Analysis. New York: Wiley, 1990.

Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast (FACT-B) quality of life instrument. J Clin Oncol 1977; 15:974-86.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934, 26 (4): 404-413.

de Haes JC, Olschewski M, Fayers P, Visser M, Cull A, Hopwood P, Sanderman R. The Rotterdam Symptom Checklist (RSCL): A manual. Second revised edition. UMCG / University of Groningen, Research Institute SHARE. 1996.

Study Protocol Number PUMA-NER-6201: An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Intensive Loperamide Prophylaxis. PUMA Biotechnology, Amendment 6, 26 October 2017.

Van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug;15(5):708-15

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