TITLE: DIARRHEA PREVENTION AND PROPHYLAXIS WITH CROFELEMER IN HER2 POSITIVE BREAST CANCER PATIENTS RECEIVING TRASTUZUMAB, PERTUZUMAB, AND DOCETAXEL OR PACLITAXEL WITH OR WITHOUT CARBOPLATIN

NCT: NCT02910219

Current Protocol Date June 7, 2021

HALT-D

DIARRHEA PREVENTION AND PROPHYLAXIS WITH CROFELEMER IN HER2 POSITIVE BREAST CANCER PATIENTS RECEIVING TRASTUZUMAB, PERTUZUMAB, AND DOCETAXEL OR PACLITAXEL WITH OR WITHOUT CARBOPLATIN

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Study Drug	Crofelemer
Funding Source(s)	Genentech Napo Pharmaceuticals MedStar Health Research Institute
Current Protocol Date	June 7, 2021

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization guidelines.

Sponsor Dr. Sandra M. Swain, MD, FACP, FASCO

Sponsor Signature _____

Date _____

SCHEMA

Figure 1: Flow chart of patient enrollment

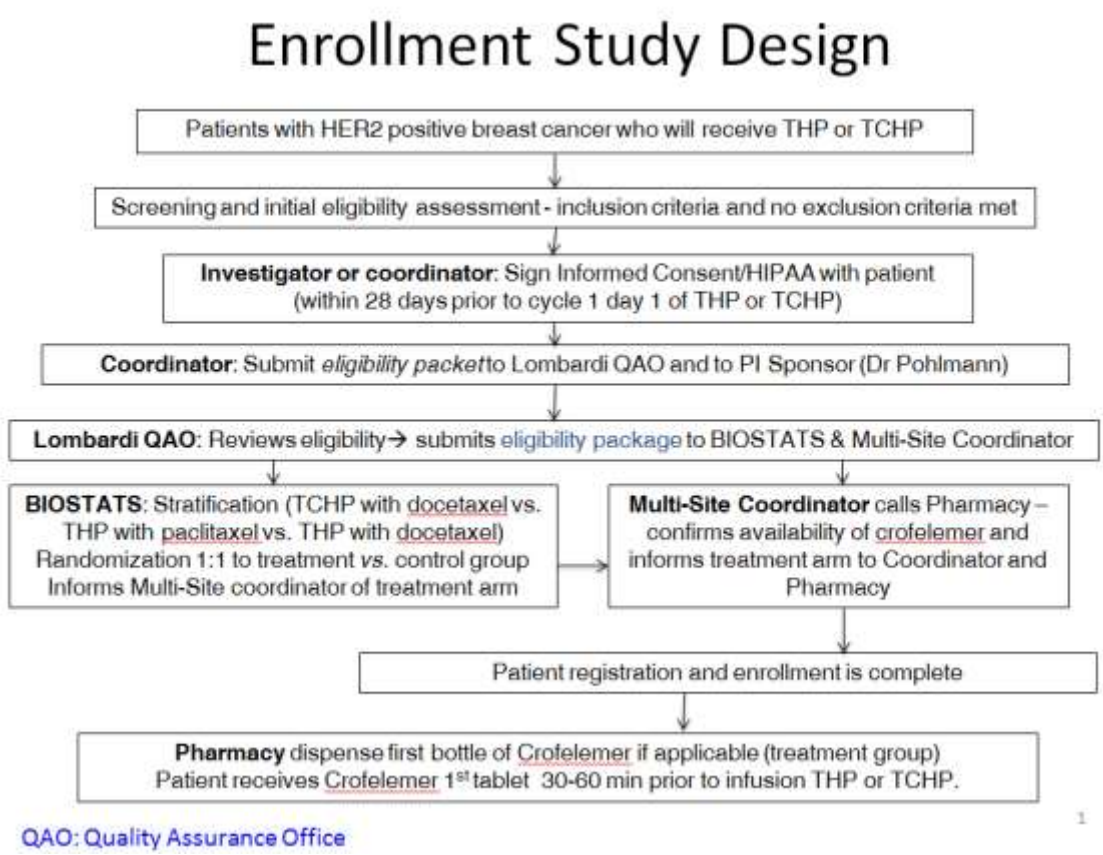


Figure 2: Treatment group schema

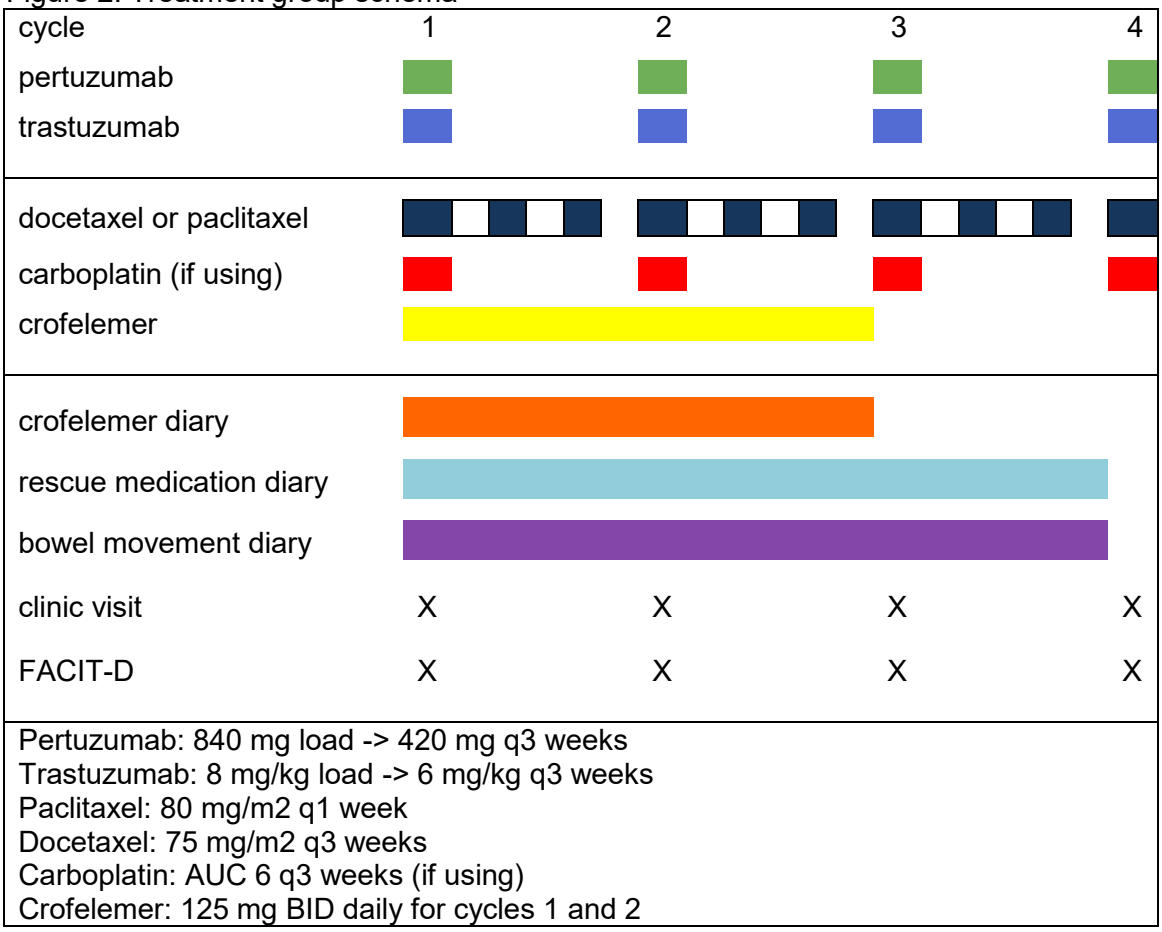
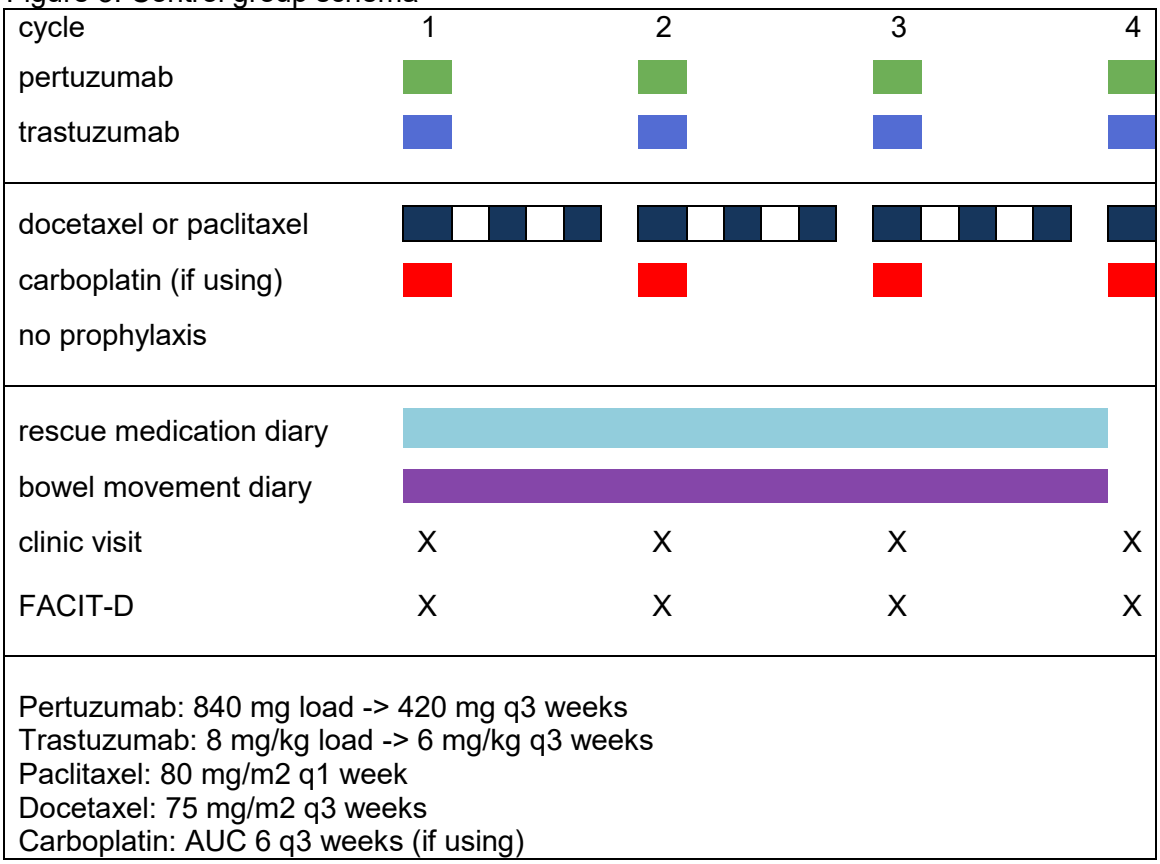


Figure 3: Control group schema



STUDY SYNOPSIS

Title:
Diarrhea prevention and prophylaxis with crofelemer in HER2 positive breast cancer patients receiving trastuzumab, pertuzumab, and docetaxel or paclitaxel with or without carboplatin: HALT-D

Investigators:
Sponsor: Sandra M. Swain, MD, FACP, FASCO

Study Center(s):
This study will be open at multiple sites in the United States.

Concept and Rationale:
Chemotherapy induced diarrhea (CID) occurs in 40-80% of breast cancer patients who receive HER2 directed therapy with trastuzumab, pertuzumab, and a taxane, with most patients experiencing grade 1-2 diarrhea. In the CLEOPATRA trial, in which patients received a median of 8 cycles of trastuzumab, pertuzumab, and docetaxel, 67% had all grade diarrhea and 8% experienced grade 3 diarrhea. Patients on the TRYPHAENA trial received 6 cycles of neoadjuvant trastuzumab, pertuzumab, and docetaxel, with 72.4% of patients experiencing all grade diarrhea and 11.8% experiencing grade 3 diarrhea; the results were similar in the patients who also received carboplatin. In a phase 2 trial of trastuzumab and pertuzumab with weekly paclitaxel, in which patients received a median of 10 cycles of treatment, 81% of patients had all grade and 3% had grade 3-4 diarrhea.

In addition to impacting kidney function and causing electrolyte imbalance, diarrhea even at grades 1-2 can significantly impact a patient's quality of life. Various anti-diarrheal agents, including loperamide, codeine, octreotide, non-absorbed steroids, atropine, antibiotics, opium, bismuth, probiotics, and bile acid sequestrants, are available for symptom management. Of these, loperamide is most commonly used and recommended as a first line agent in the treatment setting. Octreotide is generally reserved for refractory diarrhea due to its cost and requirement for subcutaneous dosing. However, none of these target the underlying mechanism of CID.

Chloride ions and channels play a large role in the underlying mechanism of secretory diarrhea. In the luminal side of the colon, chloride efflux is mediated via apical chloride channels, of which there are three types: 1) cystic fibrosis transmembrane regulator (CFTR), a cyclic AMP stimulated chloride channel; 2) calcium activated chloride channel (CaCC); and 3) chloride channel type 2 (ClC2). Various studies have looked at the role of epidermal growth factor receptor (EGFR) targets and the mechanism of diarrhea. These studies have suggested that blocking EGFR can cause excess chloride secretion, resulting in impaired gut absorption and a resulting secretory diarrhea.

Crofelemer is an extract from the blood red bark of Croton lechleri that inhibits luminal chloride efflux by blocking two channels that regulate chloride efflux in the colon, the calcium activated chloride channel (CaCC) and the cystic fibrosis transmembrane regulator (CFTR). Due to its size and polarity, it acts only luminally and is not systemically absorbed.

In a phase 3 randomized controlled double blinded trial, investigators looked at 376 HIV patients with diarrhea for > 1 month. The first part of the study established the optimal dose of crofelemer at 125 mg twice a day, which resulted in a 21% reduction in stool frequency. The

second part of the study compared crofelemer to placebo with a primary endpoint of ≤ 2 watery stools per week. They noted a statistically significant higher response rate of 18% for patients on crofelemer versus 8% for those on placebo. When patients initially on placebo crossed over to the crofelemer arm, 36% met the criterion of response. Possible side effects included dyspepsia, flatulence, constipation, nausea, and increased alanine transferase. Based on this study, crofelemer was approved by the FDA in 2012 for secretory diarrhea in patients with HIV/AIDS receiving anti-retroviral therapy.
We propose a trial of crofelemer versus standard of care (no anti-diarrheal prophylaxis) for prevention of CID in HER2 positive breast cancer patients on trastuzumab, pertuzumab, and docetaxel or paclitaxel with or without carboplatin. We hypothesize that crofelemer, which targets two of the chloride channels responsible for secretory diarrhea, will be an effective and targeted approach to reducing the incidence of CID in this patient population.

Primary Objective(s):
To determine the efficacy of crofelemer in preventing chemotherapy induced diarrhea (CID) in patients with HER2 positive breast cancer receiving chemotherapy with trastuzumab, pertuzumab, and docetaxel or paclitaxel (THP) or trastuzumab, pertuzumab, carboplatin, and docetaxel (TCHP).

Secondary Objectives:
If possible, the secondary objectives will be:

- To determine the incidence of diarrhea of any grade, as measured by CTCAE v4.0, by cycle;
- To determine the incidence of diarrhea of grade 3-4, as measured by CTCAE v4.0, by cycle;
- To determine the time to onset of first event of diarrhea of any grade, defined as the number of days from day one of THP or TCHP until the day in which the first episode of diarrhea classified as of grade 1 or higher occurs, or is censored at the date of the last treatment cycle for patients who do not experience diarrhea, overall and by stratum;
- To determine the duration (days) of any grade diarrhea, by cycle in which the episode started and by stratum;
- To determine the duration (days) of grade 3-4 diarrhea, by cycle in which the episode started and by stratum;
- To assess use of anti-diarrheal medications (other than study drug), by cycle, grade of diarrhea, and stratum;
- To determine the quantitative FACIT-D total score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum;
- To determine the quantitative FACIT-D diarrhea subset (DS) score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum;
- To determine the frequency table for stool consistency, as measured by the Bristol Stool scale, by cycle and stratum for each treatment group.

Main Criteria for Inclusion/Exclusion:

Inclusion Criteria

1. Willing and able to provide written informed consent;
2. Men and women ≥18 years of age;
3. Pathologically confirmed diagnosis of HER2 positive breast cancer of any stage (previous treatment is allowed without limits on lines of prior therapy);
4. Scheduled to receive at least 3 consecutive cycles of THP or TCHP;
5. Performance status of 0-2 according to the ECOG scale;
6. Negative pregnancy test within 2 weeks prior to starting THP or TCHP treatment for women of childbearing potential;
7. Able to read, understand, follow the study procedure and complete crofelemer, rescue medication, and bowel movement diaries;
8. Patients may enroll simultaneously on this study and other studies
9. Patients with brain metastases (including concurrent steroid treatment) are allowed on this study.
10. Left Ventricular Ejection Fraction (LVEF) greater or equal to 50% at baseline as determined by either ECHO or MUGA

Exclusion Criteria

Any patient who at the time of signing consent is/has:

1. Pregnant and/or breastfeeding;
2. Ongoing irritable bowel syndrome (IBS) or colitis (including but not limited to ulcerative colitis, Crohn's disease, microscopic colitis, etc.);
3. Use of investigational drugs within 3 weeks of starting THP or TCHP treatment or foreseen use during the study;
4. Use of chemotherapy, trastuzumab, or pertuzumab within the past 2 (two) weeks;
5. ~~Use of laxatives within the past 7 days~~ - deleted;
6. ~~Use of chronic laxatives (≥ 30 consecutive days)~~ - deleted;
7. ~~Use of anti-diarrheal agents (including but not limited to loperamide, octreotide, bismuth, tincture of opium, atropine, probiotics in any form other than food) within the past 7 days~~ - deleted;
8. Use of antibiotics within the past 7 days (up to 2 prophylactic doses of antibiotic for procedures, including but not limited to port placement, is permitted)
9. Any type of ostomy;
10. Total colectomy;
11. Fecal incontinence;
12. Ongoing radiation induced diarrhea or constipation or planned radiotherapy to the abdomen or pelvis while on study;
13. Active systemic infection requiring ongoing intervention, including but not limited to oral and intravenous antibiotics, anti-fungals, anti-parasites, anti-virals;
14. Abdominal or pelvic surgery without recovery of bowel function;
15. Inadequate organ function for starting THP or TCHP, which may include the following laboratory results within 28 days prior to starting THP or TCHP treatment (Please refer to the prescribing label instructions on the use of each drug in the setting of abnormal organ function):
    - Serum creatinine > 2.0 mg/dL or 177 µmol/L
    - Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)
    - Exclusion criteria specific for THP with PACLITAXEL (Taxol®) group:
        - Transaminases greater than 10 times ULN

- Exclusion criteria specific for TCHP/THP with DOCETAXEL (Taxotere®) group:
  - AST and/or ALT > 2.5x ULN

  AST and/or ALT > 1.5x ULN with concurrent alkaline phosphatase >2.5 x ULN (unless bone metastases are present).

Intervention and Mode of Delivery:
Treatment group: crofelemer 125 mg orally twice a day daily during cycles 1-2 of THP or TCHP chemotherapy.
Control group: no prophylaxis (current standard of care).

Study Design:
This is a randomized, 1:1, stratified, open-label phase II study in patients with HER2 positive breast cancer receiving THP or TCHP in any setting. Randomization will be stratified according to TCHP with docetaxel vs. THP with paclitaxel vs. THP with docetaxel.

Patients randomized to the treatment group will receive oral crofelemer 125 mg twice daily during cycles 1-2 of THP or TCHP chemotherapy. The primary endpoint is the total number of patients with all grade diarrhea for two or more consecutive days that is definitely, probably, or possibly due to THP or TCHP during cycles 1 and 2. All patients will keep a daily diary of bowel movement number and consistency.

Statistical Methods:
Definition of primary endpoint:
The primary endpoint is incidence of diarrhea of any grade for two or more consecutive days felt to be definitely, probably, or possibly due to THP or TCHP, as assessed by NCI CTCAE v4.0, during cycle 1 and cycle 2 of chemotherapy. The CTCAE v4.0 coding for diarrhea is 10012727.

Definition of secondary endpoints:
If possible, the secondary endpoints will be:

- Incidence of diarrhea of any grade, as measured by CTCAE v4.0, by cycle and by stratum;
- Incidence of diarrhea of grade 3-4, as measured by CTCAE v4.0, by cycle and by stratum;
- Time to onset of first episode of diarrhea of any grade, defined as the number of days from day one of THP or TCHP until the day in which the first episode of diarrhea classified as of grade 1 or higher occurs, or is censored at the date of the last treatment cycle for patients who do not experience diarrhea, overall and by stratum;
- Duration (days) of any grade diarrhea, by cycle in which the episode started and by stratum;
- Duration (days) of grade 3-4 diarrhea, by cycle in which the episode started and by stratum;
- Use of anti-diarrheal medications (other than study drug), by cycle and grade;
- Quantitative FACIT-D total score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum;
- Quantitative FACIT-D diarrhea subset (DS) score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum;
- Frequency table of stool consistency, as measured by the Bristol Stool scale, by cycle stratum between treatment groups.

Analytic plan for primary objective:
The number and percent of patients who experience diarrhea of any grade for two or more consecutive days (felt to be definitely, probably, or possibly due to THP or TCHP) during cycle 1 and 2 will be summarized with two-sided 90% confidence interval overall and by treatment assignment, and compared between treatment arms using a Fisher's exact test. The analysis population is defined as all randomized patients who complete 2 cycles of THP or TCHP chemotherapy.

Analytic plan for secondary objectives:
We plan on using the following analytic plan for secondary objectives and endpoints, if possible.

According to treatment group, for each of the cycles and stratum, we will summarize: 1) the

number and percent of patients (and 95% CI) who experience diarrhea of any grade; 2) the number and percent of patients (and 95% CI) who experience diarrhea of grade 3-4; 3) the median, range, and interquartile range of the duration of the episodes; and 4) the number (%) of patients requiring anti-diarrheal rescue medication.

The time to onset of first episode of diarrhea will be summarized using the Kaplan-Meier method, and compared between treatment groups and stratum using log-rank test.

The FACIT-D and FACIT-D DS scores will be summarized descriptively and graphically by cycle, treatment assignment, and stratum. The change in FACIT-D and FACIT-D DS scores between day 1 of cycles 1-3 and end of study (within 5 days of cycle 4 day 1) will be compared at each time point between treatment groups using a Wilcoxon rank sum-test.

The stool consistency, as measured by the Bristol Stool scale, will be summarized in frequency tables by cycle and stratum and compared between treatment groups using a Wilcoxon rank sum-test.

Adverse events will be summarized by type, grade, and stratum, according to treatment arm.

Sample size justification:
With a sample size of 46 patients (23 per treatment group), the study has 81% power to detect a 40% absolute decrease (from 60% to 20%) in incidence of all grade diarrhea for two or more consecutive days that is definitely, probably, or possibly due to THP or TCHP during cycles 1 and 2 of chemotherapy, with a two sided significance level of 0.10 based on Fisher's exact test.

Funding:
Genentech
Napo Pharmaceuticals
MHRI

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1 LIST OF ABBREVIATIONS

AD	Associate Director
ADL	Activities of Daily Living
ADEERS	Adverse Events Expedited Reporting System
AE	Adverse event(s)
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CaCC	Calcium activated chloride channel
CFTR	Cystic fibrosis transmembrane regulator
CI	Confidence Interval
CID	Chemotherapy induced diarrhea
ClC2	Chloride channel type 2
CRC	Clinical Research Committee
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event(s)
DS	Diarrhea Subscale
DSMC	Data and Safety Monitoring Committee
EGFR	Epidermal Growth Factor Receptor
EST	Eastern Standard Time
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-D	Functional Assessment of Chronic Illness Therapy – Diarrhea
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HJWCI	Harry and Jeanette Weinberg Cancer Institute
IBS	Irritable bowel syndrome
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LCCC	Lombardi Comprehensive Cancer Center
MHRI	MedStar Health Research Institute
MMMC	MedStar Montgomery Medical Center
MUMH	MedStar Union Memorial Hospital
NCI	National Cancer Institute
PHI	Protected Health Information
PO	By mouth
SAE	Serious adverse event
TCHP	Trastuzumab, pertuzumab, carboplatin, and docetaxel
THP	Trastuzumab, pertuzumab, docetaxel or paclitaxel

2 BACKGROUND AND RATIONALE

2.1 Normal Intestinal Function

Approximately 9000 cc of fluid passes through the human small intestine on a daily basis, a combination of ingested fluid (~ 2000 cc), saliva (~ 1500 cc), gastric secretions (~ 2000 cc), pancreatic secretions (~ 1500 cc), bile (~ 500 cc), and intestinal secretions (~ 1500 cc). The small intestine reabsorbs approximately 90% of this fluid, passing about 1000 cc into the large intestine. The large intestine reabsorbs an additional 90% of fluid, ultimately leaving only approximately 100 cc of fluid to be excreted in feces. A decrease in 1-2% of intestinal water absorption, as little as 50 cc, will increase stool weight to more than 200 g per 24 hours (the upper limit of normal) and result in diarrhea. [1]

2.2 Types of Diarrhea

When evaluating diarrhea, both the duration and underlying mechanism are important to ascertain. Acute diarrhea is defined as greater than or equal to three stools daily of decreased form, with symptoms lasting less than 14 days. Persistent diarrhea occurs when the symptoms last more than 14 days but less than 1 month. If the symptoms persist more than 1 month, then the diarrhea is considered chronic. [1-3]

There are many different mechanisms of diarrhea. Secretory diarrhea is due to decreased reabsorption or increased secretion of fluid and electrolytes within the gastrointestinal (GI) tract. Osmotic diarrhea occurs when osmotically active, poorly absorbed solutes inhibit the reabsorption of fluid and electrolytes. Various forms of colitis, including microscopic, ischemic, and autoimmune, can also cause diarrhea due to inflammation and mucosal damage. If the cause of diarrhea is a direct consequence of chemotherapy, then the diarrhea is called chemotherapy induced diarrhea (CID). [1-3]

2.3 Diarrhea Grading

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 assigns grades to CID depending on the amount of stool produced. Grade 1 diarrhea is defined by an increase of less than 4 stools per day over baseline. Grade 2 diarrhea is an increase of 4-6 stools per day over baseline, but not interfering with activities of daily living (ADLs). Grade 3 diarrhea occurs when there is an increase of 7 or more stools per day over baseline, the presence of incontinence, symptoms that limit self care ADLs, or requirement for hospitalization. Finally, grade 4 diarrhea is defined as diarrhea that can cause life-threatening consequences, warranting urgent medical intervention.

2.4 Assessing Quality of Life with Diarrhea

The Functional Assessment of Chronic Illness (FACIT) is a health related quality of life questionnaire that focuses on four primary quality of life domains: physical, social/family, emotional, and functional well-being. FACIT has been validated in all cancers. A FACIT questionnaire for diarrhea (FACIT-D) incorporates the original four quality of life domains and includes additional questions addressing how diarrhea affects quality of life.

2.5 Chemotherapy Induced Diarrhea: Breast Cancer

While chemotherapy and targeted therapy can be highly effective in breast cancer, the side effects of each can cause significant problems resulting in loss of quality of life, dose reductions, and dose delays. Diarrhea in particular can be seen in 40- 80% of patients who are on breast cancer therapy. Therapies targeted at HER2 positive breast cancer patients and their diarrhea incidences will be discussed below.

2.5.1 Breast Cancer: EGFR Targets

Human epidermal growth factor receptor 2 (HER2) is a member of the EGFR family. Chemotherapy induced diarrhea (CID) occurs in 40-80% of breast cancer patients who receive

HER2 directed therapy with trastuzumab, pertuzumab, lapatinib, or neratinib. Various studies have looked at the role of EGFR targets and the mechanism of diarrhea. In the luminal side of the colon, chloride efflux is mediated via apical chloride channels, of which there are three types: 1) cystic fibrosis transmembrane regulator (CFTR), a cyclic AMP stimulated chloride channel; 2) calcium activated chloride channel (CaCC); and 3) chloride channel type 2 (ClC2). These prior studies have suggested that blocking EGFR can cause excess chloride secretion, resulting in impaired gut absorption and producing secretory diarrhea. [4-6]

2.5.2 Breast Cancer: Docetaxel and Paclitaxel

Docetaxel and paclitaxel are chemotherapy agents in the class of taxanes. Taxanes stabilize tubulin in the microtubules, thus preventing mitosis and halting cell division. Both docetaxel and paclitaxel are used in the treatment of breast cancer either in combination chemotherapy, as a single agent, or with monoclonal antibodies such as trastuzumab and pertuzumab. Sparano et al. showed that docetaxel given every 3 weeks or paclitaxel given weekly had the best disease free survival in the adjuvant setting when used with combination chemotherapy. Diarrhea was more frequent in the docetaxel arm, as well as neutropenia, febrile neutropenia, and infections; neuropathy was higher in the paclitaxel arm. Thus while both docetaxel and paclitaxel are in the same class of medications, their side effect profiles do differ. [7]

Hainsworth et al. conducted a phase 1 dose escalation trial of weekly docetaxel in 38 patients with solid tumors, seven of whom were breast cancer patients. The dose limiting toxicity was found to be fatigue and asthenia, particularly at the higher dose levels of 43 mg/m2/wk and 52 mg/m2/wk. Other toxicities noted at these dose levels included skin and nail changes and diarrhea. In a phase 2 study of docetaxel in 35 patients with metastatic anthracycline resistant breast cancer, Valero et al. reported 31 patients developed neutropenia, with 18 experiencing febrile neutropenia and one patient dying of resulting sepsis. Other common side effects included stomatitis, myalgia, and fluid retention. [8, 9]

More serious complications in docetaxel include colitis and typhlitis. Ibrahim et al. reported 6 cases of ischemic colitis in metastatic breast cancer patients receiving docetaxel based regimens. Typhlitis was noted in 3 patients on vinorelbine and docetaxel, with 2 patients ultimately dying of necrotic bowel and neutropenic fever. The other three patients with colitis were receiving docetaxel monotherapy or with pamidronate or cyclophosphamide. Three out of the six patients received dedicated abdominal imaging, all of which were positive for colitis. Other case reports published have shown docetaxel induced cecal perforation in a patient being treated for gastro-esophageal junctional adenocarcinoma and a patient who died of Clostridium perfrigens septic shock, with a source hypothesized to be due to typhlitis. [10]

Phase 1 studies of paclitaxel in patients with metastatic breast and ovarian cancer showed neutropenia, diarrhea, mucositis, neuropathy, and myalgia was seen at various doses, with neutropenia predominant at higher doses of 90-100 mg/m2. These results have been corroborated by various phase 2 studies in metastatic breast cancer patients. Seidman et al. looked a paclitaxel in 49 patients. Of the grade 3-4 events, 36% had neutropenia, 16% had arthralgia/myalgia, 8% had neuropathy, and 4% had mucositis. Reichman et al. looked at paclitaxel in 28 patients; 20 patients developed neutropenia, of which 6 had febrile neutropenia, and 24 had grade 1-2 neuropathy. Diarrhea was seen in 14, mucositis in 20, nausea in 16, and arthralgia/myalgia in 27 patients. [11, 12]

As in docetaxel, typhlitis is also seen in patients receiving paclitaxel. In a phase 2 trial of 63 patients with small cell lung cancer on paclitaxel, topotecan, and etoposide, one patient died of febrile neutropenia and one of febrile neutropenia and typhlitis. In a phase 1/2 trial of 42 patients with metastatic breast cancer, Fisherman et al. reported that all three patients who had received the highest dose of a 72 hour infusional regimen of paclitaxel and doxorubicin

experienced typhlitis with radiographic corroboration. All 42 patients had grade 4 neutropenia with an absolute neutrophil count of less than 500. The dose limiting toxicity was diarrhea. There have also been case reports of patients experiencing acute transient encephalopathy while receiving paclitaxel; this has not been reported with docetaxel. [13]

While typhlitis, colitis, and acute transient encephalopathy are rarer side effects of docetaxel and paclitaxel, neutropenia (including febrile neutropenia), neuropathy, and gastrointestinal symptoms are well established and in some studies, diarrhea is even the dose limiting toxicity. [7-10, 13-18]

2.5.3 Breast Cancer: Trastuzumab and Pertuzumab

Trastuzumab is a monoclonal antibody that binds to the extracellular segment of the HER2 receptor, causing cell cycle arrest and antibody-dependent cell-mediated cytotoxicity (ADCC). Pertuzumab is a monoclonal antibody that binds to the extracellular dimerization domain of HER2, thus inhibiting HER signaling pathways and ultimately also resulting in ADCC.

The BCIRG 006 study looked at patients with early stage HER2 positive breast cancer. Patients were randomized to doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), AC-T with 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). Overall, grade 3 or 4 diarrhea was seen in 3.0% (32/1050) of patients who received AC-T, 5.6% (60/1068) of patients who received AC-T plus trastuzumab, and 5.4% (57/1056) of patients who received TCH. [19]

The CLEOPATRA study launched the combination of trastuzumab, pertuzumab, and docetaxel (THP) into the forefront of treatment for advanced or metastatic HER2 positive breast cancer. Patients on this regimen saw a benefit not only in progression free survival (PFS), but also overall survival (OS). However, 66.8% (272/407) of patients experienced all grade diarrhea, and 7.9% (32/407) had grade 3-4. In subsequent trials using this three drug regimen, authors report a similar incidence of diarrhea. In the TRYPHAENA study, patients who received six cycles of THP experienced 72.4% (55/76) all grade diarrhea and 11.8% (9/76) grade 3-4 diarrhea. Similarly, in the NEOSPHERE study, patients who received THP experienced 46% (49/107) all grade diarrhea and 6% (6/107) grade 3-4 diarrhea. Patients who received trastuzumab and docetaxel experienced 34% (36/107) all grade and 4% (4/107) grade 3 or higher diarrhea. Patients who received pertuzumab plus trastuzumab experienced 28% (30/108) all grade diarrhea and no patients had grade 3 or higher diarrhea. Finally, patients who received pertuzumab plus docetaxel experienced 54% (51/94) all grade and 4% (4/94) grade 3 or higher diarrhea. In a recent publication looking at paclitaxel with trastuzumab and pertuzumab, Dang et al. reported 81% (56/69) all grade diarrhea and 3% (2/69) grade 3-4, showing that both patients on docetaxel and paclitaxel have similar incidences of diarrhea when combined with trastuzumab and pertuzumab. [20-23]

Prior studies of pertuzumab and trastuzumab suggest that while pertuzumab can cause a high incidence of diarrhea, trastuzumab usually does not. A phase 1 study of pertuzumab of 21 patients showed 43% (9/21) experienced all grade diarrhea and 5% (1/21) had grade 3-4. In a phase 2 study of trastuzumab monotherapy, only two grade 2 diarrhea events occurred out of 768 administrations of trastuzumab in 46 patients, and no grade 3 events occurred. Finally, a study of pertuzumab with or without trastuzumab in patients who had previously progressed on trastuzumab showed that in the pertuzumab monotherapy arm, 48.3% (14/29) had all grade diarrhea and 3% (1/29) had grade 3-4. Interestingly in the two drug pertuzumab-trastuzumab arm, 29% (5/17) had all grade diarrhea and 6% (1/17) had grade 3-4. [20, 22-27]

2.5.4 Breast Cancer: Carboplatin

Carboplatin is a platinum-based antineoplastic agent that interferes with DNA repair. It is related to cisplatin, although carboplatin has less nephrotoxicity. Cisplatin is currently not routinely used in the treatment of breast cancer.

Isakoff et al. conducted a phase 2 study of carboplatin or cisplatin in the first or second line setting in patients with metastatic triple negative breast cancer. Both groups of patients experienced fatigue, nausea, electrolyte abnormalities, and hematologic toxicities. Patients in the carboplatin arm had more thrombocytopenia, while patients on the cisplatin arm had more anemia, neutropenia, hypomagnesemia, tinnitus, and anorexia. [28]

Von Minckwitz et al. looked at patients with untreated, non-metastatic triple negative and HER2 positive breast cancer who received paclitaxel and non-pegylated liposomal doxorubicin as their chemotherapy backbone, with or without carboplatin in the neoadjuvant setting. Triple negative cancer patients also received bevacizumab and HER2 positive cancer patients also received trastuzumab and lapatinib. Patients who received carboplatin had a statistically higher incidence of anemia, neutropenia, thrombocytopenia, nausea, anorexia, hand-foot syndrome, nail changes, and pneumonitis. [29]

The BCIRG 007 Study was a phase 3 randomized trial comparing TH (docetaxel and trastuzumab) versus TCH (docetaxel, trastuzumab, carboplatin) as first line treatment for patients with HER2 positive metastatic breast cancer. Patients who received carboplatin had increased thrombocytopenia, motor neuropathy, myalgia, rash, nail changes, nausea, and vomiting compared to the patients who did not receive carboplatin. All grade diarrhea was seen in 51.1% (67/131) of patients on the TH arm and 56.5% (74/131) in the patients on TCH. Grade 3 or 4 diarrhea was seen in 2.3% (3/131) of the patients who received TH and 9.9% (13/131) of the patients who received TCH. The difference in diarrhea was not statistically significant. [9]

2.5.5 Breast Cancer: Neratinib and Lapatinib

Neratinib and lapatinib are oral tyrosine kinase inhibitors of HER2 and EGFR; neratinib is an irreversible inhibitor that targets cysteine in the ATP-binding pocket of the receptors and lapatinib is a reversible inhibitor that blocks the phosphorylation of the receptors. Lapatinib has also been shown to inhibit cyclin D in human tumor cell lines in vitro.

Burstein et al. looked at neratinib monotherapy in patients with advanced HER2 positive breast cancer both with and without previous trastuzumab therapy. All grade diarrhea was seen in 93% (126/136) of patients and grade 3-4 diarrhea in 21% (29/136). At the American Society of Clinical Oncology (ASCO) meeting in 2015, the results of the ExteNET study looking at with localized HER2 positive cancer treated with neratinib versus placebo for one year showed patients had 95.4% (1343/1408) all grade diarrhea and 39.9% (562/1408) grade 3-4 diarrhea on the neratinib arm. In comparison, 35.4% (499/1408) had all grade diarrhea and 1.6% (23/1408) had grade 3-4 diarrhea for patients on the placebo arm. Patients on this study did not receive prophylactic anti-diarrheal agents and diarrhea resulted in dose reduction in 26.4% and drug discontinuation in 16.8% of patients. In the NEfERT-T trial, patients received either neratinib+paclitaxel or trastuzumab+paclitaxel. In the neratinib+paclitaxel arm, 92.5% (222/240) had all grade diarrhea, and 30.4% (73/240) had grade 3-4; patients on the trastuzumab+paclitaxel arm had 33.3% (78/234) all grade diarrhea and 3.8% (9/234) grade 3-4. [30-32]

Lapatinib has a similar diarrhea side effect profile as compared to neratinib. In a phase 1 study of single agent lapatinib in breast cancer patients, 80% (32/40) had all grade diarrhea and 20% (8/40) had grade 3-4. In the NeoALTTO study, a phase 3 trial looking at lapatinib, trastuzumab, or lapatinib plus trastuzumab in the neoadjuvant setting, the incidence of diarrhea was much

higher in the arms that contained lapatinib. In the lapatinib with or without trastuzumab arm, approximately 85% experienced all grade diarrhea and 25% had grade 3-4 diarrhea. In comparison, the trastuzumab monotherapy arm had 35% all grade diarrhea and 3% grade 3-4. [30-34]

2.5.6 Breast Cancer: Immunotherapy

Immunotherapy agents such as ipilimumab, nivolumab, and pembrolizumab have been approved in melanoma and lung cancer; studies into these agents as well as other checkpoint inhibitors are underway in the field of breast cancer.

PD-1 is present on activated T cells. The binding of PD-L1 to PD-1 results in inactivation of T cells. Nivolumab and pembrolizumab are anti-PD1 antibodies that inhibit PD-L1 from binding to PD1, thereby stopping the inhibitory signal. Both agents have been shown to have a high incidence of diarrhea, ranging from 11-37% in nivolumab, 13-16% in pembrolizumab, and up to 45% in combination therapy with nivolumab and pembrolizumab. In a phase 1 study of nivolumab of 39 patients, only one grade 3 adverse event, inflammatory colitis, was reported, which resolved with infliximab and steroids. There have been no reports of pembrolizumab associated colitis. [6, 35-44]

Ipilimumab is a monoclonal antibody targeting CTLA-4, a protein receptor on the surface of T cells that downregulates the immune system; ipilimumab blocks this downregulatory signal. Pooled analyses in melanoma patients have shown that the toxicities are primarily due to activation of the immune system. Twenty-seven to thirty-one percent of patients on ipilimumab developed diarrhea, with 5% of cases at grade 3-4; treatment is primarily with steroids, with one case report of a patient who required infliximab to stop the diarrhea. Other serious side effects of ipilimumab include colonic perforation, necrotic and hemorrhagic colitis, hypohysitis, and uveitis. In a recent publication looking at nivolumab, ipilimumab, or nivolumab plus ipilimumab in melanoma, diarrhea and colitis were seen much more frequently in the combination arm. All grade diarrhea was reported in 19.2% of patients on nivolumab, 33.1% on ipilimumab, and 44.1% on nivolumab plus ipilimumab. All grade colitis was seen in 1.3% on nivolumab, 11.6% on ipilimmab, and 11.8% on nivolumab plus ipilimumab. [6, 35-44]

Anti-PDL1 agents are also currently being studied. Brahmer et al. conducted a study looking at the safety and activity of the anti-PDL1 agent BMS-936559 in 207 cases of advanced solid tumors, 4 of which were breast. The three most common side effect were an infusion reaction (seen in 10% of patients), diarrhea (seen in 9% of patients), and pruritus (seen in 6% of patients). [6, 35-44]

2.6 Chemotherapy Induced Diarrhea: Guidelines and Management

Currently, there are no guidelines for prophylactically treating CID in patients on regimens known to have high incidences of diarrhea. Guidelines do exist for treating diarrhea once it occurs.

Loperamide is an opioid receptor agonist and the most commonly used anti-diarrheal medication in the front line setting. It decreases both colonic mass movements and activity of the myenteric plexus, thereby increasing transit time and water reabsorption. For grade 1-2 diarrhea, the guidelines recommend a 4 mg loading dose and then 2 mg either on a scheduled basis or after every loose stool with a maximum of 16 mg daily. Once the diarrhea reaches grade 3-4, hospitalization is needed to aggressively control symptoms and avoid dehydration. Loperamide can be continued and adding other agents, such as octreotide, fluoroquinolone antibiotics, or other anti-diarrheal agents should be considered. Stool studies and imaging should also be considered if there is an indication. [4, 5, 45]

2.7 Anti-Diarrheal Agents

2.7.1 Loperamide

While guidelines recommend loperamide as a first line agent against CID after the diarrhea occurs, there have been very few studies looking at loperamide in the prophylactic setting. A case report published in Korea documents the use of loperamide in a 72-year-old gentleman on treatment with cisplatin and docetaxel for stage 4 non-small cell lung cancer. The patient developed grade 3 docetaxel induced diarrhea during cycle 2 on days 4-10. With prophylactic loperamide 2 mg every 8 hours and fasting during cycle 3, the patient experienced no diarrhea. [46, 47]

Jankowitz et al. looked at neratinib and trastuzumab with paclitaxel in a phase 1 dose-escalation study of 21 patients with metastatic breast cancer. Patients were started on loperamide 4 mg after the first episode of diarrhea and then 2 mg after each loose stool; however, the authors found that patients still consistently had diarrhea during the first week of therapy. Therefore, the authors amended the protocol to include prophylactic loperamide for all patients. During cycle 1, patients received 4 mg of loperamide with the first dose of neratinib, followed by 2 mg every 4 hours for 3 days. During the remaining 3 weeks of cycle 1, patients received 2 mg of loperamide every 6-8 hours. In total, 90% patients had all grade diarrhea and 38% had grade 3. The authors did not state how many patients who received anti-diarrhea prophylaxis experienced diarrhea. [46, 47]

Currently, there is a phase 2 underway looking at the incidence and severity of diarrhea in patients receiving neratinib and prophylactic high dose loperamide (NCT02400476). [48]

2.7.2 Octreotide

Octreotide is a somatostatin analog that works by inhibiting secretion of gastrointestinal hormones (such as gastrin, glucagon, growth hormone, etc.), reducing fluid secretion in the intestines, and reducing gastrointestinal motility. It is administered subcutaneously (SQ) under the skin with a starting dose of 100-150 mcg three times a day, up to a maximum tolerated dose of 2000 mcg three times a day.

There have been many studies looking at octreotide in the setting of CID. Cascinu et al. enrolled 41 patients who experienced grade 2-3 diarrhea on a 5-fluorouracil containing regimen, the majority with gastrointestinal cancers. Patients were randomized to octreotide 100 mcg SQ twice a day for 3 days (n=21) or loperamide with a 4 mg loading dose and then 2 mg every 6 hours for 3 days (n=20). Seventeen patients on the octreotide arm had diarrhea resolution compared with only three patients on the loperamide arm, suggesting a superior efficacy for octreotide. In the STOP trial, 147 patients on 5-fluorouracil or irinotecan based regimens were randomized to receive long acting octreotide LAR intramuscularly (IM) at either 30 mg or 40 mg with the first dose 7-14 days before cycle 1 and each subsequent dose during the first day of the next chemotherapy cycle, with a total of 6 doses. While fewer patients were noted to have severe diarrhea in the 40 mg group compared to the 30 mg group (62% vs. 48%, p=0.14), the differences were not statistically significant. Finally, in the phase 3 LARCID trial, patients receiving 5-fluorouracil, capecitabine, or irinotecan containing regimens were randomized to receive either octreotide LAR 30 mg IM every 4 weeks or physician's choice, which was primarily loperamide. The incidence of diarrhea was equal in the two groups, with a 76% incidence of diarrhea in the octreotide LAR and 79% incidence in the physician's choice group, with no difference noted in quality of life as assessed based on the FACIT-D score between the two groups. [49-52]

2.7.3 Atropine

Atropine is a muscarinic acetylcholine receptor antagonist and is an anticholineric medication given in intravenous (IV) or subcutaneous (SQ) form. It is not directly an anti-diarrheal agent.

However, patients on irinotecan based chemotherapy regimens frequently experience a cholinergic syndrome within 1 hour of drug infusion, marked by increased lacrimation and salivation, sweating, flushing, rhinitis, and ultimately diarrhea; these symptoms can all be avoided with atropine administered before irinotecan. Thus though atropine is not an anti-diarrheal agent, it is used prophylactically to prevent irinotecan induced diarrhea. [53]

2.7.4 Lactobacillus

Lactobacillus is a gram-positive facultative anaerobic rod shaped bacteria that converts lactose to lactic acid. It is present as normal floral in the human gastrointestinal tract and also used in food preparation such as bread, yogurt, pickles, and beer. It has also been studied in cancer treatment related diarrhea.

In a study of 490 patients who received adjuvant post-operative radiation therapy for sigmoid, rectal, or cervical cancer, patients were randomized to receive one packet of VSL#3 three times a day or placebo. VSL#3 is a combination of 4 strains of lactobacillus, 3 strains of bifidobacteria, and 1 strain of streptococcus, with a total of 450 billion bacteria per gram. Patients who received VSL#3 had a statistically significant lower incidence of grade 3-4 diarrhea, fewer daily bowel movements, and a longer time to requiring the anti-diarrheal agent loperamide, suggesting an efficacy for treating radiation induced diarrhea. Another study looked at 150 patients with colorectal cancer who were receiving adjuvant 5-fluorouracil based therapy. Patients were randomized to lactobacillus capsules twice a day (total of $1\text{-}2x10^{10}$ daily) plus fiber (11 grams guar gum daily) on days 7-14 of each cycle of treatment versus no treatment. Those who received lactobacillus and fiber had statistically significant lower incidence of grade 3-4 diarrhea, abdominal discomfort, and fewer chemotherapy dose reductions. [54, 55]

2.7.5 Elsiglutide

Elsiglutide is a synthetic glucagon-like peptide-2 analog (GLP-2) that is administered subcutaneously and promotes proliferation of epithelial cells and small intestinal mucosa. A phase 2 clinical trial sponsored by Helsinn in colorectal cancer patients receiving 5-fluorousacil based chemotherapy in the prophylactic setting showed positive numerical but not statistically significant results earlier in 2016.

2.7.6 Crofelemer

Previous studies have looked at the use of various anti-diarrheal agents in treating chemotherapy diarrhea and there are current studies looking at preventing diarrhea in colorectal patients on 5-fluorouracil based regimens. However, none of these previous and ongoing studies focused on breast cancer and HER2 regimens, even though 40-90% of patients will experience diarrhea on HER2 directed therapies.

Crofelemer ~~(Fulyzaq®)~~ (Mytesi®) is an FDA-approved anti-diarrheal agent that is derived from the red sap of the Croton lechleri plant in South America. It acts luminally in the intestine and is not systemically absorbed due to its size and polarity. In the large intestine, it is a dual inhibitor of the calcium activated chloride channel (CaCC) and the cystic fibrosis transmembrane regulator (CFTR), two of the three channels that control chloride efflux.

The incidence of diarrhea in HIV/AIDS patients on anti-retroviral therapy is as high as 28%. In a randomized controlled study in HIV/AIDS patients with a history of diarrhea for at least 1 month while on anti-retroviral therapy, 180 patients were randomized to crofelemer 125 mg orally twice a day versus placebo for 4 weeks. The primary endpoint was the percentage of patients who had two or fewer watery stools per week during at least two out of the four weeks of treatment. Patients who received crofelemer had a significant improvement in their daily stool consistency and number of daily watery bowel movements. Patients tolerated the drug well with minimal side

effects. Based on this trial, on December 31, 2012, the FDA approved the use of crofelemer in HIV patients on anti-retroviral therapy. [56-58]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

To determine the efficacy of crofelemer in preventing chemotherapy induced diarrhea (CID) in patients with HER2 positive breast cancer receiving chemotherapy with trastuzumab, pertuzumab, and docetaxel or paclitaxel (THP) or trastuzumab, pertuzumab, carboplatin, and docetaxel (TCHP).

3.2 Secondary Objectives

If possible, our secondary objectives are:

- 3.2.1 To determine the incidence of diarrhea of any grade, as measured by CTCAE v4.0, by cycle and by stratum
- 3.2.2 To determine the incidence of diarrhea of grade 3-4, as measured by CTCAE v4.0, by cycle and by stratum
- 3.2.3 To determine the time to onset of first event of diarrhea of any grade, defined as the number of days from day one of THP or TCHP until the day in which the first episode of diarrhea classified as of grade 1 or higher occurs, or is censored at the date of the last treatment cycle for patients who do not experience diarrhea, overall and by stratum
- 3.2.4 To determine the duration (days) of any grade diarrhea, by cycle in which the episode started and by stratum
- 3.2.5 To determine the duration (days) of grade 3-4 diarrhea, by cycle in which the episode started and by stratum
- 3.2.6 To assess use of anti-diarrheal medications (other than study drug), by cycle and grade of diarrhea and by stratum
- 3.2.7 To determine the quantitative FACIT-D total score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum
- 3.2.8 To determine the quantitative FACIT-D diarrhea subset (DS) score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum
- 3.2.9 To determine the frequency table for stool consistency, as measured by the Bristol Stool scale, by cycle and stratum for each treatment group

3.3 Primary Endpoint

The primary endpoint is incidence of diarrhea of any grade for two or more consecutive days felt to be definitely, probably, or possibly due to THP or TCHP (refer to Section 13.4 Attribution), as assessed by NCI CTCAE v4.0, during cycle 1 and cycle 2 of chemotherapy. The CTCAE v4.0 coding for diarrhea is 10012727.

3.4 Secondary Endpoints

If possible, our secondary endpoints are:

- 3.4.1 Incidence of diarrhea of any grade, as measured by CTCAE v4.0, by cycle and by stratum
- 3.4.2 Incidence of diarrhea of grade 3-4, as measured by CTCAE v4.0, by cycle and by stratum
- 3.4.3 Time to onset of first episode of diarrhea of any grade, defined as the number of days from day one of THP or TCHP until the day in which the first episode of diarrhea classified as of grade 1 or higher occurs, or is censored at the date of the last treatment cycle for patients who do not experience diarrhea, overall and by stratum
- 3.4.4 Duration (days) of any grade diarrhea, by cycle in which the episode started and by stratum
- 3.4.5 Duration (days) of grade 3-4 diarrhea, by cycle in which the episode started and by stratum
- 3.4.6 Use of anti-diarrheal medications (other than study drug), by cycle and grade
- 3.4.7 Quantitative FACIT-D total score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum
- 3.4.8 Quantitative FACIT-D diarrhea subset (DS) score, collected day 1 of each cycle and at the time of study completion (defined as cycle 4 day 1, but patients may complete this final FACIT-D questionnaire within 5 days of cycle 4 day 1), by cycle and by stratum
- 3.4.9 Frequency table of stool consistency, as measured by the Bristol Stool scale, by cycle stratum between treatment groups

4 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

- 4.1.1 Willing and able to provide written informed consent
- 4.1.2 Men and women ≥18 years of age
- 4.1.3 Pathologically confirmed diagnosis of HER2 positive breast cancer of any stage (previous treatment is allowed without limits on lines of prior therapy)
- 4.1.4 Scheduled to receive at least 3 consecutive cycles of THP or TCHP
- 4.1.5 Performance status of 0-2 according to the ECOG scale (Appendix B)
- 4.1.6 Negative pregnancy test within 2 weeks prior to starting THP or TCHP treatment for women of childbearing potential
- 4.1.7 Able to read, understand, follow the study procedure and complete crofelemer, rescue medication, and bowel movement diaries
- 4.1.8 Patients may enroll simultaneously on this study and other studies
- 4.1.9 Patients with brain metastases are allowed on this study (concurrent treatment with steroids is allowed).
- 4.1.10 Left Ventricular Ejection Fraction (LVEF) greater or equal to 50% at baseline as determined by either ECHO or MUGA

4.2 Exclusion Criteria

4.2.1 Pregnant and/or breastfeeding
4.2.2 Ongoing irritable bowel syndrome (IBS) or colitis (including but not limited to ulcerative colitis, Crohn's disease, microscopic colitis, etc.)
4.2.3 Use of investigational drugs within 3 weeks of starting THP or TCHP treatment or foreseen use during the study
4.2.4 Use of chemotherapy, trastuzumab, or pertuzumab within the past 2 (two) weeks
4.2.5 ~~Use of laxatives within the past 7 days~~ - deleted
4.2.6 ~~Use of chronic laxatives (≥ 30 consecutive days)~~ - deleted
4.2.7 ~~Use of anti-diarrheal agents (including but not limited to loperamide, octreotide, bismuth, tincture of opium, atropine, probiotics in any form other than food) within the past 7 days~~ - deleted
4.2.8 Use of antibiotics within the past 7 days (up to 2 prophylactic doses of antibiotic for procedures, including but not limited to port placement, is permitted)
4.2.9 Any type of ostomy
4.2.10 Total colectomy
4.2.11 Fecal incontinence
4.2.12 Ongoing radiation induced diarrhea or constipation or planned radiotherapy to the abdomen or pelvis while on study
4.2.13 Active systemic infection requiring ongoing intervention, including but not limited to oral and intravenous antibiotics, anti-fungals, anti-parasites, anti-virals
4.2.14 Abdominal or pelvic surgery without recovery of bowel function
4.2.15 Inadequate organ function for starting THP or TCHP, which may include the following laboratory results within 28 days prior to starting THP or TCHP treatment (Please refer to the prescribing label instructions on the use of each drug in the setting of abnormal organ function):

- Serum creatinine > 2.0 mg/dL or 177 µmol/L
- Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)
- Exclusion criteria specific for THP with PACLITAXEL (Taxol®) group:
  - Transaminases greater than 10 times ULN
- Exclusion criteria specific for TCHP/THP with DOCETAXEL (Taxotere®) group:
  - AST and/or ALT > 2.5x ULN
  - AST and/or ALT > 1.5x ULN with concurrent alkaline phosphatase >2.5 x ULN (unless bone metastases are present)

4.3 Inclusion of Women, Minorities, and Other Underrepresented Populations

The study will be open to men and women of all racial and ethnic groups. There are no separate accrual targets for men and women.

5 REGISTRATION PROCEDURES

5.1 Study Sites

This study will be open at multiple sites in the United States.

5.2 Study Coordinators and Pharmacists

There will be a multi-site study coordinator overseeing the study. At each individual study site, there will be a designated study coordinator, co-investigator, and pharmacist.

5.3 Patient Enrollment

Please refer to the procedures below for patient enrollment:

1. Study site study coordinator or treating physician screens patient for eligibility criteria.

a. If patient does not meet eligibility criteria, stop and report screen failure and/or reason.

2. If patient meets initial eligibility screening, patient can sign informed consent and HIPAA authorization form. Consent obtained by site study coordinator or treating physician.
3. Study coordinator or treating physician at site completes eligibility checklist in Appendix F. Investigators can use Appendix K as an additional form for documentation of eligibility or put the contents of Appendix K in the screening clinic note.
4. Study coordinator or treating physician at site sends the full eligibility packet (outlined below) and completed Lombardi QAO Patient Registration Form (Appendix L) to the following within 1 business day of signing consent:
    a. Via fax to the Lombardi QAO at 202-687-9361 or scanned/emailed to lcccqao@georgetown.edu.
    b. To Sandra Swain at sandra.swain@georgetown.edu
5. Lombardi QAO verifies patient eligibility and sends Subject Study ID information to the multi-site study coordinator and the designated biostatistician(s) at LCCC Biostatistics and Bioinformatics Shared Resource.
    a. If patient's eligibility is not verified, stop.
6. If patient's eligibility is verified by Lombardi QAO and a Subject Study ID is assigned, then multi-site study coordinator does the following:
    a. Registers the patient on the study and in the database
    b. Calls the pharmacist at the study site to make sure crofelemer is available should the patient be randomized to the treatment arm
    c. LCCC QAO Informs the biostatistician(s) at LCCC Biostatistics and Bioinformatics Shared Resource whether the patient is on TCHP or THP, and if on THP, whether the patient will receive docetaxel or paclitaxel via the Patient Randomization Form (Appendix I).
        i. The biostatistician stratifies the patient
        ii. The biostatistician randomizes patient to treatment or control group
        iii. The biostatistician completes Appendix I Patient Randomization Form and emails or faxes completed Appendix I to the multi-site study coordinator, taking no more than 1 business day to do so (from when the multi-site study coordinator contacted the biostatistician)
        iv. QAO scans to patient's EMR the completed Patient Randomization Form (Appendix I), signed by the statistician. The original Patient Randomization Form must be stored in the HALT-D study binder.
    d. Multi-site study coordinator emails patient study number and randomization results to study coordinator and treating physician at the study site, the study site pharmacist, and Dr. Sandra Swain.
7. Patient registration and enrollment is complete.
8. Site study coordinator or treating physician to inform patient of randomization results at their earliest convenient, no later than cycle 1 day 1 of chemotherapy.
9. Patient receives first dose of crofelemer on cycle 1 day 1 of THP or TCHP, ideally 30-60 min prior to chemotherapy.

The full **eligibility packet** must contain the following:

1. Signed and dated Eligibility Checklist (Appendix F); filled out completely
2. Signed and dated Lombardi QAO Patient Registration Form (Appendix L)
3. Signed and dated informed consent form
4. Signed and dated HIPAA form
5. All source documents required for verification of eligibility:
    a. Pathology report stating diagnosis of breast cancer
    b. Pathology report stating diagnosis of HER2+ disease

c. Current negative beta HCG test report for women of childbearing potential
d. Current Bilirubin levels and normal range at local laboratory
e. Current Creatinine levels and normal range at local laboratory
f. Current AST levels and normal range at local laboratory
g. Current ALT levels and normal range at local laboratory
h. Clinic notes containing information on ECOG PS, previous and current treatments, co-morbidities, and information pertaining to eligibility for the trial

The full eligibility packet must be faxed or emailed to Lombardi QAO and the Sponsor at sandra.swain@georgetown.edu within 1 business day of the patient signing informed consent. Please send these during business hours Monday - Friday between 8am and 4:30pm (EST). In the event that there is a time constraint, please notify the research office to discuss possibility of expediting the process.

The informed consent form should be uploaded to the patient's electronic medical record system, in addition to keeping the physical document signed by the patient and treating physician in the study binders, as per standard operating practice.

All participants must be registered and enrolled through the Oncology Research office at MedStar Georgetown University Hospital.

5.4 Informed Consent

The study coordinator or treating physician at each site will discuss with and obtain written informed consent from the patient. Informed consent must be signed within 28 days of cycle 1 day 1 of chemotherapy with THP or TCHP. Patients will be informed that participation is voluntary and not necessary for receiving standard of care chemotherapy for their cancer and that they can choose to withdraw consent from the study at any time. This will also be documented in writing on the consent form.

The study will not include participants less than 18 years of age. For adult participants who lack decision-making capacity, the legally authorized representative will serve as the proxy. In the event a patient or their proxy does not read, write, or understand English, a trained medical interpreter must be present, either in person or via phone or video remote access, to translate.

6 DRUG FORMULATION AND ADMINISTRATION

6.1 Crofelemer Acquisition and Storage

Crofelemer is an FDA approved drug, dispensed in 30-day bottles with 60 pills per bottle.

Crofelemer will be provided without charge to the patients or MedStar by Napo and given to the patients on the treatment arm. Shipment to each study site will be coordinated by a dedicated pharmacist at each study site by filling out the Investigational Drug Order Form (Appendix J) and stored in the pharmacy until needed, as per standard operating procedures. The dedicated pharmacist at each site will also be responsible for dispensing the drug to the treatment group patients, as per standard operating practices.

Crofelemer is to be stored at room temperature of 20-25 degrees Celsius, with a range of 15-35 degrees Celsius permitted. There is no placebo control for this study.

6.2 Drug Accountability

The dedicated pharmacist at each study site must maintain a careful record of the inventory of crofelemer, per standard operating procedures.

Patients are to bring their medication bottles, bowel movement diary (Appendix E), crofelemer diary (Appendix C, treatment group only), and rescue medication diary (Appendix D) to the study coordinator during each office visit. The study coordinator will count the remaining pills and review the bowel movement and medication diary with the patient. Remaining/unused pills will be counted and documented in the CRF by the study coordinator. At the end of the treatment period, any remaining pills must be returned to the pharmacist at the study site.

6.3 Trastuzumab, Pertuzumab, Docetaxel, Paclitaxel, and Carboplatin Administration

Trastuzumab, pertuzumab, docetaxel, paclitaxel, and carboplatin should be administered per standard operating procedures at each institution.

The following are the suggested doses for each drug, although the prescribing physician should decide the appropriate dose for each individual patient:

1. Trastuzumab: administered IV at a loading dose of 8 mg/kg for cycle 1, then 6 mg/kg for subsequent cycles
2. Pertuzumab: administered IV at a 840 mg loading dose during cycle 1, then 420 mg for subsequent cycles
3. Docetaxel: administered IV at 75 mg/m^2 every 3 weeks
4. Paclitaxel: administered IV at 80 mg/m^2 every week
5. Carboplatin: administered IV with AUC 6 every 3 weeks

7 EXPECTED TOXICITIES AND DOSING DELAYS AND MODIFICATIONS

7.1 Chemotherapy Dose Modifications and Delays

In the event of a chemotherapy dosing delay or reduction, crofelemer is to be continued at 125 mg twice a day without dose interruptions or adjustments.

7.2 Crofelemer Side Effects

Crofelemer is generally well tolerated with the FDA medical review reporting no adverse events (AEs) of special interest identified from clinical trials.

Possible side effects of crofelemer include dyspepsia, flatulence, constipation, nausea, or increased alanine aminotransferase (ALT). All ALT elevations in the phase 3 trial of crofelemer in HIV/AIDS patients were grade 1 and felt to be due to the underlying patient population due to high prevalence of hepatitis B and C infection, alcohol and/or drug abuse, or anti-retroviral medication-related hepatotoxicity.

While there have been no studies looking at crofelemer concurrently with chemotherapy, studies have shown that crofelemer is not systemically absorbed due to its size and polarity. This is confirmed by the FDA Medical Review Document where they note the following: [59]

a. At therapeutic dose level, its systemic absorption is minimal. Thus, pharmacodynamics studies are not applicable
b. The absorption of Crofelemer (enteric-coated tablets or beads) was minimal following oral dosing in healthy adults or in human immunodeficiency virus- positive (HIV+) subjects, in either the fasted or fed state. Across all the PK studies, less than 5% of healthy and HIV-associated diarrhea subjects had detectable plasma concentrations of Crofelemer following oral dosing. Crofelemer was detected in plasma samples in 3 of the 6 trials; however, the plasma Crofelemer concentrations were low, sporadic, discontinuous, and not sufficient for calculation of pharmacokinetic parameters. The high degree of human plasma protein binding (approximately 97%) further limits

systemic exposure to Crofelemer. At the therapeutic Crofelemer dose of 125 mg twice daily in ADVENT, less than 1% of plasma samples had Crofelemer concentrations above the limit of quantification (LOQ).

c. In vitro data indicate, at clinical concentrations, no cytochrome P450 (CYP)-mediated metabolism or gastrointestinal (GI) absorption-based interactions with other drugs.

Given this information from the FDA, we have low concern for systemic absorption of crofelemer and believe it will not interfere with chemotherapy and therefore a phase 1 study of safety is not needed.

7.3 Crofelemer Dose Modifications

There are no dose modifications for crofelemer, given there were very few anticipated side effects based on the FDA review and phase 3 study. [56]

If a patient develops a CTCAE grade 1 or 2 side effects attributable to crofelemer, provided they have no underlying disease or are taking any medication that predisposes them to these conditions, or are not related to their metastatic breast cancer (if present), the treating physician has the option to hold crofelemer one time for up to 3 consecutive days (6 consecutive doses) and must document the reason for holding and how many doses crofelemer was held for. The treating physician must also document if any diarrhea develops during this period of time off crofelemer

If a patient develops a CTCAE grade ≥3 side effects attributable to crofelemer, provided they have no underlying disease or are taking any medication that predisposes them to these conditions, or are not related to their metastatic breast cancer (if present), they will be withdrawn from the study.

8 TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than THP or TCHP may be administered with the intent to treat the patient's breast cancer.

The average baseline number of stools must be collected at baseline and detailed in the Bowel Movement Endpoint Form (Appendix M) by the research team, preferably the study coordinator. During each cycle and at the end of treatment, detailed diarrhea information, including but not limited to duration, onset, grading, FACIT score, rescue medication usage etc., must be collected for ALL patients and documented in the Bowel Movement Endpoint Form (Appendix M). Appendix M must be fully completed by the research team, preferably the study coordinator, for each patient at each cycle and end of treatment visit and scanned into the patient's electronic medical record.

8.1 Crofelemer Arm

Patients on the treatment arm will take one tablet of crofelemer twice a day (each tablet is 125 mg), to be swallowed whole without chewing or crushing, during cycles 1-2 of chemotherapy with THP or TCHP. Each chemotherapy cycle is 21 days (3 weeks). If, for any reason, chemotherapy is delayed, the patient should continue to take crofelemer daily without dose interruptions until the end of cycle 2 of chemotherapy. There are no dosage adjustments for crofelemer, even if there is a chemotherapy dose reduction.

Patients on the treatment arm will be on study for a total of 3 full cycles of THP or TCHP. Crofelemer will be dispensed in 30 day commercially available containers. Patients will be instructed to take one tablet twice a day, to not take any additional tablets, and to bring the pill container with them to each clinic visit. Pills will be counted at each clinic visit. On cycle 2 day

1 of THP or TCHP, the study coordinator will count the remaining pills from cycle 1 and dispense a new 30-day supply of crofelemer for cycle 2. The remainders of the pills from cycle 1 and 2 should be returned to the study site pharmacist. All remaining pills and bottles should be sent back to the MedStar Georgetown University Hospital pharmacy, where unused pills will be destroyed, or be destroyed at the local pharmacy site per SOP.

On day 1 of cycle 1, the morning dose of crofelemer should be administered prior to initiating chemotherapy, ideally 30-60 minutes prior. The date and time (hour and minute) of this dose should be documented in Appendix H Crofelemer Flowsheet for C1D1. Thereafter patients should take crofelemer twice a day with no dose interruptions or delays until the end of cycle 2. The Crofelemer Flowsheet for C1D1 should be filled out by the nurse administering crofelemer to the patient and after completion should be scanned into the patient's EMR. The original form should be placed in the HALT-D Study Binder.

Should a patient develop diarrhea while on crofelemer, rescue medications, including but not limited to loperamide, octreotide, and opiates, should be administered as per the current standard of care for chemotherapy induced diarrhea (see Section 8.4 General Concomitant Medication and Supportive Care Guidelines below). Patients should record each instance they use the rescue medication in the Rescue Medication Diary and bring this diary with them to each office visit.

If a patient who is taking crofelemer experiences severe persistent diarrhea that does not respond to standard of care anti-diarrhea treatment, patients will be evaluated for an infectious diarrhea etiology with tests such as stool ova and parasites, stool culture, and Clostridium difficile. The patient should stop crofelemer and NOT resume crofelemer. They should still be followed until cycle 4 day 1.

If a patient comes off study prior to cycle 4 day 1 for toxicity not related to crofelemer (such as but not limited to infusion reaction to monoclonal antibodies), that patient will be replaced.

8.2 Control Arm

Patients on the control arm will be on the study for cycles 1-3 of THP or TCHP. Patients on the control arm will not receive crofelemer at any time on this study.

Should a patient develop diarrhea while on the control arm, rescue medications, including but not limited to loperamide, octreotide, and opiates, should be administered as per the current standard of care for chemotherapy induced diarrhea (see Section 8.4 General Concomitant Medication and Supportive Care Guidelines below). Patients should record each instance they use the rescue medication in the Rescue Medication Diary and bring this diary with them to each office visit.

If a patient experiences severe persistent diarrhea that does not respond to standard of care anti-diarrhea treatment, patients will be evaluated for an infectious diarrhea etiology with tests such as stool ova and parasites, stool culture, and Clostridium difficile.

8.3 Diarrhea Grading

All patients will maintain a daily bowel diary which will be reviewed by the study coordinator or treating physician at each office visit. Grading of diarrhea will be according to NCI CTCAE V4.0 and is defined as follows:

- Grade 1: increase of < 4 stools per day over baseline;
- Grade 2: increase of 4-6 stools per day over baseline;

- Grade 3: increase of ≥ 7 stools per day over baseline, incontinence, hospitalization indicated, limiting self care activities of daily living (ADLs);
- Grade 4: life threatening consequences, urgent intervention indicated.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

8.4 General Concomitant Medication and Supportive Care Guidelines

Because crofelemer is not systemically absorbed, it is unlikely to interact systemically with other concomitantly administered drugs. If anti-diarrheal rescue medications are used, patients on the treatment arm should continue crofelemer.

Anti-diarrheal agents are to be used as rescue medications for diarrhea that develops during treatment with THP or TCHP is allowed. Rescue medication must only be used to treat diarrhea symptoms on an as-needed basis. Rescue medication is not to be taken to prevent diarrhea or to increase the expected anti-diarrheal effect of the study medication. Administration of rescue medication should follow the current treatment guidelines for CID, which includes, but is not limited to the following:

- Loperamide at a 4 mg by mouth loading dose followed by 2 mg every 4 hours or after every unformed stool, up to 16 mg daily
- Lomotil 5 mg 3-4 times a day until control of diarrhea is achieved (maximum 20 mg/day) may be used at the discretion of the treating physician if deemed medically appropriate. Maintenance doses may be as low as 25% of the initial daily dose required to control the diarrhea. Dose reductions are also at the discretion of the treating physician.

In case of need, add:

- Tincture of opium 6 mg PO 4 times a day may be used at the discretion of the treating physician, if deemed medically appropriate.

For all patients with diarrhea:

- Any patient with diarrhea should be reminded to increase non-alcoholic PO fluid intake
- Any patient who needs intravenous fluids on a regular basis due to side effects of diarrhea may need to be evaluated for an infectious cause of diarrhea, with stool studies that may include stool ova and parasites, stool culture, and Clostridium difficile.

For severe diarrhea (grade 3-4 diarrhea):

- Octreotide at a dose of 100-150 micrograms subcutaneously three times a day is recommended as first line therapy
- Patients may continue to take loperamide if felt appropriate by the treating physician.

The rescue medication agent and dose and date should be documented in the Rescue Medication Diary (Appendix D). If a patient is using loperamide, each pill taken on any given day should be documented in the Rescue Medication Diary. The Rescue Medication Diary should be brought to each office visit and scanned into the patient's EMR at the end of each cycle.

Patients are allowed to take anti-nausea medications, including but not limited to ondansetron, while on study. Treating physicians should document frequency, duration, and amount of anti-nausea medication used in each office visit note.

9 FOLLOW-UP PLAN

9.1 Duration of Follow Up

All patients will be followed until cycle 4 day 1 while on THP or TCHP, or until 30 days have elapsed since their last dose of crofelemer, whichever occurs later.

9.2 Criteria for Removal from Study

Treatment with crofelemer may continue for 2 cycles or until one of the following criteria applies:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Lost to follow-up;
- Change in chemotherapy regimen;
- If a patient develops a CTCAE grade ≥3 side effect attributable to crofelemer, they will be withdrawn from the study.

9.3 Criteria to Terminate the Study

- If ≥4 patients develop the same CTCAE grade 3 side effect attributable to crofelemer, the study will be terminated;
- If ≥1 patient develops a CTCAE grade 4 or 5 side effect attributable to crofelemer, the study will be terminated.

10 STUDY CALENDAR

		Pre-Study	C1D1	C2D1	C3D1	End of Study[a]
Research	Crofelemer		X----------X			
	Crofelemer Diary (Appendix C)		X----------X			
	Rescue Medication Diary (Appendix D)		X----------X			
	Bowel Movement Diary (Appendix E)		X----------X			
	FACIT-D (Appendix A)		X	X	X	X
	Informed Consent	X				
	Adverse Events[b]		X----------X			
Standard Treatment[d]	Demographics	X				
	Medical History	X				
	Concurrent Medications	X	X----------X			
	Physical Exam	X	X	X	X	X
	Vital Signs	X	X	X	X	
	Weight	X	X	X	X	X
	Breast Cancer Diagnosis	X				

	HER2 Positive Status	X				
	Organ function confirmation (bilirubin, creatinine, AST, ALT)	X				
	Performance Status (ECOG)	X	X	X	X	X
	Beta-HCG[c]	X				
	Clinic Visit[d]	X	X	X	X	X
	ECHO or MUGA	X				X[e]

[a] within 5 days of cycle 4 day 1
[b] all adverse events will be captured from signing consent to 30 days after completing study or 30 days after last dose of crofelemer, whichever occurs later
[c] women of childbearing potential only
[d] date of clinic visit each cycle to be determined by treating physician and does not have to be on day 1 of each cycle
[e] this may occur at cycle 4 day 1 +/- 2 weeks (if LVEF measured every 3 cycles); or at cycle 5 day 1 +/- 2 weeks (if LVEF measured every 12 weeks)

11 QUALITY OF LIFE ASSESSMENT

The Functional Assessment of Chronic Illness Therapy (FACIT) is a health-related quality of life questionnaire started in 1987 that looks at four primary quality of life domains: physical, social, emotional, and functional well-being. FACIT has been validated in all cancers and there is a specific FACIT that focuses on diarrhea symptoms, called FACIT-D.

For each quality of life domain, there are 6-7 questions asking specific questions that reflect how the patients are doing in that domain. Results are scored from 0-4, with 0 reflecting “Not at all” and 4 reflecting “Very much”. There are an additional 11 questions asking patients about their bowel function and how diarrhea impacts their quality of life, also scored from 0-4.

FACIT-D scoring will be performed according to FACIT-D Scoring Guidelines (Version 4). Comparisons will be made between the treatment and control groups of the total FACIT-D score, as well as the diarrhea subscale (DS) score alone.

All patients will be asked to complete the FACIT-D on day 1 of cycles 1-3 and within 5 days of cycle 4 day 1 (depending on when their clinic visit is scheduled) of THP or TCHP.

The FACIT questionnaire and scoring guidelines are found in Appendix A.

12 STATISTICAL CONSIDERATIONS

This is a randomized, 1:1, stratified, open-label phase II study in patients with HER2 positive breast cancer receiving THP or TCHP in the neoadjuvant, adjuvant, or metastatic setting. Randomization will be stratified according to docetaxel versus paclitaxel.

Patients randomized to the treatment group will receive oral crofelemer 125 mg twice daily during cycles 1-2 of THP or TCHP chemotherapy. The primary endpoint is number of patients with all grade diarrhea felt to be definitely, probably, or possibly due to THP or TCHP during cycles 1 and 2. All patients will keep a daily diary of bowel movement number and consistency based on the Bristol Stool Scale.

Should a subject decide to withdraw or drop out before study completion, data will still be collected and analyzed if they completed at least 2 cycles of THP or TCHP. Patients who completed fewer than 2 cycles of THP or TCHP will not be included in the analysis population.

12.1 Sample Size/Accrual Rate

With a sample size of 46 patients (23 per treatment group), the study has 81% power to detect a 40% absolute decrease (from 60% to 20%) in incidence of all grade diarrhea for two or more consecutive days that is definitely, probably, or possibly due to THP or TCHP during cycles 1 and 2 of chemotherapy, with a two sided significance level of 0.10 based on Fisher's exact test. Anticipating a 10% withdrawal rate, we will accrue 52 patients.

12.2 Futility

The futility monitoring of the trial is based on a stochastic curtailing approach based on the trial design described above [60]. The statistician will start to calculate information time as soon as 23 patients have completed two cycles of chemotherapy. Once the information time reaches 50%, a planned interim analysis for futility will be performed. The test statistic at this time point is the proportion of patients with no diarrhea from the treatment group minus the proportion of patients with no diarrhea from the control group divided by its standard deviation. It will be converted to Brownian motion scale for trial monitoring accounting for unequal incidences of diarrhea from the two groups. We will examine conditional powers relative to several expected rates of diarrhea and also discordance probabilities of a trend reversal based on the primary endpoint (all grade diarrhea) and the main secondary endpoint (high grade diarrhea). If predictive powers over uniform prior are all less than 20%, the trial may be considered futile. The overall clinical benefit based on both endpoints will be examined in the report to the Medstar-Georgetown LCCC DSMC. The protocol may be amended based on the recommendations of this DSMC.

12.3 Randomization and Stratification Factors

Stratified randomization will be used to assign patients into the two arms. There will be three strata: THP with docetaxel, THP with paclitaxel, and TCHP with docetaxel. Within each stratum, blocked randomization with randomly selected block sizes will be used. The stratified randomization procedure will be carried out by the biostatistician(s) at the LCCC Biostatistics and Bioinformatics Shared Resource. They will implement the randomization, such as generate the randomization table and hold the randomization key.

12.4 Patient Accrual

We anticipate recruiting 2-3 patients per month across the study sites combined, for an accrual duration of approximately 17-26 months. Currently at each of the study sites, about 5 patients are newly treated with THP or TCHP each month.

12.5 Analytic Plan for Primary Objective

The number and percent of patients who experience diarrhea of any grade during cycle 1 or 2 for two or more consecutive days and that is felt to be definitely, probably, or possibly due to THP or TCHP will be summarized with two-sided 90% confidence interval overall and by treatment assignment, and compared between treatment arms using a Fisher's exact test. The analysis population is defined as all randomized patients who complete 2 cycles of THP or TCHP chemotherapy.

12.6 Analytic Plan for Secondary Objectives

We plan on using the following analytic plans for the secondary objectives, if possible.

According to treatment group, for each of the cycles and stratum, we will summarize: 1) the number and percent of patients (and 95% CI) who experience diarrhea of any grade; 2) the

number and percent of patients (and 95% CI) who experience diarrhea of grade 3-4; 3) the median, range, and interquartile range of the duration of the episodes; and 4) the number (%) of patients requiring anti-diarrheal rescue medication.

The time to onset of first episode of diarrhea will be summarized using the Kaplan-Meier method, and compared between treatment groups and stratum using log-rank test.

The FACIT-D and FACIT-D DS scores will be summarized descriptively and graphically by cycle, treatment assignment, and stratum. The change in FACIT-D and FACIT-D DS scores between day 1 of cycles 1-3 and end of study (within 5 days of cycle 4 day 1) will be compared at each time point between treatment groups using a Wilcoxon rank sum-test.

The stool consistency, as measured by the Bristol Stool scale, will be summarized in frequency tables by cycle and stratum and compared between treatment groups using a Wilcoxon rank sum-test.

Adverse events will be summarized by type, grade, and stratum, according to treatment arm.

If the primary endpoint is not met statistically, the previously stated secondary endpoints and overall incidence of all grade diarrhea in both arms will still be evaluated for clinical benefit.

13 SAFETY REPORTING OF ADVERSE EVENTS

Safety assessments will consist of monitoring and recording adverse events (AEs) and serious adverse events (SAEs) during cycles 1-3 of treatment with THP or TCHP. The Sponsors or their designee are responsible for reporting relevant SAEs to the FDA, DSMC, Genentech, and Napo.

Please refer to the FDA-approved package insert for a comprehensive listing of adverse events related to crofelemer. The FDA medical review reported no adverse events (AEs) of special interest identified from clinical trials.

13.1 Assessment of Safety

13.1.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

13.1.2 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subjects that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with [insert condition being studied] that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

13.1.3 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

13.2 Methods and Timing for Assessing AND Recording Safety variables

The Sponsor is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), Napo, and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

13.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

13.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to crofelemer, trastuzumab, and pertuzumab and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of crofelemer, trastuzumab, or pertuzumab and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to crofelemer, trastuzumab, and pertuzumab; and/or the AE abates or resolves upon discontinuation of crofelemer, trastuzumab, or pertuzumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than crofelemer, trastuzumab, or pertuzumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant

medication); and/or the AE has no plausible temporal relationship to crofelemer, trastuzumab, or pertuzumabadministration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I.) or Investigational Brochure (I.B.)

Unexpected adverse events are those not listed in the P.I., or I.B., or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

Please refer to Section 7.2 Crofelemer Side Effects for a list of expected side effects associated with crofelemer.

13.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

Adverse events can be "Expected" or "Unexpected". Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk. For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

When faxing reports to Genentech, please use the cover sheet found in Appendix G.

13.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

13.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

13.3.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

13.3.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

13.3.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

13.3.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

13.3.2.5 Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 30 days after the last dose of crofelemer, trastuzumab, or pertuzumab a report should be completed and expeditiously submitted to Genentech and Napo. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to crofelemer, trastuzumab, or pertuzumab should be reported as an SAE.

Additional information on any crofelemer, trastuzumab, or pertuzumab - exposed pregnancy and infant will be requested by Genentech Drug Safety at specific time points (i.e. after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant’s life).

13.3.2.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior crofelemer, trastuzumab, or pertuzumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

13.3.2.7 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-

case basis until satisfactory resolution. The Sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

13.3.2.8 AEs of Special Interest (AESIs)
AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

Please refer to Section 7.2 Crofelemer Side Effects for a list of expected side effects associated with crofelemer.

Trastuzumab AESI:
Congestive heart failure

Pertuzumab AESI:
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of monoclonal antibodies

Patients will have Left Ventricular Ejection Fraction (LVEF) evaluated at enrollment to fulfill eligibility criteria. A second standard of care measurement of LVEF will be done at end of study. This may occur within 5 days of cycle 4 day 1 (if LVEF measured every 3 cycles); or within 5 days of cycle 5 day 1 (if LVEF measured every 12 weeks).

13.3.2.9 Adverse Event Reporting
All AEs and SAEs will be captured for the full study duration. Investigators must report all SAEs to Genentech and Napo within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at: **(650) 238-6067 and to Napo at (415) 371-8311.**

Serious adverse events (SAEs), pregnancy reports and AEs of special interest (AESIs), where the patient has been exposed to the Product, will be sent on a MedWatch or CIOMS I form to Genentech and Napo. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SAEs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech and Napo within fifteen (15) calendar days of the awareness date.

  The Sponsor or their designee will notify the IRB and DSMC of relevant SAEs (i.e., death, a life-threatening experience, inpatient hospitalization, prolonged hospitalization or significant disability/incapacity) to the by a written safety report within 1 business day of learning of the SAE.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech and Napo within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**
  While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech and Napo within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

- **AESIs**
  AESIs requiring expedited reporting shall be forwarded to Genentech and Napo within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

- **Special situation reports**
  In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech and Napo even in the absence of an Adverse Event within thirty (30) calendar days:

  Data related to the Product usage during pregnancy or breastfeeding
  Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
  Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
  Lack of therapeutic efficacy

  In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

13.3.2.10 Aggregate Reports (For Non-serious AE)

The Sponsor will forward a copy of the final study report to Genentech and Napo upon completion of the study.

The Sponsor will forward periodically listings of non-serious AEs originating from the study to Genentech and Napo.

13.3.3 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

13.3.3.1 Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report).

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or Napo or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety and Napo as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

13.4 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Napo. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech and Napo. Copies of such reports should be mailed to the Oncology Research office at Georgetown.

13.4.1.1 Seven Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of crofelemer, trastuzumab, or pertuzumab. An unexpected adverse event is one that is not already described in the crofelemer, trastuzumab, or pertuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA, Napo, and Genentech within 7 calendar days of first learning of the event.

13.4.1.2 Fifteen Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of crofelemer, trastuzumab, or pertuzumab. An unexpected adverse event is one that is not already described in the crofelemer, trastuzumab, or pertuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, Napo, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety at (650) 225-4682 or (650) 225-4630 and to Napo at: (415) 371-8311

And to the Site IRB:
MedStar Health Research-Georgetown University Oncology Institutional Review Board
SW104 Medical Dental Building
3900 Reservoir Road, NW
Washington, DC. 20057
Fax: (202) 687-4847
Phone: (202) 687-1506
E-mail: irboard@georgetown.edu

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630
And Napo: (415) 371-8311

13.4.2 IND Annual Reports

13.4.2.1 Copies to Genentech and Napo:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Napo. Copies of such reports should be faxed to Genentech Drug Safety at (650) 225-4682 or (650) 225-4630; and Napo at (415) 371-8311.

13.5 Reporting to the Sponsor
All AEs and SAEs will be recorded for the entire study duration and reported to the Sponsor. All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Sponsor. This includes but is not limited to the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Participating investigators must report each serious adverse event to the Sponsor within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Sandra M. Swain, MD, FACP, FASCO
4000 Reservoir Road NW
120 Building D
Washington, DC 20057

Phone: 202-687-4600
Fax: 202-687-1110
Email: Sandra.swain@georgetown.edu

Within the following 1-2 business days of awareness, the participating investigator must provide follow-up information on the serious adverse event if a full description of events was not included with the initial reporting of the event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. This information should be submitted to the Sponsor at sandra.swain@georgetown.edu. All non-serious adverse events will be reported to the Sponsor on the adverse events CRFs.

13.6 Compliance With Laws and Regulations

This study will be conducted in accordance with FDA regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local, state, and federal laws.

13.7 Information Regarding Genentech Product Complaints

WHAT IS A PRODUCT COMPLAINT?
A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

HOW DO I FILE A COMPLAINT?
For all Investigator Initiated Studies (interventional and non-interventional):

Product Complaints with an AE (adverse event) should be reported via email/fax to:
usds_aereporting-d@gene.com OR 650-238-6067.

Product Complaints without an AE (adverse event) should be reported via email to:
For Interventional Investigator Initiated Studies:
kaiseraugst.global_impcomplaint_management@roche.com

For Non-Interventional Investigator Initiated Studies:
us-acmo-d@gene.com

All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

14 DATA SAFETY MONITORING COMMITTEE

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this trial. This study is an investigator initiated study utilizing a FDA approved drug for the same indication as the FDA approval (diarrhea), though in a different patient population (chemotherapy induced as opposed to anti-retroviral therapy induced). The Sponsor has applied for an IND exemption with the FDA. This drug is not systemically absorbed and this is therefore a low risk study, requiring reviews by the LCCC Data and Safety Monitoring Committee (DSMC) every six months.

The Sponsor or their designee will review the data including safety monitoring at institution based disease group meeting and on any meetings with participating sites. All Severe Adverse

Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC DSMC every six months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the Sponsor to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the Sponsor and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the Sponsor must act to implement the change as expeditiously as possible. If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the LCCC Associate Director for Clinical Research.

14.1 Collection of Private Information on Individuals Other than Study Subject

This research will not involve collection of private information pertaining to individuals other than the study subject.

14.2 Subject Compensation

Subjects will not be compensated in cash or in kind.

14.3 Privacy and Confidentiality of Data Records

Personal information about the patients, including but not limited to name, date of birth, sex, race, ethnicity, previous treatment (including but not limited to pathology reports, imaging reports, laboratory reports, surgery, radiation oncology, medical oncology, etc.), office notes, physical exam, history, medications, adverse events, etc. will be collected on each study patient. This data is important for evaluating the primary and secondary endpoints of the study and will be protected from improper use and disclosure as per MedStar standard operating procedures. This plan will be implemented at the time of signing consent for each patient.

Protected Health Information (PHI) will be accessed in this study. PHI will be received via a CRF and also be recorded in a CRF. PHI information will be retained until all follow up publications and studies stemming from this study have been completed. This information will only be shared within the research team. Confidentiality will be maintained via standard MedStar standard operating procedures. All electronic transmission of PHI data will be in encrypted/secured form. No names of subjects will be included in the publication. No digital, video, audio, or photographic recordings of the subject will be made public.

14.4 Privacy and Confidentiality of Data Records – Data Security

All hardcopy and electronic data will be kept in accordance with the MedStar standard operating procedures. Upon completion of all publications related to this study, the data will be destroyed in accordance with institutional protocols. No members other than those on the research team will have access to the study data. Data will not be shared outside of the research team.

15 STUDY MANAGEMENT

15.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by MHRI or LCCC. All investigators will follow the MHRI and LCCC conflict of interest policy.

15.2 Institutional Review Board (IRB) Approval and Consent

All oncology clinical research protocols must be submitted to the Clinical Research Committee (CRC) for scientific review before submission to and final approval by the IRB. The initial review includes an assessment of the specific plans for data and safety monitoring, which vary depending on the study type, phase, size, and sponsorship.

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

15.3 Required Documentation

Before the study can be initiated at any site, the following documents must be filed at MGUH Regulatory (Study Binder):

- Original U.S. FDA Form 1572. The names of all investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations;
- Sponsor's and sub-Investigator's medical licenses, CITI training, Current *curriculum vitae*
- Written documentation of IRB approval of protocol and informed consent document;
- A copy of approved protocol
- A copy of the IRB-approved informed consent document and IRB communications;
- CRC communication
- A signed Clinical Research Agreement
- Delegation of authority log
- Lab CAP/CLIA, Laboratory normals
- Any sponsor communication, including newsletters
- Monitoring visits letters – pre/post

15.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being

of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Minor deviations should be summarized and reported to the IRB at the time of continuing review. Major deviations should be summarized and reported to the Regulatory Affairs Coordinator who will submit to the IRB as soon as possible, but not more than 10 calendar days after acquiring information reasonably suggesting that a reportable (major) deviation has occurred.

15.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the PI. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

15.6 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor or their designee correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB 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 study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Sponsor. Study documents should be kept on file until after the study is fully completed, including but not limited to publications related to the study.

15.7 Obligations of Investigators

The Sponsor is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor must assure that all study site personnel, including sub- investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

A dedicated co-investigator at each study site will be responsible for assuring that all the required data will be collected and entered onto the CRFs. At the completion of the study, all CRFs will be reviewed by the Sponsor and will require her final signature to verify the accuracy of the data.

15.8 Study Close-Out

Any study report submitted to the FDA by the Sponsor or their designee should be copied to Genentech and Napo. Additionally, any literature articles that are a result of the study should be sent to Genentech and Napo.

16 APPENDICES

16.1 APPENDIX A: FACIT-D AND SCORING GUIDELINES (Version 4)

Patient #:_____ Cycle #:_____ Study Site_____

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient #:_____ Cycle #:_____ Study Site_____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

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

Patient #:_____ Cycle #:_____ Study Site_____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
C3	I have control of my bowels.....	0	1	2	3	4
ITF1	I move my bowels more frequently than usual	0	1	2	3	4
ITU2	I am afraid to be far from a toilet	0	1	2	3	4
D1	I have to limit my social activity because of diarrhea (diarrhoea)	0	1	2	3	4
D2	I have to limit my physical activity because of diarrhea (diarrhoea)	0	1	2	3	4
D3	I have to limit my sexual activity because of diarrhea (diarrhoea)	0	1	2	3	4
D4	I am embarrassed by having diarrhea (diarrhoea)	0	1	2	3	4
D5	I have abdominal cramps or discomfort due to my diarrhea (diarrhoea)	0	1	2	3	4
D6	My problem with diarrhea (diarrhoea) keeps/wakes me up at night	0	1	2	3	4
ITF3	I must move my bowels frequently to avoid accidents.....	0	1	2	3	4
ITF5	I wear pads or protection to prevent soiling my underwear	0	1	2	3	4

Patient #:_____ Cycle #:_____ Study Site_____

FACIT-D SCORING GUIDELINES (VERSION 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACIT-D).
5. **The higher the score, the better the QOL**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

Patient #:_____ Cycle #:_____ Study Site_____

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
DIARRHEA SUBSCALE (DS)	C3	0	+	_____	=_____
	ITF1	4	-	_____	=_____
	ITU2	4	-	_____	=_____
	D1	4	-	_____	=_____
Score range: 0-44	D2	4	-	_____	=_____
	D3	4	-	_____	=_____
	D4	4	-	_____	=_____
	D5	4	-	_____	=_____
	D6	4	-	_____	=_____
	ITF3	4	-	_____	=_____
	ITF5	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 11: _____
Divide by number of items answered: _____=**D Subscale score**

To derive a FACIT-D Trial Outcome Index (TOI):
Score range: 0-100

_____ + _____ + _____ =_____=**FACIT-D TOI**
(**PWB** score) (**FWB** score) (**DS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACIT-D total score:
Score range: 0-152

_____ + _____ + _____ + _____ + _____ =_____=**FACIT-D Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**DS** score)

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.2 APPENDIX B: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

16.3 APPENDIX C: CROFELEMER DIARY

Patient #:_____ Cycle #:_____ Study Site_____

Cycle start date (mm-dd-yyyy) _____ Cycle end date (mm-dd-yyyy) _____

- In this study your treatment is described in "cycles". A cycle for this study is a "21 day" length of time. The days of the cycle are numbered 1 through 21; therefore, "Day 1" is the first day of the 21-day cycle. The cycle may start on any calendar date, thus a cycle Day does not usually match the calendar date.
- Take one tablet of crofelemer 125 mg by mouth with water every 12 hours ±2 hours at approximately the same time each day, with or without food.
- Take crofelemer tablets whole – do not chew or crush.
- If you miss a dose or vomit after dosing, do not retake this medication. Document it in this medication diary and report it to your health care provider at your next visit.
- On Day 1 of every cycle, you should take the a.m. dose of crofelemer before you start chemotherapy, ideally 30-60 minutes prior.
- Write the date and time when you took your medication at home in the tables below for all days through the last day of every cycle.
- Keep crofelemer tablets out of reach of children.
- The crofelemer tablets need to be stored in the original package. Please see product label for appropriate storage conditions.
- You will receive a new Crofelemer Diary and crofelemer supply at the first day of each cycle.
- **If, for any reason, you run out of crofelemer tablets, or anticipate running out before your next clinic appointment, please contact the research nurse at 202-877-8100 IMMEDIATELY.**
- **While you are taking crofelemer, always bring your medication bottle(s) even if empty and/or unused capsules to the clinic to your next visit.**

Patient #:_____ Cycle #:_____ Study Site_____

Day	Date (mm-dd-yyyy)	Time (write the time you took crofelemer in hh:mm format)		Comments
1		AM	:	
		PM	:	
2		AM	:	
		PM	:	
3		AM	:	
		PM	:	
4		AM	:	
		PM	:	
5		AM	:	
		PM	:	
6		AM	:	
		PM	:	
7		AM	:	
		PM	:	
8		AM	:	
		PM	:	
9		AM	:	
		PM	:	
10		AM	:	
		PM	:	
11		AM	:	
		PM	:	

Patient #:_____ Cycle #:_____ Study Site_____

12		AM	:	
		PM	:	
13		AM	:	
		PM	:	
14		AM	:	
		PM	:	
15		AM	:	
		PM	:	
16		AM	:	
		PM	:	
17		AM	:	
		PM	:	
18		AM	:	
		PM	:	
19		AM	:	
		PM	:	
20		AM	:	
		PM	:	
21		AM	:	
		PM	:	

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.4 APPENDIX D: RESCUE MEDICATION DIARY

Patient #:_____ Cycle #:_____ Study Site_____

We ask you to keep a daily count of how many doses of rescue medication you used, if any. The "Day" column refers to which day in the chemotherapy cycle you are. Each time you use a rescue medication, please check off one of the boxes to document this.

Day	Date	Loperamide (check one box for each pill used, no more than 8 pills a day)								Notes (if using a rescue medication other than loperamide, please document the name and dose here)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.5 APPENDIX E: BOWEL MOVEMENT DIARY AND BRISTOL STOOL SCALE

Patient #:_____ Cycle #:_____ Study Site: _____

After each bowel movement, record in the box under the appropriate day the consistency of the stool.

Please refer to the attached Bristol Stool Chart for stool consistency definitions.

Day	Date	Bowel Movements									
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											
21											

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

16.6 APPENDIX F: ELIGIBILITY CHECKLIST

Patient #:_____ Cycle #:_____ Study Site: _____

#	Yes	No	N/A	Inclusion Criteria
I1				Willing and able to provide written informed consent
I2				Men and women ≥18 years of age
I3				Pathologically confirmed diagnosis of HER2 positive breast cancer of any stage (previous treatment is allowed without limits on lines of prior therapy)
I4				Scheduled to receive at least 3 consecutive cycles of THP or TCHP
I5				Performance status of 0-2 according to the ECOG scale
I6				Negative pregnancy test within 2 weeks prior to starting THP or TCHP treatment for women of childbearing potential
I7				Able to read, understand, follow the study procedure and complete crofelemer, rescue medication, and bowel movement diaries
I8				Patients may enroll simultaneously on this study and other studies
I9				Patients with brain metastases are allowed on this study (concurrent treatment with steroids is allowed).
I10				Left Ventricular Ejection Fraction (LVEF) greater or equal to 50% at baseline as determined by either ECHO or MUGA

#	Yes	No	N/A	Exclusion Criteria
E1				Pregnant and/or breastfeeding
E2				Ongoing irritable bowel syndrome (IBS) or colitis (including but not limited to ulcerative colitis, Crohn's disease, microscopic colitis, etc.)
E3				Use of investigational drugs within 3 weeks of starting THP or TCHP treatment or foreseen use during the study
E4				Use of chemotherapy, trastuzumab, or pertuzumab within the past 2 (two) weeks
E5				~~Use of laxatives within the past 7 days~~ - deleted
E6				~~Use of chronic laxatives (≥ 30 consecutive days)~~ - deleted
E7				~~Use of anti-diarrheal agents (including but not limited to loperamide, octreotide, bismuth, tincture of opium, atropine, probiotics in any form other than food) within the past 7 days~~ - deleted
E8				Use of antibiotics within the past 7 days (up to 2 prophylactic doses of antibiotic for procedures, including but not limited to port placement, is permitted)
E9				Any type of ostomy
E10				Total colectomy
E11				Fecal incontinence
E12				Ongoing radiation induced diarrhea or constipation or planned radiotherapy to the abdomen or pelvis while on study
E13				Active systemic infection requiring ongoing intervention, including but not limited to oral and intravenous antibiotics, anti-fungals, anti-parasites, anti-virals
E14				Abdominal or pelvic surgery without recovery of bowel function

E15				Inadequate organ function for starting THP or TCHP, which may include the following laboratory results within 28 days prior to starting THP or TCHP treatment (Please refer to the prescribing label instructions on the use of each drug in the setting of abnormal organ function):
				• Serum creatinine > 2.0 mg/dL or 177 µmol/L
				• Total bilirubin > upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)
				• Exclusion criteria specific for THP with PACLITAXEL (Taxol®) group:
				  o Transaminases greater than 10 times ULN
				• Exclusion criteria specific for TCHP/THP with DOCETAXEL (Taxotere®) group:
				  o AST and/or ALT > 2.5x ULN
				  o AST and/or ALT > 1.5x ULN with concurrent alkaline phosphatase >2.5 x ULN (unless bone metastases are present)

Enrolling Physician Signature Date

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.7 APPENDIX G: SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 2
Effective 14-Jan-2016

16.8 APPENDIX H: CROFELEMER FLOWSHEET FOR C1D1

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

Crofelemer Flowsheet for C1D1

HALT-D Study: LCCC #2015-0547

Coordinator _____

Pager (if available) _____

Patient Name		IRB Number	2015-0547
DOB		Patient ID	
MRN		Physician	
Today's Date			
Cycle	C1D1		

CROFELEMER

Time administered _____ RN Initials _____

INFUSION(S)

Time 1st infusion started _____ RN Initials _____

NOTE: Crofelemer must be given **BEFORE** any infusion is started, ideally 30-60 minutes prior. After the document is fully filled out, please scan it into the electronic medical record immediately.

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.9 APPENDIX I: PATIENT RANDOMIZATION FORM

Patient Randomization Form: HALT-D (IRB 2015-0547)

Site and Patient Information	
Site Name	
Site ID	
Patient Initials	
Patient DOB	
Patient #	

Action	Staff Name	Staff Role	Date
Screening Date			
Screened By			
Eligibility Confirmed by			

Randomization

Arm	Group	Treatment	Assigned (check one)	Description
CROFELEMER	A	TCHP Crofelemer		**Taxotere®, Carboplatin,** Trastuzumab, Pertuzumab + **CROFELEMER**
Control	B	TCHP Control		**Taxotere®, Carboplatin** Trastuzumab, Pertuzumab
CROFELEMER	C	THP Docetaxel Crofelemer		**Taxotere®,** Trastuzumab, Pertuzumab + **CROFELEMER**
Control	D	THP Docetaxel Control		**Taxotere®,** Trastuzumab, Pertuzumab
CROFELEMER	E	THP Paclitaxel Crofelemer		**Taxol®,** Trastuzumab, Pertuzumab + **CROFELEMER**
Control	F	THP Paclitaxel Control		**Taxol®,** Trastuzumab, Pertuzumab

Taxotere = docetaxel, Taxol = paclitaxel

Biostatistician Signature _____ **Date** _____

Biostatistician Print Name _____

PLEASE RETURN COMPLETED FORM TO MULTI-SITE COORDINATOR WITHIN 1 BUSINESS DAY OF RECEIPT AND SCAN INTO PATIENT'S ELECTRONIC MEDICAL RECORD.

16.10 APPENDIX J: INVESTIGATIONAL DRUG ORDER FORM

MedStar Georgetown University Hospital

MEDSTAR RESEARCH INSTITUTE
MEDSTAR GEORGETOWN UNIVERSITY HOSPITAL
DEPARTMENT of PHARMACY
Phone: 202-444-3771 Fax: 202-444-4883

INVESTIGATIONAL DRUG DOCTOR'S ORDER FORM

GUH IRB# 2015-0547

PROTOCOL # MHRI GU 2015-0547

Title: Diarrhea Prevention and Prophylaxis With Crofelemer in HER2 Positive Breast Cancer Patients Receiving Trastuzumab, Pertuzumab, and Docetaxel or Paclitaxel With or Without Carboplatin: HALT-D

Name: _____ **MGUH MRN#** _____

Patient allergy(s): _____ **DOB#**_____

Subject # _____ **Screening/Random#** *(if applicable)*: _____

Order date: _____ **Informed consent signed?** ❑ **YES** ❑ **NO**

For new subjects only– please provide a copy of signed ICF to pharmacy with this order!

Investigational Drug: Crofelemer 125mg Tablets (60 tabs/bottle)

Sig: Take one tablet by mouth twice daily (first dose of each cycle to be given 30-60 min prior to starting infusion in the clinic).

Quantity: Please dispense quantity sufficient for the following visits.

❑ **Cycle 1 Day 1** ❑ **Cycle 2 Day 1** ❑ **Unscheduled**

Additional Instructions:_____

_____

_____

Principal Investigator: Paula Pohlmann, MD **Signature/Date:** _____

OR

Co-Investigator:_____ **Signature/Date:**_____

IMPORTANT: *Only investigators listed on the current FDA Form 1572 are allowed to sign this prescription!*

For Pharmacy Use Only: Date Filled: ____/____/____ Pharmacists Initials: ____/____

3800 Reservoir Road, NW, Washington, DC 20007 Last Update: 18-Jan-17

16.11 APPENDIX K: ADDITIONAL ELIGIBILITY INFORMATION

HALT-D: Additional Clinic Note Information (Optional for Documentation)

PATIENT: _____

MRN: _____

DOB: _____

The patient will start systemic chemotherapy with one of the regimens listed below:

- ☐ TCHP – Docetaxel (Taxotere), carboplatin, trastuzumab and pertuzumab
- ☐ THP – Docetaxel (Taxotere), trastuzumab and pertuzumab
- ☐ THP – Paclitaxel (Taxol), trastuzumab and pertuzumab

PS: 0 – 1 – 2

- ☐ Currently the patient is not pregnant and not breast feeding.
  If unknown, beta HCG test will be done on ____ / ____ / _____
- ☐ The patient denies any history or diagnosis of irritable bowel syndrome (IBS) or colitis (UC, Crohn's, microscopic colitis).
- ☐ The patient is not receiving investigational drugs and has not received chemotherapy within the past 2 weeks
- ☐ The patient did not use antibiotics in the past 7 days (up to 2 prophylactic doses of antibiotic for procedures, including but not limited to port placement, is permitted)
- ☐ The patient denies history of total colectomy, ostomy, fecal incontinence, current infection or abdominal or pelvic surgery without recovery of bowel function.
- ☐ There is no plan for radiation involving abdomen or pelvis while on study.
- ☐ I reviewed the treatment plan, diarrhea treatment and bowel movement diaries. Patient manifested understanding of all instructions.

PROVIDER NAME (PRINT): _____

PROVIDER SIGNATURE: _____

DATE: _____

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.12 APPENDIX L: QAO PATIENT REGISTRATION FORM

Patient Registration Form

Patient Initials: _____ **Study ID (IRB#): _____**

Instructions: This form and all supporting documentation should be completed by the research staff and faxed to the Lombardi QAO at 202-687-9361 or scanned/emailed to lcccqao@georgetown.edu .
Patient may not start treatment until eligibility is verified and Subject Study ID is assigned by LCCC QAO.

Enrolling site:
☐ MedStar Georgetown University Medical Center ☐ MedStar Union Memorial Hospital ☐MedStar Good Samaritan Hospital ☐ Hackensack University Medical Center ☐ MedStar Franklin Square Medical Center ☐ MedStar Montgomery Medical Center ☐ Other: _____

1. Site PI: _____
2. Enrolling MD: _____
3. Date Informed Consent signed: ___/___/_____
4. Date HIPAA authorization signed: ___/___/_____
5. Proposed Start date for Treatment: ___/____/_____
6. Treatment Location: _____
7. Date of last chemotherapy: ___/____/_____
8. Prior antineoplastic therapy- ie. Cytotoxic, Cytokine base immunotherapy, immunoregulatory antibody therapy, radiation (Date/Type):
   _____
   _____
   _____
9. Please fax documentation supporting eligibility per protocol (Check those included):

   - ❑ Eligibility Checklist
   - ❑ Pathology Report
   - ❑ Physicians Note
   - ❑ CT showing RECIST
   - ❑ Laboratory Results (per protocol)
   - ❑ Past Medical History
   - ❑ EKG
   - ❑ ECOG score
   - ❑ Genetic Test Summary (if applicable)
   - ❑ Tumor tissue block. (per protocol)
   - ❑ Other _____

ON-STUDY CARD

MRN: _____
DOB: ____/____/____
Zip Code: _____
Race ☐ African American
☐ Asian
☐ Caucasian
☐ Hispanic
☐Native American
☐ Pacific Islander
☐ Other
☐ Unknown

Gender: ☐ Male ☐ Female☐ Unknown
Treating Physician _____ RN_____

Ethnicity: ☐Hispanic or Latino
☐Not Hispanic or Latino
☐ Unknown
Consent Approval Date: ___/___/___
Screen Failure ☐ Yes ☐ No
Baseline Start Date: ___/____/____
On Study Date ____/____/____

Protocol Waiver: ☐ Yes ☐ No
Reason _____
Registration Site: _____
First Scheduled Date: ____/_____/_____
Primary Site: _____

FOR QAO USE ONLY:

Subject Study ID: _____

Comments:

PLEASE SCAN THIS COMPLETED FORM TO THE PATIENT'S ELECTRONIC MEDICAL RECORD

16.13 APPENDIX M: ENDPOINT FORM

HALT-D BOWEL MOVEMENT

HALT-D Bowel Movement Endpoint Form
Study: IRB #2015-0547

Patient Name _____
Patient DOB _____
Patient Study ID Number _____
MRN _____
Site ID _____

1) Baseline number of stools per day at the time of screening: _____ BM/day
2) Current treatment cycle number on HALT-D trial:

   □ 1 □ 2 □ 3 □ End of Treatment

3) Did the patient have diarrhea during this cycle?

Diarrhea is defined as bowel movements that are increased in frequency from baseline AND are loose or watery.

   □ Yes □No (*primary endpoint*)

4) Regarding diarrhea timeline in days
   a) Date of first diarrhea episode in this cycle: ___ / ___ / _____
   b) Date of last diarrhea episode in this cycle: ___ / ___ / _____
   c) Total number of days of diarrhea during this cycle: _____
   d) Did the patient have 2 or more **CONSECUTIVE** days of diarrhea during this cycle?

      □ Yes □No

5) Regarding number and grade of diarrhea episodes
   a) Total number of diarrhea episodes during this cycle: _____

b) Did the patient have diarrhea GRADE ≥3 during this cycle (refer to CTCAE grading below)?

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

□ Yes □No

c) Date of first diarrhea GRADE ≥3 in this cycle : ___ / ___ / _____

d) Date of last diarrhea GRADE ≥3 in this cycle : ___ / ___ / _____

6) Regarding diarrhea breakthrough medication use during this cycle

a) Did patient use anti-diarrheal medication in this cycle?

□ Yes □No

b) What medication did the patient use?

i) Medication A: Loperamide 2mg (Imodium®)

(1) Date of first dose in this cycle : ___ / ___ / _____

(2) Total mg amount in this cycle _____

ii) Medication B: Lomotil, specify strength:_____

(1) Date of first dose in this cycle : ___ / ___ / _____

(2) Total mg amount of medication B in this cycle _____

iii) Medication C: OTHER, specify name and strength:_____

(1) Date of first dose in this cycle : ___ / ___ / _____

(2) Total mg amount of medication C in this cycle _____

iv) Medication D: OTHER, specify name and strength:_____

(1) Date of first dose in this cycle : ___ / ___ / _____

(2) Total mg amount of medication D in this cycle _____

7) FACIT-D total score in this cycle _____

8) FACIT-D diarrhea subset score in this cycle _____

9) Mean Bristol Stool Score in this cycle _____

10) Median Bristol Stool Score in this cycle _____

PROVIDER NAME (PRINT): _____

PROVIDER ROLE: _____

PROVIDER SIGNATURE: _____

DATE: _____

PLEASE SCAN THIS COMPLETED FORM INTO THE PATIENT'S ELECTRONIC MEDICAL RECORD

17 REFERENCES

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