UCSF Helen Diller Family Comprehensive Cancer Center

**TITLE:** An open label study to characterize the incidence and severity of diarrhea in patients with HER2+ breast cancer treated with neratinib with or without trastuzumab

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# 1.0 BACKGROUND

## 1.1 HER2+ breast cancer

Approximately 15 to 20% of women with breast cancer are HER2-positive, which, if left untreated, is associated with aggressive disease and poor prognosis, including enhanced cell proliferation, reduced progression-free survival (PFS), and reduced overall survival (OS) [1].

## 1.2 Treatment of HER2+ early stage breast cancer

Trastuzumab is a HER2-targeted monoclonal antibody that improves disease free and overall survival (DFS, OS) when added to chemotherapy as treatment of early stage HER2-positive breast cancer. More than 8 year follow-up from NSABP B-31/NCCTG 9831 and BCIRG 006 trials demonstrates OS from 83-86%[2,3], a victory for a disease subtype previously associated with poor prognosis. Despite this, up to a quarter of patients will experience disease recurrence. Various approaches have been tested to further improve the outcome of HER2-positive breast cancer. Since the approval of trastuzumab, we have seen the approval of 3 additional agents for the treatment of metastatic HER2+ breast cancer including lapatinib, pertuzumab, and TDM-1. However, no new agents have been approved for the treatment of early stage HER2+ breast cancer.

The ExteNet study was the first report of a therapeutic adjuvant strategy resulting in a statistically significant improvement in DFS over the current standard combination of chemotherapy and trastuzumab. In this study, 2840 subjects with early stage HER2+ breast cancer who had received prior adjuvant trastuzumab were randomized to a year of neratinib monotherapy (240 mg/d) or placebo. This study demonstrated improved 2-year DFS in patients receiving neratinib compared to patients receiving placebo (12 month extended adjuvant neratinib versus placebo following one year of trastuzumab). The absolute reduction in invasive DFS (iDFS) was 2.3%, with the majority of benefit occurring in the hormone receptor-positive subset where the absolute benefit in iDFS rose to 4.2%, and 9% in the hormone receptor-positive (HR+) and HER2+ centrally confirmed subset. A recent update of 3 year DFS showed similar results with iDFS of 88.6 and 90.5% for the placebo and neratinib arms, respectively. In this study grade 3 diarrhea occurred in 40% of patients receiving neratinib, and at least grade 2 diarrhea occurred in 72%; approximately 17% of patients discontinued drug due to diarrhea [4].

The ExteNet data are promising in that we may have yet another option for patients with early stage HER2+ breast cancer, however this will largely depend on how well the neratinib-associated diarrhea can be controlled. In addition it is important to characterize the diarrhea and general toxicity profile of neratinib in combination with trastuzumab in this patient population, as many patients would prefer to take the drugs concurrently rather than prolong their overall treatment with sequential treatment as previously studied. The combination of trastuzumab and neratinib has been studied in the metastatic setting already and the rate of diarrhea was not significantly different than neratinib monotherapy, and no additional or overlapping toxicities were noted. The objective of this study is to determine the incidence of grade 3 diarrhea with concomitant treatment of trastuzumab and neratinib in patients with early stage breast cancer in the setting of proactive anti-diarrheal management.

## 1.3 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 [5].

Neratinib has undergone extensive clinical testing in phase 1-3 trials in both the metastatic and early stage breast cancer settings. The dose of 240 mg/d is the recommended dose, both as monotherapy and in combination with trastuzumab.

Neratinib has demonstrated clinical activity in HER2+ breast cancer, both in trastuzumab naïve patients and patients that have previously received trastuzumab. A phase 2 trial studied neratinib 240 mg/d in 136 patients with HER2+ metastatic breast cancer (MBC), including 2 cohorts (prior trastuzumab, n = 66; no prior trastuzumab, n = 70). The primary end point of the study was 16-week PFS in both cohorts. The 16-week PFS rates were 59% for patients with prior trastuzumab treatment and 78% for patients with no prior trastuzumab treatment. Median PFS was 22.3 and 39.6 weeks, respectively. Objective response rates (ORR) were 24% among patients with prior trastuzumab treatment and 56% in the trastuzumab-naïve cohort[6] . A phase I/II study of the combination of neratinib and capecitabine showed a 50% ORR among 22 evaluable patients who had previously received treatment with trastuzumab and a taxane[7]. In addition, in a phase 2 trial comparing neratinib with capecitabine and lapatinib, neratinib was not found to be inferior to combination therapy[8].

In a study of 37 subjects with advanced HER2-positive breast cancer who received neratinib 240 mg/d in combination with trastuzumab, 28 patients were evaluable for efficacy. The efficacy-evaluable population had a 16-week PFS rate of 44.8%. The ORR was 28.6%. The clinical benefit rate was 35.7%, and the median PFS for the 28 subjects was 15.9 weeks.

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).

### 1.4 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 gastrointestinal (GI) disorders, such as diarrhea, nausea, and vomiting, account for the most-frequently reported treatment-emergent adverse events (TEAEs). Fatigue, decreased appetite, abdominal pain, headache, rash, and hepatotoxicity (abnormal liver function tests) have also been reported in patients treated with neratinib.

Although patients in the early neratinib studies received standard-of-care diarrhea management upon 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). The phase 1 study of the combination of neratinib and trastuzumab showed a similar toxicity profile as neratinib monotherapy with no increase in rates of diarrhea, and no signal of increased

cardiac toxicity.

In particular, anti-diarrheal prophylaxis was not protocol mandated in the ExteNET study. Most diarrhea events occurred in the first month of treatment. 40% of neratinib-treated patients had a grade 3 diarrhea event (there was only 1 grade 4 event). 29% of patients had grade 3 diarrhea in the first month of treatment, and only 2.5% of patients had first onset of grade 3 diarrhea after month 3. The median duration of grade 3 diarrhea was 5 days.

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. Puma is currently conducting a single arm phase 2 toxicity study (PUMA-NER-6201) where patients with early stage HER2+ breast cancer are treated with neratinib monotherapy after trastuzumab in the setting of upfront high dose prophylactic loperamide starting on day 1. Preliminary data from this ongoing study shows improvement in diarrhea outcomes compared to what was seen in the ExteNet study.

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

**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 most current version of the neratinib Investigator's Brochure (IB) for more detailed information.

### 1.5 Mechanism of Neratinib-induced diarrhea and plans for future study

Early findings from a rat model of neratinib- induced diarrhea indicate that the pathogenesis is multifactorial and could include components of inflammatory, secretory, and bile acid malabsorption (due to ileal mucosal disruption) diarrhea. Histopathology shows increased infiltration of polymorphonuclear cells and lymphocytes in the proximal and distal ileum, as well as marked villous blunting and fusion and crypt hyperplasia. Preliminary data suggest a reduction of grade 1, 2, and high grade diarrhea in patients with brain cancer receiving concomitant steroids. Rat models to test novel interventional agents including 3 anti-inflammatory agents are ongoing. Based on these preclinical findings, Puma is adding additional cohorts to their ongoing 6201 study testing upfront prophylactic loperamide in early stage HER2+ breast cancer in order to determine whether an anti-inflammatory agent can reduce neratinib-associated diarrhea. In these pilot cohorts locally acting steroid budesonide, mesalamine, and bismuth subsalicylate will be investigated along with concomitant intensive loperamide prophylaxis.

## 2.0 STUDY RATIONALE

The ExteNet study demonstrated a statistically significant 2% DFS benefit (and ~4% benefit in the HR+ subset) in women with early stage HER2+ breast cancer treated with 1 year of neratinib 240 mg/d vs. placebo after completing 1 year of adjuvant trastuzumab therapy. One of the potential barriers to adoption of 1 year of neratinib after completion of adjuvant trastuzumab is that patients may not wish to extend treatment further, especially if the rate of GI toxicity is unacceptably high. In ExteNET, in which no antidiarrheal prophylaxis was mandated, grade 3 diarrhea was observed in 40% of patients and 17% discontinued neratinib due to diarrhea. This trial is being conducted to describe the toxicity profile of neratinib with or without trastuzumab in the adjuvant setting.

The international, open-label, sequential-cohort, phase II CONTROL study is investigating several

strategies to improve tolerability. In CONTROL, patients who completed trastuzumab-based adjuvant therapy received neratinib 240 mg/day for 1 year plus multiple cohorts assessing prophylaxis or dose escalation. In addition to the dose escalation cohort the trial had cohorts that included loperamide and loperamide with additional budesonide or colestipol prophylaxis (days 1-28). The primary end point was the incidence of grade 3 diarrhea. Grade 3 diarrhea rates were lower than ExteNET in all cohorts and lowest in the dose escalation cohort (120 mg/d week1, 160 mg/d week 2, 240 mg/d week 3) with 15% grade 3 diarrhea and no grade 4 diarrhea. Loperamide was used as needed (prn) in this cohort. This was a well-tolerated approach with acceptable G3 diarrhea rates, thus this trial is being amended to use a modified dose escalation strategy (120 mg/d week 1, 160 mg/d week 2, 200 mg/d week 3, 240 mg/d thereafter) instead of crofelemer and loperamide to mitigate GI toxicity. The modified dose-escalation is to see if the addition graduated escalation is better tolerated than the one studied in the CONTROL study. In order for participants to receive the full dose and duration of the approved neratinib treatment, participants will receive up to 52 weeks of neratinib after the dose-escalation cycle (55 weeks total).

With the KATHERINE results demonstrating improved outcomes with adjuvant ado-trastuzumab emtansine (T-DM1) compared to trastuzumab in the setting of residual disease after neoadjuvant chemotherapy, we are amending the trial to test the dose-escalation strategy in patients who have received prior T-DM1 since these patients were not included in the CONTROL study and no data exist in this population. For patients who start neratinib during their course of maintenance trastuzumab, they can continue neratinib monotherapy after completing trastuzumab maintenance therapy. Neratinib monotherapy will continue on study until the patient has completed up to 55 total weeks of neratinib (including neratinib treatment with trastuzumab).

## 3.0 STUDY OBJECTIVES

**Primary objective**: To characterize the incidence and severity of diarrhea in patients with early stage breast cancer receiving adjuvant neratinib with or without trastuzumab in the setting of anti-diarrheal strategies.

Primary endpoint: Incidence of grade 3 or greater diarrhea with 2 cycles (6 weeks) of neratinib using anti-diarrheal strategies.

**Secondary objectives:**

1. To evaluate the incidence of grade 3 or higher diarrhea using the dose-escalation strategy and anti-diarrhea medications prn in patients who received prior T-DM1.
2. To assess neratinib adherence, holds, delays, and early discontinuation throughout the course of study therapy which includes patients receiving neratinib for >1 year.
3. To assess overall toxicity including constipation and cardiac toxicity with concomitant neratinib and trastuzumab.

## 4.0 INVESTIGATIONAL PLAN

### 4.1 Overall Study Design

This is an open-label adjuvant/post-neoadjuvant single arm phase 2 trial. We plan to enroll 23 patients into the initial cohort, with the plan to possibly add a second cohort of an additional 23

patients based on the results of ongoing preclinical studies as well as the 6201 study investigating the effects of budesonide, mesalazine, bismuth, dose-escalation on neratinib-associated diarrhea.

Patients will receive dose-escalated neratinib as follows:

- Neratinib 120 mg/day po days 1-7,
- Neratinib 160 mg/day po days 8-14, and
- Neratinib 200 mg/day po days 15-21
- Neratinib 240 mg/day po thereafter
- Anti-diarrheal medications, namely loperamide prn, as described in Section 7.0 Diarrhea Management.

Patients will receive one of the following treatment regimens:

- Neratinib Monotherapy: Patients will receive dose-escalated neratinib once a day for up to 55 weeks on study. Neratinib is to be taken continuously in 21-day cycles with no rest between cycles unless related to toxicity.
    - Participants who are within 1 year of completing trastuzumab +/- pertuzumab or T-DM1 will receive neratinib monotherapy .

  OR

- Neratinib and Trastuzumab : Patients will receive dose-escalated neratinib orally while receiving standard of care maintenance adjuvant trastuzumab (duration of maintenance trastuzumab up to the treating physician) for up to 55 weeks on study. After the completion of trastuzumab maintenance therapy (determined by treating physician), neratinib can continue as monotherapy to complete a maximum of 55 weeks of neratinib therapy on study (with or without trastuzumab). Neratinib is to be taken continuously in 21-day cycles with no rest between cycles unless related to toxicity.

Each cycle is 21 days. Clinic visits and laboratory studies are planned on day 1 of every cycle for the first 4 cycles, then q4 cycles thereafter. An end of treatment visit will occur 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).

### 4.2 Study Duration and Termination of Study

Patients may receive neratinib for up to 55 weeks on study. If determined by the treating physician, standard of care trastuzumab can be received concurrently with neratinib on study. If the treating physician discontinues trastuzumab maintenance therapy, patients can continue neratinib monotherapy to complete a maximum of 55 weeks neratinib on study (with or without trastuzumab). Patients will come off study for disease recurrence, death, unacceptable toxicity, or withdrawal of consent. The study will end when all patients have been followed up for 28 days after the last dose of neratinib.

## 5.0 ELIGIBILITY CRITERIA

### 5.1 Inclusion Criteria

1. Aged ≥18 years at signing of informed consent.
2. Histologically confirmed clinical or pathological stage 2 through stage 3c primary adenocarcinoma of the breast.
3. Documented HER2 overexpression or gene-amplified tumor by a validated approved method.
4. Patients can have HR+ or HR-negative disease.
5. Concurrent adjuvant endocrine therapy and bone-modifying agents is allowed
6. Patients can be premenopausal or postmenopausal
7. Completion of neoadjuvant or adjuvant chemotherapy
8. Completion of adjuvant locoregional radiation, if indicated, is required prior to starting study treatment.
9. At the time of study enrollment, patients can still be receiving adjuvant trastuzumab monotherapy or be within 2 years of completing adjuvant trastuzumab +/- pertuzumab maintenance, or adjuvant T-DM1.
    - Patients who are within 2-years of completing trastuzumab +/- pertuzumab or T-DM1 will receive neratinib monotherapy (and not neratinib + trastuzumab).
    - Adjuvant T-DM1 is the standard of care for patients who have residual disease after neoadjuvant chemotherapy. Patients with residual disease after neoadjuvant chemotherapy should receive T-DM1 before enrolling on the study. If not, the option of T-DM1 should be discussed with the patient.
10. Clinically no evidence of metastatic disease at the time of study entry. Patients with fully resected locoregional recurrence with no evidence of disease are eligible.
11. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
12. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
13. 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].
14. Trastuzumab can cause embryo-fetal harm when administered during pregnancy and the effects of neratinib on the developing human fetus are unknown. Women of child-bearing potential must agree and commit to use of a highly effective double-barrier method of contraception (e.g., a combination of male condom with an intravaginal device such as the cervical cap, diaphragm, or vaginal sponge with spermicide) or a non-hormonal method, from the signing of informed consent until 28 days after the last dose of neratinib and 7 months after the last dose of trastuzumab, or consent to total sexual abstinence (abstinence must occur from randomization and continue for 28 days after the last dose of neratinib and 7 months after the last dose of trastuzumab). Men without confirmed vasectomy must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of investigational products, or consent to total sexual abstinence (abstinence must occur from randomization and continue for 3 months after the last dose of study medication).
15. Recovery (i.e., to Grade 1 or baseline) from all clinically significant AEs related to prior therapies (excluding alopecia, neuropathy, and nail changes).
16. 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 metastatic disease prior to or at the time of study entry. Locoregional recurrent disease that is resected is allowed.
2. Currently receiving chemotherapy, radiation therapy, investigational immunotherapy, or investigational biotherapy for breast cancer.
3. Major surgery (including breast surgery) within <30 days of starting treatment or received chemotherapy, investigational agents, or other cancer therapy <14 days prior to the initiation of investigational products (except adjuvant endocrine therapy).
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 seconds (females), or known history of QTc prolongation or Torsade de Pointes (TdP).
6. Screening laboratory assessments outside the following limits:

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≤1,000 /µL |
| Platelets | ≤100,000 /µL |
| Hemoglobin | ≤9 g/dL |
| **Renal** | |
| Serum creatinine<br>or calculated creatinine clearance† | ≥1.5 x upper limit of normal (ULN) OR<br>≤30 mL/min for patients with creatinine levels >1.5 x institutional ULN |
| **Hepatic** | |
| Serum total bilirubin | ≥1.5 x ULN OR direct bilirubin ≥ ULN for patients with total bilirubin levels >1.5 x ULN |
| | |
| AST (SGOT) and ALT (SGPT) | ≥2.5 x ULN |
| † Creatinine clearance should be calculated per institutional standard. | |

7. Second malignancy for which the patient will be receiving active treatment during the time of study participation.
8. Currently pregnant or breast-feeding.
9. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., 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).
10. Clinically active infection with hepatitis B or hepatitis C virus.

11. 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.
12. Known hypersensitivity to any component of the investigational products.
13. Unable or unwilling to swallow tablets.

## 6.0 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.

### 6.1 Administration of Trastuzumab, Neratinib and Dose Modifications

*Trastuzumab Administration*

Trastuzumab will be administered per the treating physician as standard of care treatment. While every 3 week dosing is recommended, the dose and schedule of trastuzumab is at the discretion of the treating physician. The dose of trastuzumab will not be modified and should not be delayed or held unless clinically indicated per the treating physician. Cardiac monitoring will be performed with every 3-month echocardiograms or MUGA scans per standard guidelines. Management of abnormal ejection fractions will be based on standard clinical guidelines at the discretion of the treating physician. If trastuzumab is held or discontinued for cardiac toxicity, neratinib should be held or discontinued as well.

*Neratinib Administration*

Neratinib will be dose escalated (120 mg as three 40 mg tablets D1-7, 160 mg as four 40 mg tablets D8-14, 200 mg as five 40 mg tablets D15-21, and 240 mg/d provided as six 40 mg tablets thereafter) will be self-administered orally by patients on a daily basis. Neratinib should be taken with food, preferably in the morning and at approximately the same time each day. Neratinib should be taken continuously with or without concurrent trastuzumab for up to 55 weeks until disease progression, intolerable toxicity, or at the discretion of the treating physician.

*Neratinib Dose Modifications*

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

**Table 3: Dose Reduction Table**

| Dose Level | Neratinib dose (mg/day) |
|---|---|
| Starting Dose | 240 mg |
| -1 | 160 mg |
| -2 | 120 mg |

If a patient develops a toxicity requiring a dose reduction below Dose level -2 (120mg), neratinib should be permanently discontinued.

If doses of neratinib are held, study procedures for that cycle will proceed on schedule as planned, without any delay. Missed dose(s) of neratinib (i.e., any dose that is not administered within the

protocol-defined administration window) will not be made up. Note: Patients should take one dose per calendar day. The dose adjustment guidelines represent the minimum set of measures the Investigator must follow. However, additional measures may be taken, as necessary, for certain patients per the Investigator's medical judgment. All dose modifications/adjustments should be documented in the patient's source file. Once the neratinib dose has been reduced for a patient, all subsequent cycles should be administered at that dose, unless further dose reduction is required. If the treating provider wishes to re-escalate the dose in a given patient, this must be discussed with the PI on a case to case basis.

### 6.2 Dose adjustment levels

Recommended dose reductions for the -1 and -2 dose levels of neratinib are listed in Table 3 in Section 6.1.

### 6.3 Toxicities Requiring Neratinib Dose Adjustments

Neratinib dose modifications and/or discontinuation and/or management of toxicity should be performed according to the following guidelines, but can be modified based on treating physician's discretion.

**General Toxicities:**

The guidelines for general toxicities are shown in Table 4.

**Table 4: 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.<br>• 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

### 6.4 Gastrointestinal Toxicity:

Guidelines for adjusting doses of neratinib in the event of gastrointestinal toxicity diarrhea are shown in Table 5. Refer to section 7.0 for additional dietetic measures and pharmacological treatment.

**Table 5. 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.]<br>OR<br>• **Grade 2 Diarrhea** [Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline;] lasting <5 days<br>OR<br>• **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**<br>• | • Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea (Section 7.0) at the first onset of diarrhea. Continue **neratinib** at full dose.<br>• Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea.<br>• Fluid intake of ~2L should be maintained to avoid dehydration.<br>• Once the event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration. |

| NCI CTCAE V4.0 | Action |
|---|---|
| • 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**<br>OR<br>• **Grade 3 Diarrhea** lasting > 2 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia**<br>OR<br>• **Any Grade 4 diarrhea** [Life-threatening consequences; urgent intervention indicated] | • Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea (Section 7.0) at the first onset of diarrhea.<br>• Hold **neratinib** until recovery to ≤ Grade 1 or baseline.<br>• Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea.<br>• Fluid intake of ~2L should be maintained, intravenously if needed.<br>• If recovery occurs:<br>○ ≤1 week after withholding treatment, resume same dose of neratinib.<br>○ Within 1-4 weeks after withholding treatment, reduce neratinib dose to the next lower dose level.<br>• If subsequent events occur, reduce **neratinib** dose to the next lower dose level<br>• 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

### 6.5 Pulmonary Toxicity:

Guidelines for adjusting doses of neratinib in the event of pulmonary toxicities are shown in Table 6. 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 6. 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.<br>• 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

### 6.6 Liver Toxicity:

Guidelines for adjustment of neratinib in the event of liver toxicity are shown in Table 7.

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 7. Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib**

| NCI CTCAE V4.0 | Action |
|---|---|
| **Grade 3 ALT** (>5 – 20x ULN)<br>**OR**<br>**Grade 3 bilirubin** (>3-10x ULN) | • Hold **neratinib** until recovery to ≤ Grade 1 for patients with ALT ≤ Grade 1 at baseline.<br>• Evaluate alternative causes.<br>• 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)<br>**OR**<br>**Grade 4 Bilirubin** (>10x ULN) | • Permanently discontinue **neratinib**.<br>• Evaluate alternative causes. |
| **ALT >**3x ULN<br>AND<br>**Total bilirubin** >2x ULN<br>AND<br>**Alkaline phospatase <**2x ULN<br>(potential Hy's law indicators of drug-induced liver damage) | • Hold **neratinib**.<br>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 |

| NCI CTCAE V4.0 | Action |
|---|---|
| | 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 (e.g., 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.<br>• Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product.<br>• **These events must be reported as SAEs.** |
| **Grade 1-2 Transaminitis** | • Continue neratinib, and consider close monitoring with repeat labs |

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

### 6.7 Cardiac Toxicity

Echocardiograms or MUGA scans will be performed every 3 months (consistent with standard clinical practice) if the patient is receiving concurrent trastuzumab. Management of trastuzumab-related decreases in ejection fraction with regard to holding or discontinuing trastuzumab, initiation of cardiac medications, timing and frequency of subsequent echo/MUGA surveillance, and whether/when to re-challenge with trastuzumab will be managed per standard clinical guidelines at the discretion of the treating physician. If trastuzumab is held for cardiac toxicity, neratinib will be held as well.
Neratinib can be resumed if and when trastuzumab is resumed.

No signals of cardiac toxicity were noted in the ExteNet study. Echocardiogram/MUGA scans will not be continued during the neratinib monotherapy phase of treatment. A final echocardiogram or MUGA scan will be performed within 4 weeks of the last dose of neratinib (end of treatment).

## 7.0 DIARRHEA MANAGEMENT

Diarrhea is the major dose-limiting toxicity of neratinib with onset typically occurring early in the course of treatment (during the first few days of treatment).

The Investigator must review with the patient the Patient Instructions for the Management of Diarrhea (Appendix A) and the Patient Diary used by the patient to record daily the number of stools, use of loperamide, and other anti-diarrheals, and the use of neratinib. 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 neratinib 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 (Appendix B) 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 and other antidiarrheals noted on the diary will be reviewed and recorded on the CRF.

Loperamide and Neratinib will be dispensed directly by the site on or before Cycle 1/Day 1 and during subsequent visits as needed. It is recommended that a prescription for Lomotil also be provided to the patient and filled on or before Cycle 1/Day 1 in order to prevent delays in symptom management.

**Lomotil should only be initiated after discussion and instruction by a trained delegate (MD, NP, RN).**

The Investigator or suitably trained and qualified delegate (e.g., MD, RN, NP, study coordinator etc.) must contact the patient by phone at 1 business day, 2 business days, and 3 business days after the first dose of neratinib, as well as once during week 2 and once during week 3:

i. to inquire about any diarrhea and about potential AEs; to instruct patient to promptly report diarrhea symptoms and to report the number of stools per day and the dose of any anti-diarrheal medication taken each day
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 adequate loperamide and Lomotil available
iv. to inquire about the first date of neratinib dosing

**These phone calls are very important and should be recorded in the clinical records together with response from the patient and action taken.**

**<u>Diarrhea management</u>**

- For patients who develop ≥Grade 1 diarrhea, loperamide can be increased up to a maximum of 16 mg a day.
    - 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 (maximum16 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).
- If ≥ grade 1 diarrhea continues to be bothersome to the patient despite loperamide, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 2 tablet (5 mg) every 6 to 8 hours should be added (not to exceed 8 tablets/24 hours). Patients should speak to a trained and qualified delegate (e.g., MD, RN, NP) prior to starting Lomotil. A prescription for Lomotil should be provided to the patient and filled on or before Cycle 1/Day 1 to prevent delays in symptom management. Lomotil and loperamide should be discontinued for any grade constipation.
- For persistent any grade diarrhea (>24 hours) that is bothersome to the patient, despite the aforementioned intensive anti-diarrheal therapy and strategies including loperamide up to 16 mg/day, and Lomotil up to 8 tabs/24 hours, 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 (or equivalent as approved by the Investigator). Crofelemer 125 mg bid can also be considered.

**The following dietetic measures should also be taken:**

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

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

- Follow diarrhea management guidelines above for G1 and G2 diarrhea.
- Use IV fluids as appropriate.
- Consider octreotide (100-150 µg SC BID or intravenously (IV) (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID).
- Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia. Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 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 recorded in the clinical records.

Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction per Dose Modification guidelines listed in Table 5.

# 8.0 PACKAGING, LABELING, AND STORAGE

## 8.1 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 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 manual. Neratinib will be labeled according to local regulations and include the study number.

## 8.2 Loperamide

Commercially available loperamide will be dispensed by the study site and reimbursed by the study sponsor.

# 9.0 DRUG ACCOUNTABILITY AND TREATMENT COMPLIANCE

The study site must maintain accurate records documenting dates and quantities of investigational product and loperamide received from the Sponsor. Records must be maintained documenting dates and quantities (i.e., pill counts) of neratinib 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 product on-site. On a per-patient basis, records must be maintained documenting dates and quantities (i.e., pill counts) of investigational product and loperamide dispensed and returned at each study visit. Any investigational product, or loperamide accidentally or deliberately destroyed must be documented.

Throughout the study, reconciliation will be made between the amount of investigational product and loperamide supplied, dispensed, returned, and subsequently destroyed or returned to the Sponsor. All investigational product and loperamide 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.

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.

## 9.1 Study Drug Accountability/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 loperamide and other antidiarrheal treatment will also be recorded in the Patient Diary. Investigational product and loperamide pill counts will be conducted during the first 2 cycles (42 days) of therapy only.

# 10.0 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.

## 10.1 Permitted Concomitant Treatment

Any palliative and/or supportive care for cancer-related symptoms, which are not otherwise specified in the list of prohibited medications in Section 10.2, 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 and ovarian suppression are allowed. The choice of adjuvant endocrine therapy is at the discretion of the treating physician and patient. Changes in adjuvant endocrine therapy are allowed unless the change is made due to disease progression.
- Bisphosphonates and RANK (receptor activator of nuclear factor kappa-B) ligand inhibitors (e.g., denosumab), are allowed regardless of indication.

## 10.2 Prohibited Concomitant Treatment

The following treatments are prohibited throughout the duration of the active (treatment) stage/phase of the study: Any concurrent chemotherapy, radiotherapy, surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents (except for hormonal therapies) by oral or parenteral route.

## 10.3 Potential Drug-Drug Interactions

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

Patients using concomitant drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECG) at the Investigator's discretion. Refer to Appendix D for a summary of drugs known to have a risk of causing QT/QTc prolongation, or potentially causing Torsade 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 E for a list of substrates and inhibitors of P-gp.

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

The solubility of neratinib is pH dependent and treatments that alter gastrointestinal pH such as proton pump inhibitors (PPIs), 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 dose reduces the interaction. If an H2-receptor antagonist such as ranitidine is required, neratinib should be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 2 to 4 hours.

## 11.0 SCHEDULE OF ASSESSMENTS

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 toxicity and safety.

**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, 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 must be retrieved.

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

- Medical history:
  - Demography: date of birth, sex, ethnicity, race
  - Physical examination including vital signs, height and weight
- ECG
- LVEF by MUGA or ECHO (must be within one month of study enrollment)
- Laboratory tests (may be accepted as baseline assessment if they are performed within 72 hours of initiation of protocol therapy. Laboratory endpoints including: CBC with differential, AST, ALT, Total bilirubin, Alkaline Phosphatase, Sodium, Potassium, Chloride, BUN, Creatinine, Calcium, Magnesium, Phosphorus, Albumin, glucose (non-fasting)
- In women of child-bearing capacity, serum or urine pregnancy test
- ECOG Performance Status

**Active Treatment Phase**

Neratinib will be self-administered by patients daily during each 21-day cycle. Trastuzumab dose and schedule will be given at the discretion of the treating physician.

The following will be performed in accordance with the Schedule of Assessments (Table 9). Unless otherwise stated these procedures will be done on Day 1 +/- 3 days of every cycle x 4 cycles, then every 4 cycles thereafter)

- History and physical exam
- ECOG performance status
- AE assessment
- During Cycle 1, AE assessments will also be conducted via telephone at the following time points: 1 business day, 2 business days, and 3 business days after the first dose of neratinib, as well as once during week 2 and once during week 3Concomitant medication assessment
- Vital signs including weight
- ECHO of MUGA (every 4 cycles while on trastuzumab only). Management of abnormal ejection fraction (i.e.. timing of repeat echo/MUGA) will be based on standard clinical guidelines/practices at the discretion of the treating physician.
- Laboratory tests: CBC with differential, AST, ALT, Total bilirubin, Alkaline Phosphatase, Sodium, Potassium, Chloride, BUN, Creatinine, Calcium, Magnesium, Phosphorus, Albumin, glucose (non-fasting)

**Treatment Discontinuation or End-of-Treatment Assessments**

The end of treatment (EOT) visit will occur within 5 business days of the last dose of neratinib. When a patient discontinues study treatment for reasons of toxicity or disease progression, EOT visit will occur within 5 business days of the last dose of neratinib.

The following will be performed at the EOT visit:

- AE assessment
- Concomitant medication assessment
- Physical examination
- Vital signs, including weight
- ECG
- LVEF (must be either 4 weeks before or after the last neratinib dose)
- Laboratory tests:
    - CBC with differential, AST, ALT, Total bilirubin, Alkaline Phosphatase, Sodium, Potassium, Chloride, BUN, Creatinine, Calcium, Magnesium, Phosphorus, Albumin, glucose (non-fasting) )
- Collect Patient Diary for treatment compliance assessment

**Table 9: Schedule of Assessments**

| Cycles (cycle = 21 days) | Real-life time clock | Consent | Neratinib[3] | Trastuzumab[4] | H&P, ECOG, Con-Med Review | CBC w/ diff, Chem panel [2] | Pregnancy Test[1] | ECG | LVEF[5] (MUGA/ECHO) | AE Assessment |
|---|---|---|---|---|---|---|---|---|---|---|
| **Screening** | Within 4 weeks | X | | | X | X | X | X | X | |
| **Cycle 1** | Day 1 | | X | X | X | X | X | | | X[6] |
| **Cycle 2** | Day 1 | | X | X | X | X | | | | X |
| **Cycle 3** | Day 1 | | X | X | X | X | | | | X |
| **Cycle 4** | Day 1 | | X | X | X | X | | | X | X |
| **Cycle 8 and every 4 cycles thereafter** | Day 1 | | X | X | X | X | | | X | X |
| **End-of-treatment Assessments** | Within 5 days of last dose of neratinib | | | | X | X | | X | X | X |

1. 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 only, which should be performed, both, at screening and within 72 hours prior to Cycle 1/Day 1.
2. Chemistry panel includes: AST, ALT, Total bilirubin, Alkaline Phosphatase, Sodium, Potassium, Chloride, BUN, Creatinine, Calcium, Magnesium, Phosphorus, Albumin, glucose(non-fasting)
3. Neratinib will be self-administered by patients daily during each 21-day cycle.
4. Trastuzumab dose and schedule will be given at the discretion of the treating physician. Some patients will not receive trastuzumab.
5. ECHO will be performed every 4 cycles while patient is receiving trastuzumab. End of treatment Echo must be done within 4 weeks of last neratinib dose (either before or after)
6. During Cycle 1, AE assessments will also be conducted via telephone at the following time points: 1 business day, 2 business days, and 3 business days after the first dose of neratinib, as well as once during week 2 and once during week 3

**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 or 28 days after the EOT visit to collect AEOIs/SAEs.

**Long-term Follow-up**

Not applicable for this study.

**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.

## 12.0 PATIENT WITHDRAWAL AND REPLACEMENT

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. Every effort should be made to document why patients are lost to follow up.

### 12.1 Neratinib Discontinuation

Patients must be discontinued from neratinib under the following circumstances listed below unless otherwise agreed upon by the Principal Investigator:

- If the patient requires more than 2 dose reductions of neratinib
- If neratinib is withheld due to a AEOIs/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 Study PI
- Once the patient has completed 55 weeks of neratinib
- 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 (except adjuvant hormone therapy)
- Pregnancy
- Investigator request
- Patient request (i.e., withdrawal of consent for treatment).
- AEs/toxicity. Withdrawal due to AE should be distinguished from withdrawal due to other causes, and recorded on the appropriate AE page of CRF. If a patient withdraws due to toxicity, even if discontinuation is not otherwise required per protocol guidelines, the withdrawal should be classified as withdrawal due to AE.

### 12.2 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 for the following reasons:

- At the discretion of the Investigator.
- At patient's request
- Lost to follow-up (defined as after three attempts at contact by phone followed by one attempt by sending a certified letter)
- Study closure

### 12.3 Patient Replacement

Patients who do not complete at least one week of study therapy due to reasons other than toxicity will be replaced.

## 13.0 PREMATURE TERMINATION OF STUDY

If the study is terminated prematurely, neratinib and the provided anti-diarrheal medications (i.e., loperamide) will be available to patients to complete up to 55 weeks of neratinib therapy.

## 14.0 EVALUATION OF SAFETY

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

### 14.1 Definitions of Adverse Events

**Adverse Event**
According to the ICH definition, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational product.

This definition includes intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

Adverse event information will be collected in an ongoing fashion through patient reporting AEs to their physician or health care provider. Seriousness and relatedness will be assessed by the treating physician, with appropriate reporting.

A designated primary contact person based at the treatment center will be responsible for the collection and reporting of AEs for patients participating in the program.

### 14.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that:

- Results in death
- Is life threatening, that is, places the subject at immediate risk of death from the event as it occurred. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of an existing in-patient hospitalization.
- Admission of a subject to the hospital as an in-patient as a result of an AE, even if the subject is released on the same day, qualifies as hospitalization.
- Results in persistent or significant disability or incapacity. An event qualifies as resulting in a persistent or significant disability or incapacity if it involves a substantial disruption of the subject's ability to carry out usual life functions. This definition is not intended to

include experiences of relatively minor or temporary medical significance.
- Is a congenital anomaly or birth defect, an AE that occurs in the child or fetus of a subject exposed to the product prior to conception or during pregnancy.
- Important medical event that does not meet any of the above criteria, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

More than one of the above criteria may apply to any specific event.

### 14.3 Pregnancy

Pregnancy in a subject being treated with the product should be reported immediately (within 24 hours of becoming aware of the pregnancy) to PUMA pharmacovigilance by using the FDA 3500A (MedWatch Form). Every effort should be made to follow the patient through resolution of the pregnancy (termination or delivery) and report the resolution of the FDA 3500A (MedWatch Form) to PUMA.

### 14.4 Recording of an Adverse Event

All adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

| Relationship | Attribution | Description |
|---|---|---|
| Unrelated to investigational drug/intervention | Unrelated | The AE *is clearly NOT related* to the intervention |
| | Unlikely | The AE *is doubtfully related* to the intervention |
| Related to investigational drug/intervention | Possible | The AE *may be related* to the intervention |
| | Probable | The AE *is likely related* to the intervention |
| | Definite | The AE *is clearly related* to the intervention |

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE 4.0. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

| | |
|---|---|
| Grade 0 | No AE (or within normal limits) |
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL) |

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death related to AE

### 14.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

### 14.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a biweekly basis. The Site Committee will review and discuss at each meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis, discussed at DSMC meetings which take place every six (6) weeks.

### 14.7 Expedited Reporting

**Reporting to the Data and Safety Monitoring Committee**

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e- mail.

**Reporting to UCSF Committee on Human Research (Institutional Review Board)**

The Principal Investigator must report internal (on-site) serious adverse events that the PI deems related to the study therapy to the CHR within 5 working days of the PI's awareness of this event. Additionally, the Principal Investigator must report external (off-site) serious adverse events that

the PI deems related to the study therapy within 10 working days of the PI's awareness of this event.

**Expedited Reporting to the Food and Drug Administration**

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.
The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

**Reporting to PUMA Biotechnology**

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events, in addition to being reported to the FDA by the investigator, must be reported by e-mail to **Puma Biotechnology, Inc.** as follows:

All expedited reports (serious, related, unlabeled, (unexpected)) adverse events will be reported to the FDA as required by 21 CFR 312.32 by the Investigator/Sponsor. These reports may be filed utilizing the Form FDA 3500A (MedWatch form). The Investigator/Sponsor will provide PUMA with a copy of this report (MedWatch form).

All serious adverse events (SAEs) and pregnancy reports whether or not considered drug-related should be reported to PUMA Biotechnology (contact information below) within 24 hours of receipt by the investigator/sponsor by using the FDA 3500A (MedWatch Form) **by e-mail to:**

[redacted]

Clinicians should not wait to collect additional information that fully documents the event before notifying PUMA Biotechnology of an SAE or pregnancy. PUMA may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore it is important that clinicians submit additional information requested by PUMA Biotechnology as soon as it becomes available.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements.

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

The period during which all non-serious AEs and SAEs will be reported begins after study treatment or procedures are initiated and will continue through 30 days after the last study visit or 30 days after the last dose of study medication, whichever comes first.
All non-serious adverse events whether or not considered drug-related should be reported to PUMA Biotechnology on a monthly basis via a line listing which includes the following information: Patient ID number, Date of Birth/Age, Gender, event term, onset date, outcome, resolution date (if applicable) and causality.

[redacted]
PUMA Biotechnology
[redacted]

## 15.0 STATISTICAL METHODS AND ANALYSIS PLAN

### 15.1 Analysis plan

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

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

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

Formal efficacy analyses will not be conducted in this study. However disease recurrence will be recorded during the course of the study and reported as appropriate.

### 15.2 Primary Safety Analysis

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

The primary endpoint is the incidence of Grade 3 or higher diarrhea with in the setting of anti-diarrheal strategies during the first 2 cycles (6 weeks). The primary endpoint will be estimated for the overall safety population, and for subgroups of patients with specific anti-diarrheal regimens.

The incidence and severity of diarrhea and compliance will be summarized descriptively, as well as the number and percentage of patients requiring multiple anti-diarrheal medications in the rescue setting, as well as the incidence and severity of diarrhea on each medication.

AEs will be graded by the Investigator according to the NCI-CTCAE version 4.0. Incidence of AEs will be summarized by grade, with worst grade toxicity being reported for each individual. SAEs and AEOIs will also be summarized.

All AEs resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of investigational product will also be listed and tabulated.

### 15.3 Sample size calculation

Assuming a 40% >=G3 diarrhea incidence without anti-diarrhea strategies, we will need to enroll 23 patients per cohort in order to have 85% power to demonstrate a reduction of G3 or greater diarrhea assuming 15% G3 diarrhea in the cohorts with anti-diarrhea strategies, with type 1 error of 5%. The sample size justification is based on normal approximation of binomial distribution.

## 16.0 STUDY MANAGEMENT

### 16.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

### 16.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and

by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

### 16.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 16.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

### 16.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom the study drug has been dispensed by patient number and initials will be included. The sponsor- investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

### 16.6 Case Report Forms (CRFs)

The Principal Investigator, and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.
All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

### 16.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI- approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. The UCSF DSM plan is described in Appendix F.

### 16.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).
Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

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# Appendix A Patient Instructions for Management of Diarrhea while on treatment with Neratinib

Please review these instructions with your study doctor/team. Once all of your questions are answered, sign at the bottom and make sure you are given a copy of these instructions to take home.

Diarrhea is the most common side effect you may have while participating in this study. Diarrhea usually starts within a few hours to a few days of the first dose of study drug. In order to reduce or even prevent diarrhea as much as possible, you will be supplied with an anti-diarrheal medicine called loperamide to take as needed at the start of the study. Loperamide will be dispensed directly by your study doctor/team on day 1 with the instruction to initiate treatment with loperamide as needed starting with first dose of the neratinib. Additional prescriptions and medications to prevent diarrhea may be given to you in case the loperamide is not enough to control the diarrhea. You should not take these additional medications without talking with your doctor and study team first.

Your study doctor/team will call you 1 day, 2 days and 3 days after your first dose of study drug, as well as once during week 2 and once during week 3, to find out if you are experiencing diarrhea and to provide further treatment instructions and advice if necessary. You will also have an easy to follow flow-chart to help you each day in the management of diarrhea if it is present.

If you are having new-onset diarrhea, persistent diarrhea, diarrhea of 4-6 stools per day compared to your normal bowel habits, or any other concerning symptoms, call your study doctor/team [redacted] to let them know so they can work with you to control the diarrhea. If you are dizzy or weak because of diarrhea, go to the study doctor's office or go to the hospital immediately.

Please record the number of stools and any anti-diarrheal medication taken during all Cycles of the study along with the daily dose of study medication in your diary and return the completed diary at the next scheduled visit.

## INFORMATION TO PROVIDE WHEN TALKING TO YOUR DOCTOR

When talking to the study doctor/team I will provide as much of the information below as possible, in order to help my study doctor/team to assess my diarrhea and decide on the best treatment:

- Number of stools per day as compared to my normal bowel habits
- Presence of diarrhea during the night
- Presence of fever, dizziness, abdominal pain/cramping, or weakness
- What the stool looks like, that is, watery stools, blood, or mucus
- When I took my last study drug
- How much loperamide and other anti-diarrheal medications I am taking
- Any other information that could explain my diarrhea (food, recent travel, contact with other people with diarrhea)

**Medications to treat diarrhea**

My study doctor/team will provide me with loperamide on day 1 with the instruction to start treatment with loperamide as needed. I will take 2 tablets/capsules (4 mg) immediately after the first loose stool and then 1 tablet (2 mg) every 4 hours or after each loose stool to a maximum dose of 8 tablets/capsules (16 mg) in any 24 hour period until I haven't had any loose stool for at least 12 hours.

If I continue to have diarrhea while taking loperamide, I should contact my study doctor/team to discuss what to do next.

□ Other medication (Study doctor/team to write in name of medication and instructions):

_____

_____

_____

In case of more severe diarrhea and any diarrhea associated with fever, pain, infection, or dehydration, I may receive IV fluids, antibiotics and/or other medications.

**Changes to my diet to treat diarrhea**

If I have diarrhea, I will:

- Stop all lactose-containing products (milk, yogurt, cheese, etc.)
- Drink 8 to 10 large glasses of clear liquids per day
- Eat frequent small meals
- Eat low fat foods such as the BRAT diet that includes **B**ananas, **R**ice, **A**pplesauce, and/or
- **T**oast:
    - The **BRAT** diet is a bland diet that is low in fat and fiber and will not irritate the stomach;
    - Bananas are high in potassium and can cause constipation which can help alleviate the diarrhea
    - Other similar foods are crackers, cooked cereals and pasta
    - This diet is not complete in nutrients and should only be taken for a short period of time and only upon the doctor's advice.

My study doctor/team may have other suggestions for me. (Study doctor/team to write in any suggestions).

_____

_____

_____

_____

**Study Medication adjustments**

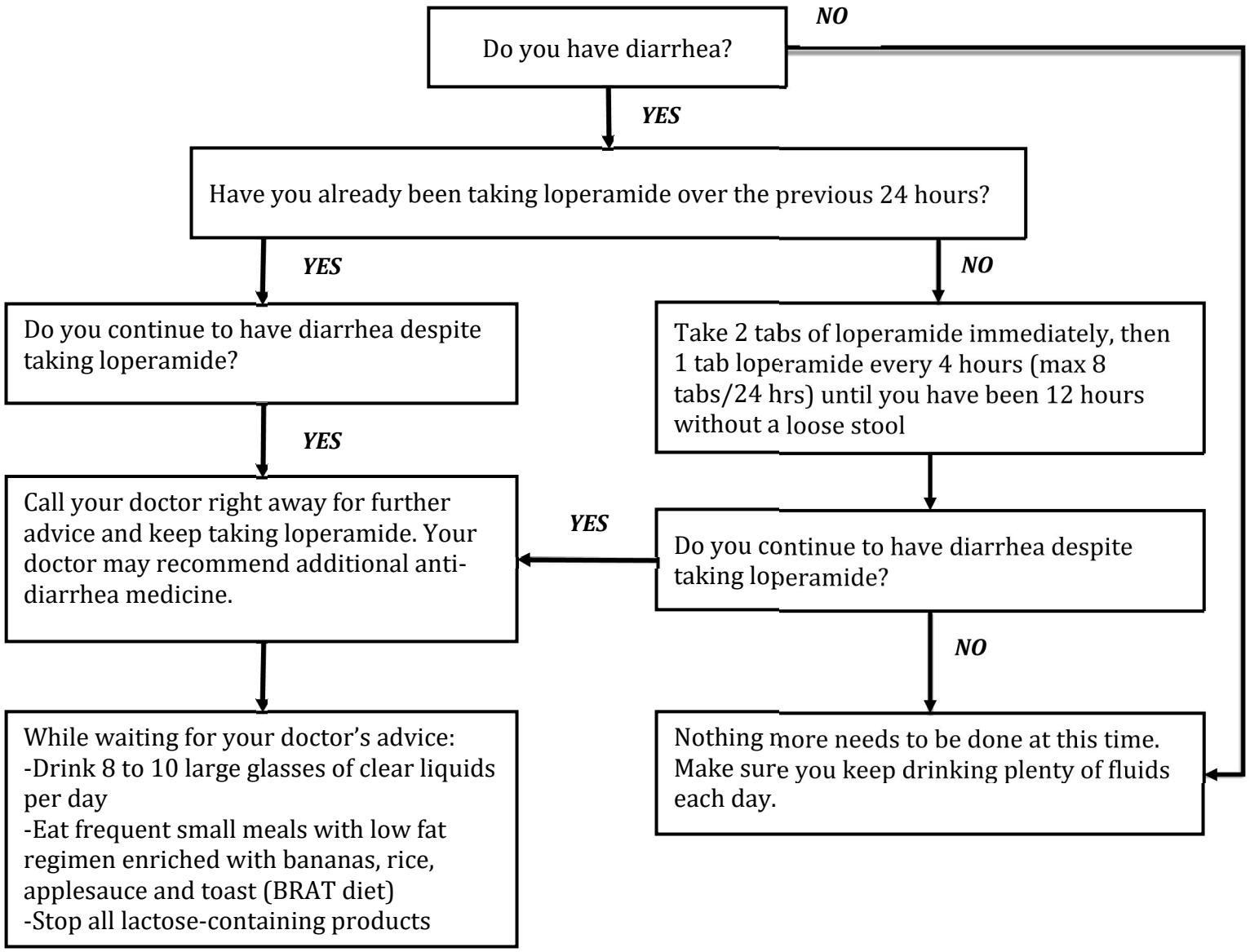
If I am experiencing loose stools or diarrhea and cannot reach my study doctor/team immediately, I will start taking anti-diarrheal medication per the instructions above until further advice is given by my study doctor/team. If I have more than 4-6 stools per day compared to normal despite taking anti-diarrheal medication for 24 hours, and I cannot reach my study doctor/team, I will stop taking the study medication and wait for further instructions from my study doctor/team.

My signature below indicates I have reviewed this information and have received the following medications:

- Neratinib tablets
- Loperamide tablets
- Lomotil prescription

| | |
|---|---|
| Study participant name | Study participant Signature and Date |
| Investigator delegate name<br>**OR** | Investigator delegate Signature and Date |
| Investigator name | Investigator Signature and Date |

# DIARRHEA MANAGEMENT FOR PATIENTS



# Appendix B Investigator Checklist for Optimal Diarrhea Management


Optimal Management of Diarrhea Checklist for Investigators
Study <*insert* Protocol No.>

This checklist must be completed for each patient by the investigator (principal or sub-) during the Day 1 visit before the patient leaves the site with study medication.

Patient Number: |___|___|___|___|___| Day 1 Visit Date: |__|__| / |__|__|__| / |__|__|

☐ I have communicated the risk and the timing of diarrhea occurrence to my patient while discussing the informed consent form and patient diarrhea instruction sheet.

☐ I have ensured that my patient takes home loperamide along with study medication.

☐ I have given my patient a prescription for Lomotil and asked him/her to fill it before starting neratinib.

☐ I have given my patient a 3-week supply of loperamide.

☐ I have reviewed with my patient dietetic measures (e.g., hydration, low lactose, low fat diet enriched with bananas, rice, applesauce and toast) recommended in case he/she experiences loose stools or diarrhea.

☐ I have instructed my patient to record the number of daily stools, the occurrence of diarrhea and any anti- diarrheal treatment along with the daily dose of study medication in his/her diary for the first 2 cycles of study therapy and he/she has agreed to return the completed diary at the next scheduled visit.

☐ I have informed my patient that he/she will receive a call at 1 day, 2 days and 3 days after first dose of study medication, as well as once during week 2 and once during week 3, to assess his/her tolerance to the study medication and to document the date the first dose of study medication was taken.

☐ I will follow-up with my patient on severe diarrhea and other adverse events until resolution.

☐ I checked with my patient that he/she can be reached at_____.

☐ My patient has received my number and knows to call me as soon as he/she experiences loose stool or diarrhea.

**Investigator's Name and Signature**:

1- Loperamide is the recommended standard anti- diarrhea medication in this study. Additional treatment may be required. Refer to the protocol for other therapy and literature

# Appendix C Inhibitors and Inducers of the Cytochrome P450 Isoenzymes

## Table A2. 1 Inhibitors and Inducers of the Cytochrome P450 Isoenzymes

| | | |
|---|---|---|
| **CYP3A4 Inducers** | | |
| Carbamazepine | Phenobarbital | Rifapentine |
| Efavirenz | Phenylbutazone | St. John's Wort |
| Glucocorticoids: | Phenytoin | Sulfinpyrazone |
| Dexamethasone | Primidone | |
| Prednisone | Rifabutin | |
| Macrolide antibiotics | Rifampin | |
| **CYP3A4 Inhibitors** | | |
| Amprenavir | Fluvoxamine | Paroxetine |
| Anastrozole | Grapefruit juice | Propranolol |
| | Indinavir | Quinidine |
| Cimetidine | Itraconazole | Quinine |
| Clarithromycin | Ketoconazole | Ranitidine |
| Clotrimazole | Mibefradil | Ritonavir |
| Danazol | Miconazole | Saquinavir |
| Delavirdine | Mirtazapine (weak) | Sertraline |
| Diethyldithiocarbamate | Nefazodone | Sildenafil (weak) |
| Diltiazem | Nelfinavir | Troglitazone |
| Erythromycin | Nevirapine | Troleandomycin |
| Fluconazole | Norfloxacin | Zafirlukast |
| Fluoxetine | Norfluoxetine | |
| **CYP3A5-7 Inducers** | | |
| Phenobarbital | Primidone | Rifampin |
| Phenytoin | | |
| **CYP3A5-7 Inhibitors** | | |
| Clotrimazole | Metronidazole | Troleandomycin |
| Ketoconazole | Miconazole | |
| **CYP2D6 Substrate** | | |
| Carvedilol | Hydrocodone | Propafenone |
| Chloroquine (possible) | Hydroxyamphetamine | Propoxyphene |
| Chlorpromazine | Labetalol | Propranolol (minor) |
| Citalopram | Maprotiline | Risperidone |
| Clozapine | Methamphetamine | Ritonavir |
| Codeine | Metoprolol | Ropivacaine |
| Cyclobenzaprine | Mexiletine (major) | Selegiline |
| Debrisoquin | Mirtazapine | Sertraline |
| Delavirdine | Morphine | Sparteine |
| Dexfenfluramine | Olanzapine | Tamoxifen |
| Dextromethorphan | Ondansetron | Thioridazine |
| Dolasetron | Oxaminiquine | Timolol |
| Donepezil | Oxycodone | Tolterodine (major) |
| Encainide | Paroxetine | Tramadol |
| Flecainide | Penbutolol | Trazodone |
| Fluoxetine | Pentazocine | Tricyclic antidepressants (Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Trimipramine) |
| Fluphenazine | Perphenazine | Venlafaxine |
| Halofantrine | Phenformin | Ziprasidone |
| Haloperidol | Primaquine (possible) | Zolpidem |

Source: Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 2012

# Appendix D Drugs Reported to Prolong QT Interval

## Table A4. 1 Drugs Associated With Risk of QT/QTc Prolongation Leading to Torsade de

| **Drugs Reported to Prolong QT Interval** | | |
|---|---|---|
| Analgesics | | |
| Celecoxib (Celebrex) | Methadone (e.g., Dolophine, Methadose) | |
| Anesthetic | | |
| Enflurane (e.g., Ethrane) | Halothane | |
| Isoflurane (e.g., Forane) | | |
| Antiarrhythmic | | |
| Class IA | Class III | |
| Disopyramide (e.g., Norpace)* | Amiodarone (e.g., Cordarone)*[b] | |
| Procainamide (e.g., Procanbid)* | Bretylium* | |
| Quinidine* | Dofetilide (Tikosyn)*[b] | |
| Class IC | Ibutilide (Corvert)*[b] | |
| Flecainide (e.g., Tambocor)*[a] | Sotalol (e.g., Betapace)*[b] | |
| Propafenone (e.g., Rythmol)*[b] | | |
| Anticonvulsant | | |
| Felbamate (Felbatol)* | Fosphenytoin (Cerebyx) | |
| Antiemetics | | |
| Dolasetron (Anzemet)[b] | Droperidol (e.g., Inapsine)*[b] | Ondansetron (Zofran) |
| Antihistamine | | |
| Desloratadine (Clarinex)[b] (overdose) | Fexofenadine (Allegra) | |
| Diphenhydramine (e.g., Benadryl) | Hydroxyzine (Atarax) | |
| Anti- | | |
| Amantadine (e.g., Symmetrel)* | Macrolides and related antibiotics | |
| Antimalarials | Azithromycin (e.g., Zithromax) | |
| Mefloquine (e.g., Lariam)[b] | Clarithromycin (e.g., Biaxin)*[b] | |
| Quinine* | Erythromycin (e.g., Ery-Tab, EES)*[b] | |
| Antivirals | Telithromycin (Ketek)[b] | |
| Efavirenz (Sustiva)* | Troleandomycin | |
| Azole antifungal agents | Pentamidine (e.g., Pentam 300, Nebupent)* | |
| Fluconazole (e.g., Diflucan)*[b] | Quinolones | |
| Itraconazole (e.g., Sporanox) | Gatifloxacin (e.g., Tequin)*[b] | |
| Ketoconazole (e.g., Nizoral) | Levofloxacin (e.g., Levaquin)*[a, b] | |
| Voriconazole (Vfend)[b] | Moxifloxacin (e.g., Avelox)[b] | |
| Chloroquine (e.g., Aralen)* | Ofloxacin (e.g., Floxin)*[b] | |
| Clindamycin (e.g., Cleocin) | Sparfloxacin (Zagam)[b] | |
| Foscarnet (Foscavir) | Trimethoprim/sulfamethoxazole (e.g., | |
| Antineoplastic | | |
| Arsenic trioxide (Trixenox)*[b] | Doxorubicin (e.g., Adriamycin) | Tamoxifen (e.g., Nolvadex) |
| Bronchodilator | | |
| Albuterol (e.g., Proventil)[b] | Salmeterol (Serevent)[b] | |
| Formoterol (Foradil)[b] | Terbutaline (e.g., Brethine)[b] | |
| Isoproterenol (e.g., Isuprel) | | |
| Calcium channel | | |
| Isradipine (DynaCirc) | Nicardipine (e.g., Cardene) | |
| Contrast | | |
| Ionic contrast media* | Non-ionic contrast media: Iohexol (Omnipaque) | |

| **Drugs Reported to Prolong QT Interval** | | |
|---|---|---|
| Corticosteroid | | |
| Prednisolone (e.g., Prelone) | Prednisone (e.g., Deltasone)* | |
| Diuretics | | |
| Furosemide (e.g., Lasix) | Indapamide (e.g., Lozol) | |
| Gastrointestinal | | |
| Cisapride (Propulsid)*[b, c] | Famotidine (e.g., Pepcid)* | |
| Immunosuppressant | | |
| Tacrolimus (Protopic)*[b] (postmarketing) | | |
| Miscellaneou | | |
| Levomethadyl | Papaverine (e.g., Pavaden three times daily [TID])* | |
| Moexipril/Hydrochlorothiazide (Uniretic) | Probucol (Lorelco)*[c] | |
| Octreotide (Sandostatin)[b] | Vasopressin (e.g., Pitressin)* | |
| Oxytocin (e.g., Pitocin; intravenous bolus) | | |
| Psychotropic | | |
| Droperidol (e.g., Inapsine)* | Primozide (Orap)*[b, d] | Trazodone (e.g., Desyrel) |
| Haloperidol (e.g., Haldol)* | Quetiapine (Seroquel)[b] | Tricyclic antidepressants |
| Lithium (e.g., Eskalith)* | Risperidone (Risperdal)[b] (overdose) | Amitriptyline* |
| Maprotiline* | Serotonin Reuptake Inhibitors (SRIs) | Clomipramine (e.g., Anafranil) |
| Phenothiazines | Citalopram (e.g., Celexa)* | Desipramine (e.g., Norpramin)* |
| Chrlorpromazine (e.g., Thorazine)* | Fluoxetine (e.g., Prozac)*[a] | Doxepin (e.g., Sinequan)* |
| Fluphenazine (e.g., Prolixin)* | Paroxetine (e.g., Paxil)* | Imipramine (e.g., Tofranil)* |
| Perphenazine | Sertraline (Zoloft)*[a, b] (postmarketing) | Nortriptyline (e.g., Pamelor) |
| Thioridazine (Mellaril)*[b] | Venlafaxine (Effexor)[b] (postmarketing) | |
| Trifluopherazine | | |
| Serotonin 5-HT[1] | | |
| Naratriptan (Amerge) | Sumatriptan (Imitrex)[b] | Zolmitriptan (Zomig)[b] |
| Skeletal muscle | | |
| Tizanidine (e.g., 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 E Substrates and Inhibitors of P-glycoprotein (P-gp)

**Table A3. 1 Substrates and Inhibitors of P-glycoprotein (P-gp)**

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

Source: Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 2012.

# Appendix F Data and Safety Monitoring Plan (DSMP) for a Phase 2 or 3 Institutional Study

## 1.Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

## 2.Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

## 3. Review and Oversight Requirements

### 3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.

- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

### 3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be

reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

### 3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

**Data and Safety Monitoring Committee Contacts:**

[redacted] (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

[redacted] (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

# Protocol Signature Page

**Protocol No.:** Version 6.0 **Version Date:** 07-23-

2021 I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).

I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.

I certify that I, and the study staff, have received the requisite training to conduct this research protocol.

I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.

I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

**UCSF Principal Investigator / Study Chair**

Amy Jo Chien, MD

_____

Printed Name

_____ _____

Signature Date

**Participating Site(s)**

| | | |
|---|---|---|
| Telephone:<br>E-mail: | Telephone:<br>E-mail: | Telephone:<br>E-mail: |

**Principal Investigator** **Site**

_____ _____

Printed Name

_____ _____

Signature Date