Official Title: **A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC**

NCT Number: NCT02659514

Document Date: Clinical Study Protocol Version 2.0: 14 July 2017

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Protocol Version/Date: Amendment 2/14 Jul 2017

Deletions below are marked with red strikethrough text and additions are marked with red underlined text.

Summary of Significant Changes to the Protocol

Section	Change
Throughout Document	Minor edits for grammar, spelling, and typos.
Throughout Document: **General Explanation**	**Primary Reasons for Amendment:** Inclusion criterion 4 stated that "at least 2, but no more than 4, prior HER2-directed therapy regimens for breast cancer, including trastuzumab and trastuzumab emtansine (T-DM1, KADCYLA®)". The majority of patients with advanced HER2 positive breast cancer have been treated with more than 4 regimens of prior anti-cancer therapies. The restriction of patients having only up to 4 prior treatment regimens significantly limits a patient's participation opportunity. In order to include more patients, the inclusion criterion was changed so that a patient must have had at least 2 prior treatments, but there is no upper limit. A change to the prior treatment washout requirement was based on the half-life of the treatments and to ensure provide enough time for recovery from side effects and minimization of influences from prior therapy. This change is intended to provide patients with study treatment earlier, as appropriate. Other changes in patient eligibility are based on the feedback from the investigators and study centers. These changes are expected to improve enrollment without an increased risk to patient safety.
Throughout Document:	**Original Text:** at least 2, but no more than 4, prior HER2-directed therapy regimens… **New Text:** at least 2~~, but no more than 4,~~ prior HER2-directed therapy regimens **Reason**: To allow more patients to participate in the trial
Title Page **Footer** **Synopsis**	**Original Text:** Protocol Version/Date: ~~Amendment 1/17 Feb 2017~~ **New Text:** Protocol Version/Date: Amendment 2/14 Jul 2017
Synopsis: Inclusion and Exclusion Criteria **Section 4**	**Original Text:** **Inclusion Criteria:** 1. At least 2~~, and no more than 4,~~ prior HER2-directed therapy regimens for breast cancer, including trastuzumab and trastuzumab emtansine (T-DM1, KADCYLA®).

Section	Change
	2. Patient has adequate hematologic, hepatic, and renal function, as defined by: • Absolute neutrophil count (ANC) ≥1.~~5~~×10^9/L 3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. **Exclusion Criteria:** 4. Patient has brain metastases that are symptomatic or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 1 month (30 days) of enrollment. 5. Patient has received anticancer chemotherapy, biologics, immunotherapy, cure-intent radiotherapy, or investigational treatment within 30 days, except for hormone therapy, palliative therapy, or supportive therapy **New Text:** **Inclusion Criteria:** 4. At least 2 prior HER2-directed therapy regimens for breast cancer, including trastuzumab and trastuzumab emtansine (T-DM1, KADCYLA®). 6. Patient has adequate hematologic, hepatic, and renal function, as defined by: • Absolute neutrophil count (ANC) ≥1.0×10^9/L 7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Life expectancy is more than 6 months. **Exclusion Criteria:** 2. Patient has brain metastases that are symptomatic or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 15 days of enrollment. **3.** Patient has received anticancer chemotherapy, biologics, immunotherapy, cure-intent radiotherapy, or investigational treatment within 15 days, except for hormone therapy, palliative therapy, or supportive therapy **Reasons:** Inclusion: 4. Reason discussed above. 6. Investigators believe that ANC ≥1.0×10^9/L is acceptable for enrollment and patient safety will not be at risk. 7. In order to measure the response properly, and since the limit of prior treatments has been removed, we have stipulated that patients must have a life expectancy of at least 6 months. Exclusion: 2 and 3. Based on the half-life of the drugs, a 15-day washout was deemed adequate for enrollment into the study.

Section	Change
Synopsis: **Pharmacokinetic Assessments** **Schedule of Assessments and Procedures** **Section 5.3.2** **Section 5.4.6**	**Original Text:** The schedule for intensive PK sampling will be **Day 1** of **Cycle 1** pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, ~~8, 12,~~ and 24 hours post-dose. **New Text:** The schedule for intensive PK sampling will be **Day 1** of **Cycle 1** pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose. **Reason**: The change was made to improve enrollment.
Section 5.4.5: Chemistry Panel	**Added:** Added GGT (only at screening) and uric acid as part of the chemistry panel. **Reason**: These were already part of the chemistry panel but are now specified.

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC
Study Number:	**SPI-POZ-201**
Study Phase:	Phase 2
Study Drug:	Poziotinib
IND Number:	127,487
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618 USA
Protocol Version/Date:	Amendment 2/ 14 Jul 2017

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Confidentiality Statement

The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board/Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Spectrum Pharmaceuticals, Inc. except to the extent necessary to obtain Informed Consent from those persons to whom the drug may be administered.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-POZ-201

A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC

I have read this protocol and agree that it contains all the necessary details for performing the study in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP).

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor (Spectrum Pharmaceuticals, Inc.), to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after the protocol and patient information/Informed Consent form have been approved by the Institutional Review Board/Ethics Committee (IRB/EC). I will submit any protocol modifications (amendments) and/or any Informed Consent form modifications to the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by a regulatory authority (e.g., FDA).

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: Poziotinib

Study Centers: Approximately 35 study centers

Planned Number of Patients: Approximately 75 patients

Duration of Study: Approximately 3 years | **Clinical Phase:** 2

Objectives:

Primary Objective

- To establish the dosing schedule for poziotinib to be used in the clinical development program
- To evaluate the **Objective Response Rate** (**ORR**) of poziotinib in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC)

Secondary Objectives

- To assess the safety and tolerability of poziotinib in patients with HER2-positive MBC
- To evaluate the pharmacokinetics of poziotinib in patients with HER2-positive MBC
- To evaluate other efficacy variables of poziotinib in patients with HER2-positive MBC, including the following:
  - **Progression Free Survival (PFS)**
  - **Disease Control Rate (DCR)**
  - **Time to Progression (TTP)**

Duration of Study: The total duration of the study will be approximately 3 years. The duration of study participation for each patient includes the following segments:

- **Screening Period:** 30 days
- **Treatment Period:** 21 days per cycle for up to 24 months
- **End-of-Treatment Visit:** 35 (±5) days after the last dose of poziotinib

Study Design and Treatment Plan:

This is a Phase 2, open-label, multicenter study to establish the dose regimen and evaluate the preliminary efficacy and the safety/tolerability of poziotinib in approximately 75 patients with HER2-positive MBC who have received at least two prior HER2-directed treatment regimens including trastuzumab and T-DM1. The **Screening** period (**Day -30** to **Day -1**) lasts up to approximately 30 days prior to **Cycle 1**, **Day 1**. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to undergoing any study procedures.

Each treatment cycle is 21 calendar days in duration. Eligible patients will be enrolled into each dose cohort as described below. In Amendment 1, in addition to the original 24 mg cohort (**Cohort 1**), two additional treatment cohorts are being added:

- **Cohort 1:** 24 mg (three 8-mg tablets once daily) for 2 weeks, rest 1 week (ENROLLMENT COMPLETE)
- **Cohort 2:** 16 mg (two 8-mg tablets once daily) continuous dosing
- **Cohort 3:** 12 mg (one 8-mg tablet and two 2-mg tablet once daily) continuous dosing

Patient enrollment in **Cohort 1** is complete. New patients will begin enrollment into **Cohort 2**. Rules for safety review and enrollment for **Cohort 2** and **Cohort 3** follow:

Cohort 2:

- Rate of Grade 3 or greater AEs of special interest (ie, diarrhea, skin rash, stomatitis) that are identified during Safety Data Review after the first 6 patients and again after 12 patients have completed **Cycle 1**:
  - **>33%:** Stop **Cohort 2** (≥3 of 6 patients or ≥5 of 12 patients with Grade 3 or greater AEs of special interest) and begin **Cohort 3**
  - **≤33%:** Keep enrolling **Cohort 2** until 30 patients are enrolled and treated and no additional patients will be enrolled.

Cohort 3 - only if Cohort 2 is stopped due to toxicity:

- Rate of Grade 3 or greater AEs of special interest (ie, diarrhea, skin rash, stomatitis) are identified during Safety Data Review after the first 6 patients and again after 12 patients have completed **Cycle 1**:
  - **>33%:** End enrollment in **Cohort 3**
  - **≤33%:** Keep enrolling **Cohort 3** until 20 patients are enrolled and treated

Toxicity will be assessed based on the grade of the Adverse events using CTCAE version 4.03.

All treatments will be taken orally, once daily (QD) at approximately the same time each morning. On **Day 1** of each cycle, the patient's absolute neutrophil count (ANC) must be $\geq 1.0\times10^9$/L and platelet count must be $\geq 100\times10^9$/L before administering poziotinib. **Day 1** of a new cycle is equivalent to **Day 22** of the previous cycle, with a window of ±3 days for the visit. If a visit is delayed during a cycle, then all subsequent cycles will be delayed sequentially. All patients will be treated until disease progression, death, intolerable adverse events, or up to a maximum of 24 months, whichever comes first.

Patient Replacement Strategy: Patients who discontinue from the study will not be replaced.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient, or patient's authorized representative, must be willing and capable of giving written Informed Consent and must be able to adhere to dosing and visit schedules as well as meet all study requirements.
2. Patient has histopathologically confirmed primary breast cancer with metastatic lesions.
3. Patient has confirmed HER2 overexpression or gene-amplified tumor via immunohistochemistry (IHC) with IHC 3+ or IHC 2+ with confirmatory fluorescence *in situ* hybridization (FISH)+.
4. At least two prior HER2-directed therapy regimens for breast cancer, including trastuzumab and trastuzumab emtansine (T-DM1, KADCYLA®).
5. Patient is at least 18, and ≤90 years of age.
6. Patient has adequate hematologic, hepatic, and renal function, as defined by:
   - Absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L.
   - Platelet count $\geq 100\times10^9$/L
   - Hemoglobin ≥9 g/dL
   - Total bilirubin ≤1.5 mg/dL, if hepatic metastases are present, ≤2.5 mg/dL
   - Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), and gamma-glutamyltransferase (GGT) ≤2.5×upper limit of normal (ULN); if hepatic metastases are present, ≤5.0×ULN
   - Creatinine ≤2.2 mg/dL or calculated creatinine clearance ≥40 mL/min
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Life expectancy is more than 6 months.
8. Patient has measurable disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1)
9. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method, from study entry until at least 30 days after the last dose of poziotinib.

10. Females of childbearing potential must have a negative pregnancy test within 30 days prior to enrollment. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or who are surgically sterilized do not require this test.

Exclusion Criteria:

1. Patient has had previous treatment with poziotinib prior to study participation.
2. Patient has brain metastases that are symptomatic or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 15 days of enrollment.
3. Patient has received anticancer chemotherapy, biologics, immunotherapy, cure-intent radiotherapy, or investigational treatment within 15 days, except for hormone therapy, palliative therapy, or supportive therapy
4. Patient has a history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment.
5. Patient has a cardiac ejection fraction <50% by either echocardiogram or multi-gated acquisition (MUGA) scan.
6. Patient has a history of other malignancies within the last 5 years, except for non-melanoma skin cancer or carcinoma *in situ* of the cervix.
7. Patient is confirmed to have clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as a main symptom (ie, acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) Grade 2 or above diarrhea due to other etiologies).
8. Patient is unable to take drugs orally due to disorders or diseases that may affect gastrointestinal function, such as inflammatory bowel diseases (eg, Crohn's disease, ulcerative colitis) or malabsorption syndrome, or procedures that may affect gastrointestinal function, such as gastrectomy, enterectomy, or colectomy.
9. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver diseases).
10. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
11. Patient has active bleeding disorders, uses warfarin or other coumadin-derived anticoagulants, has abnormal International Normalized Ratio (INR), or abnormal prothrombin time test within one month prior to the study.
12. Patient is pregnant or breast-feeding.

Investigational Product, Dose, and Route of Administration:

Poziotinib is supplied as 8-mg and 2-mg tablets and will be administered orally once daily at approximately the same time each morning according to the schedule for each cohort, either for 14 days, followed by 7 treatment-free rest days (**Cohort 1** only) or continuous (**Cohorts 2** and **3** only), during each 21-day cycle. If the morning dose is missed, this dose may be administered any time during the day, at least 8 hours prior to the next scheduled dose.

Loperamide will be supplied by Sponsor and is to be taken by all patients on the following schedule:

- **Days 1** to **56**: 4 mg two times a day (bid), or three times a day (tid) if needed
- **Days 56 until end of treatment**: 4 mg taken as needed, but not to exceed 16 mg/24 hours

The intra-patient dose modification following the first dose administration in **Cohort 2** due to toxicity will be allowed as below:

- After the first occurrence of an AE Grade ≥3, the dose of poziotinib will be temporarily withheld. Once the event has recovered to Grade ≤1, the treatment can resume at the same dose.
- If the same AE occurs a second time (Grade ≥3), the dose of poziotinib will be reduced.
- No dose reductions below 12 mg/day will be allowed.

No dose modification will be allowed in **Cohort 3** if the toxicity as described above is observed. The patient will be discontinued.

Reference Therapy, Dose, and Route of Administration: None

Efficacy Assessments:

Primary Endpoint:

- The optimal dosing schedule for poziotinib to be used in the clinical development program
- **Objective Response Rate** (**ORR**)

Secondary Endpoints:

- Safety
- Pharmacokinetics (PK)
- **Progression-Free Survival** (**PFS**)
- **Disease Control Rate** (**DCR**)
- **Time to Progression** (**TTP**)

Pharmacokinetic Assessments: All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose for sparse pharmacokinetic (PK) sampling on **Day 1** of **Cycle 1**, **Cycle 2**, and **Cycle 3** (all cohorts) and pre-dose on **Day 14** (±3 days) of **Cycle 1** (**Cohort 1** only).

Patients in Cohort 2 and Cohort 3, if consented, will undergo intensive PK sampling. Intensive PK sampling will replace sparse PK sampling in **Cycle 1**. The schedule for intensive PK sampling will be **Day 1** of **Cycle 1** pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose.

In addition, if a patient presents with a potentially drug-related serious adverse event (SAE), PK samples may be collected during the visit for PK analysis.

Safety Assessments:

Safety will be assessed by reported/elicited adverse events (AEs), laboratory assessments including hematology and biochemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.

Adverse Event and Serious Adverse Event Reporting:

Adverse events will be recorded from the first dose of study drug administration until 35 (±5) days after the last dose of study drug is administered. From the time Informed Consent is signed to the first dose of study drug administration, only serious adverse events (SAEs) related to study procedures will be recorded and reported.

Statistical Methods:

A formal statistical analysis plan (SAP) providing full technical details of the planned analyses will be finalized prior to database lock.

Sample Size Justification:

Other important treatments for HER2-positive metastatic breast cancer include trastuzumab emtansine (T-DM1), lapatinib-capecitabine combination, and neratinib. Published **ORRs** reported for these regimens are 43.6%, 30.8%, and 24%, respectively. The purpose of this study is to evaluate the safety and efficacy of poziotinib and identify the optimal dose for future clinical development. No statistical hypothesis testing will be performed.

The enrollment into **Cohort 1** is now complete. A total of 32 patients have received treatment of poziotinib in **Cohort 1**. A total of 30 patients are expected to be enrolled and treated in **Cohort 2**. If the enrollment in **Cohort 2** is stopped due to toxicity, new patients will be enrolled into **Cohort 3**. A total of 20 patients will be enrolled in **Cohort 3**.

Efficacy Analysis:

The primary efficacy variable **ORR** will be analyzed descriptively along with the 95% CI for each cohort. The secondary efficacy variables, **PFS**, **DCR,** and **TTP**, will be analyzed descriptively for each cohort.

Analysis Populations:

The following analysis populations will be defined.

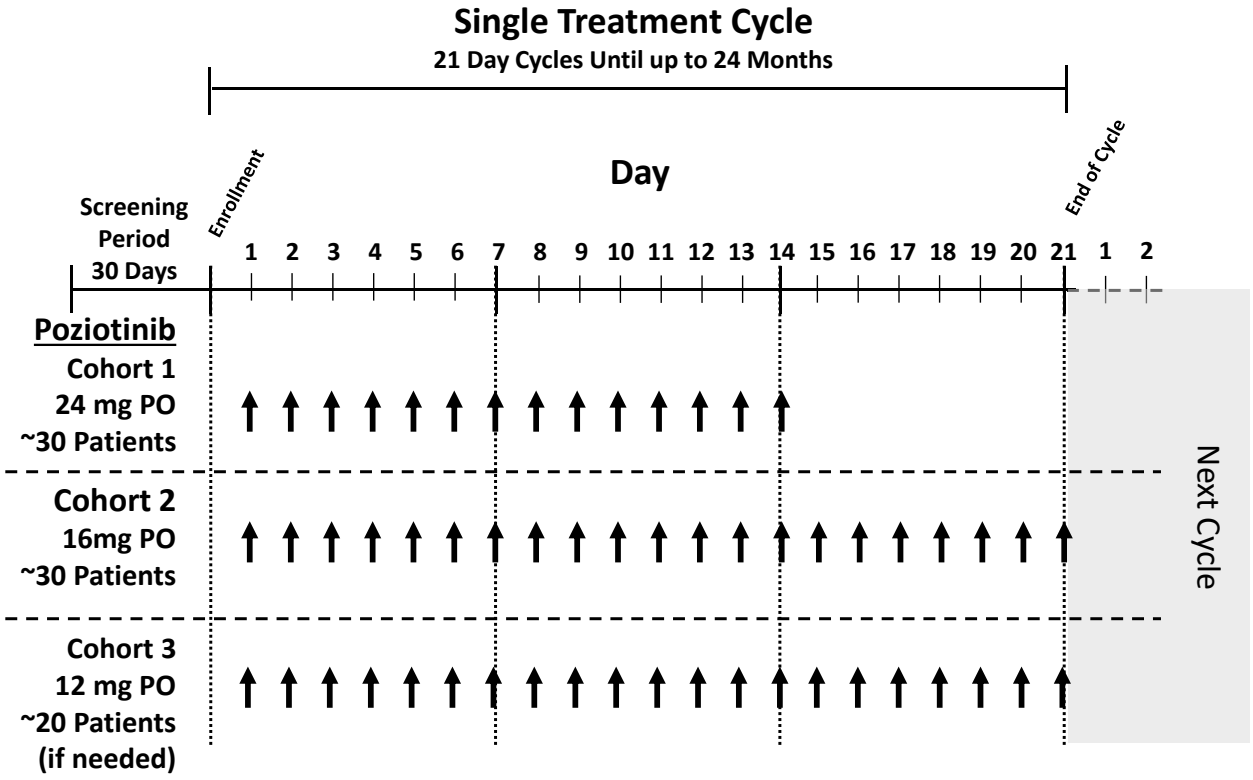
- The **Evaluable Population (EP)** consists of all patients who are enrolled, complete at least 1 cycle of poziotinib treatment, and have at least 1 post-Baseline tumor response evaluation using RECIST, Version 1.1 criteria.
- The **Safety Analysis Population (SAF)** includes all patients who signed Informed Consent, enrolled, and received at least 1 dose of poziotinib. All demographics, Baseline characteristics, and safety data will be analyzed using the **SAF** population.

Safety and Tolerability:

The following variables will be summarized and analyzed descriptively for each cohort: number of completed cycles; number and percentages of patients with TEAEs, SAEs, TEAEs leading to study drug discontinuation, TEAEs related to the study drug; and the severity of TEAEs based on CTCAE, Version 4.03.

Protocol Version/Date: Amendment 2/14 Jul 2017

Study Design Diagram



SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Screening	Treatment Period[a] (Each Cycle=21 [±3] Days) up to 24 Months						End-of-Treatment Visit
		Cycle 1			Cycle 2		Cycle 3+	
	Day -30 to Day-1	Day 1	Day 8±1	Day 14±3	Day 1	Day 8±1	Day 1	35 (±5) Days After Last Dose[b]
Informed Consent	x							
Relevant Medical History	x							
Demographic Data	x							
Height and Weight	x	x			x		x	x
Physical examination [c]	x	x			x		x	x
Vital signs	x	x			x		x	x
ECOG Performance Status	x	x			x		x	x
Pregnancy test (urine) [d]	x							
Tumor Receptor Status (ER, PR, HER2) and Stage	x							
Tumor Assessment [e]	x						x	x
CBC with 5-part differential and platelets [f]	x	x [f]	x		x	x	x	x
Serum Chemistry [g]	x	x [g]			x		x	x
Cardiac Ejection Fraction [h]	x							x
PK Samples [i]		x		x [i]	x		x	
Dispense Poziotinib and Loperamide[j]		x			x		x	
Adverse event assessment	x [k]	x	x	x	x	x	x	x
Dispense and Collect Patient Diary		x	x		x	x	x	x
Concomitant medications review	x	x	x	x	x	x	x	x

a) Each cycle is comprised of 21 days. **Day 1** of a new cycle is applicable to **Day 22** of the previous cycle, with a window period of ± 3 days. If a visit is delayed during 1 cycle, the subsequent schedules will be delayed sequentially.
b) An **End-of-Treatment Visit** will be performed 35 (±5) days after the last dose of poziotinib. An End of Study page will be recorded at that time.
c) A complete physical examination is required at **Screening**, **Day 1** of each Cycle, and at the **End-of-Treatment Visit**. Symptom-directed exams are required at other visits.
d) Pregnancy test (urine β-HCG) in women of child-bearing potential.
e) Tumor assessment will be performed at **Screening** and every 6 weeks (± 14 days) until disease progression, death, or intolerable adverse events, whichever comes earlier. Imaging studies performed prior to the signing of Informed Consent as part of the site's routine standard of practice are allowed at the discretion of the Sponsor.
f) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to poziotinib administration on **Day 1** of each cycle, at which time, the patient's absolute neutrophil count must be $\geq 1.0\times10^9$/L and platelet count must be $\geq 100\times10^9$/L before administering the next dose of poziotinib. In addition, a CBC is to be performed on **Day 8** of **Cycles 1** and **2**.
g) Blood for chemistry is to be collected within 7 days prior to poziotinib administration on **Day 1** of each Cycle.
h) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan and will be monitored at Screening, 3 months after first treatment, then every 6 months thereafter, while the patient is treated, and at the **End-of-Treatment Visit**.

i) For all cohorts, patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose for sparse pharmacokinetic (PK) sampling on **Day 1** of **Cycles 1**, **2**, and **3** and pre-dose on **Day 14** of **Cycle 1** (**Cohort 1** only). For patients in **Cohort 2** and **Cohort 3**, if consented, intensive PK samples will be drawn pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose on **Day 1** of **Cycle 1**. In addition, if a patient presents with a potentially drug-related serious adverse event (SAE), PK samples may be collected during the visit for PK analysis.

j) Poziotinib and loperamide will be dispensed on **Day 1** of each cycle. Patients will take poziotinib orally once daily at approximately the same time each morning according to the schedule for each cohort during each 21-day cycle.

k) Adverse event assessment during **Screening** will utilize National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) and record only study-related SAEs.

Poziotinib Dosing Recommendations

- After the first occurrence of an AE Grade ≥3, the dose of poziotinib will be temporarily withheld. Once the event has recovered to ≤Grade 1, the treatment can resume at the same dose.
- If the same AE occurs a second time (Grade ≥3), the dose of poziotinib will be reduced.
- No dose reductions below 12 mg/day will be allowed.

Adverse Event	Grade	1st Occurrence	2nd Occurrence	3rd Occurrence
Diarrhea	Grade ≥3 (Despite adequate anti-diarrheal prophylaxis and/or treatment)	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg → 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
	Grade ≥2 for ≥ 48 hours (Despite adequate anti-diarrheal prophylaxis and/or treatment)			
Rash	Grade ≥3	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg→ 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
Nausea and/or Vomiting	Grade ≥3 (Despite adequate anti-emetics)	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg → 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
	Grade ≥2 for ≥48 hours (Despite adequate anti-emetics)			
LVEF Dysfunction	Grade ≥3	Discontinue Treatment		

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
ACS	American Cancer Society
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-hCG	Beta human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CR	Complete Response
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DCF	Data clarification form
DCR	Disease Control Rate
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EP	Evaluable Population
ER	Estrogen receptor
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

Abbreviation/ Acronym	Definition
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-a-go-go
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA®	Medical Dictionary for Regulatory Activities
M1	Metabolite 1 (of poziotinib)
M2	Metabolite 2 (of poziotinib)
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Limit
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
PR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAER	Serious adverse event report
SAF	Safety analysis population
SAP	Statistical analysis plan
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
T-DM1	Trastuzumab emtansine
TEAE	Treatment-emergent adverse event
TTP	Time to Progression
ULN	Upper limit of normal

Abbreviation/ Acronym	Definition
US	United States
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

1.1.1 Breast Cancer

Breast cancer is one of the most common forms of cancer and the second highest cause of cancer deaths in women **[1]**. About 1 in 8 (12%) women in the United States (US) will develop invasive breast cancer during their lifetime. In the US in 2015, an estimated 231,840 new cases of invasive breast cancer will occur. Breast cancer is the second leading cause of cancer death in women, exceeded only by lung cancer. The chance that breast cancer will be responsible for a woman's death is about 1 in 36 (about 3%). Death rates from breast cancer have been declining since about 1989, with larger decreases in women younger than 50 years of age. These decreases are believed to be the result of earlier detection through screening and increased awareness, as well as improved treatment. However, even with these improvements, it is still estimated that approximately 40,290 women and 440 men are expected to die from breast cancer in 2015 **[1]**.

Important components of the treatment of breast cancer are not only the extent of the disease but its biologic features. Knowledge of these factors contributes to the determination of the disease stage, assist in the risk assessment of recurrence, and may predict response to therapy. Due to this, the National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer recommend that estrogen receptors (ERs), progesterone receptors (PRs), and the human epidermal growth factor receptor (HER2) status be determined in all breast cancer samples **[2]**.

1.1.2 Human Epidermal Growth Factor Receptor Family- Role in Breast Cancer

The human epidermal growth factor receptor (EGFR) family consists of four members: epidermal growth factor receptor (EGFR/HER1 or erbB-1), HER2 (erbB-2), HER3 (erbB-3), and HER4 (erbB-4), and these proteins regulate cell growth, apoptosis, migration, adhesion, and differentiation. Hyperactivation of these receptors triggers a complex, multilayered network of interrelated signaling pathways including downstream up-regulation of the mitogen activated protein kinase (MAPK), phosphoinositide-3-kinase/ AKT (PI3K/AKT), and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathways promoting cancer growth [3].

HER2 is overexpressed in roughly 20% to 25% of breast cancers and is a prognostic marker **[4-5]**. HER2-positive breast cancers are characterized as being more clinically aggressive and more invasive than HER2-negative subtypes, are associated with increased growth rates, early systemic metastasis, and worse outcome **[5-6]**. Treatments that specifically target HER2 have been shown to be particularly beneficial to patients with HER2-positive breast cancers, and several targeted drug therapies have been approved by the US Food and Drug Administration (FDA) to treat patients with HER2-positive breast cancer, including trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1). However, *de novo* and acquired resistance to HER2-directed approaches remains a clinical challenge and an unmet medical need. Thus, development of novel therapeutic agents aimed at preventing or circumventing resistance are still needed.

1.1.3 Poziotinib

1.1.3.1 Pharmacology of Poziotinib

Poziotinib (HM781-36B) is a novel, oral, quinazoline-based pan-HER inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors, including human epidermal growth factor receptor (HER1/ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4), as well as HER receptor mutations. This, in turn, leads to inhibition of the proliferation of tumor cells that overexpress these receptors. It is well established that several malignancies, including lung, breast, stomach, colorectal, head, and neck, and pancreatic carcinomas, are associated with a mutation in or overexpression of members of the EGFR receptor family **[7]**.

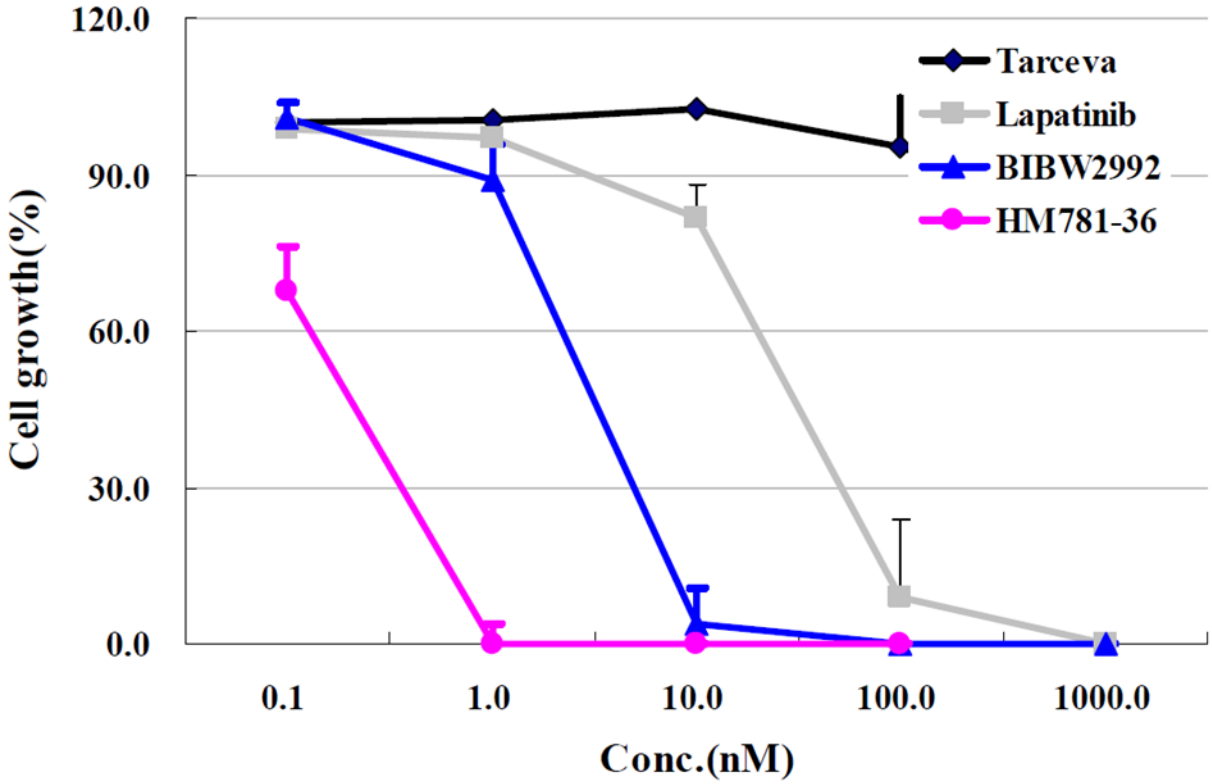
1.1.3.2 Drug Product Description

Poziotinib (HM781-36B) is formulated as a hydrochloride salt of poziotinib. The chemical formula of poziotinib is (1-[4-[4-(3,4-dichloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]-piperidin-1-yl]prop-2-en-1-one hydrochloride). For clinical trials conducted in the United States, the drug product will be supplied as tablets for oral administration, which contain 2.0 mg or 8.0 mg of poziotinib (as salt form), respectively.

1.1.4 Poziotinib Nonclinical Studies

Poziotinib demonstrated potent EGFR and HER2 inhibitory activity *in vitro*, irreversible HER-family binding and inhibition of EGFR downstream signaling, inhibition of cell growth in various human cancer cell lines, and inhibition of tumor volume and growth rate in human cancer cell line xenograft animal models. The comparative dose-response effects of poziotinib (HM781-36B), and other EGFR family inhibitors including erlotinib (Tarceva®), lapatinib, and afatinib (BIBW 2992) on cell growth in a breast cancer cell line are presented in Figure 1. The cells were treated with increasing doses of poziotinib (0.1-1000 nM) for 72 hours. In all studies, poziotinib was the most potent inhibitor of cell growth compared with the other EGFR inhibitors tested in SK-BR-3 cells.

Figure 1 ***In Vitro*** **Growth Inhibitory Activity of Poziotinib (HM781-36B) Versus Other Epidermal Growth Factor Receptor Inhibitors in SK-BR-3 Cells**



In enzyme-based, *in vitro* assays conducted in various human and mouse cancer cell lines, poziotinib effectively inhibited wild-type EGFR family kinases, including EGFR, HER2, and HER4 with 50% inhibitory doses (IC_{50}) of 3.2 nM, 5.3 nM, and 23.5 nM, respectively, and mutated EGFRs, including $EGFR^{T790M}$ and $EGFR^{L858R/T790M}$ with IC_{50} values of 4.2 nM and 2.2 nM, respectively. In *in vivo* cancer models, poziotinib monotherapy blocked the phosphorylation of EGFR and HER2 in HCC827, N-87, and NCI-H1975 cancer cell lines.

Poziotinib was also shown to irreversibly bind to its target enzymes, which led to excellent *in vivo* anti-tumor effectiveness of poziotinib in xenograft models with various EGFR-dependent cancer cell lines harboring high expression levels of $EGFR^{WT}$ or HER2, $EGFR^{Del\ E746\_A750}$ and $EGFR^{L858R/T790M}$. *In vitro* and *in vivo* studies have also been conducted to evaluate the effects of poziotinib when administered in combination with the well-established monoclonal antibody cancer drug trastuzumab. These studies were performed in HER2-driven cancer models, including breast cancer and gastric cancer, and indicate that poziotinib has synergistic antineoplastic effects when given in combination with trastuzumab.

Safety pharmacology studies of poziotinib were conducted, including a rat Irwin study, a rat respiratory study, and a cardiovascular telemetry study in dogs. The inhibition of human ether-a-go-go (hERG) tail current observed *in vitro* was not predictive of cardiovascular effects in telemetry-instrumented beagle dogs *in vivo*. The nonclinical efficacy and safety data support the continued development of poziotinib.

1.1.4.1 Poziotinib Absorption, Distribution and Metabolism

Poziotinib is a compound with high plasma clearance, moderate oral bioavailability, high protein binding, slow metabolism *in vitro*, and extensive metabolism *in vivo*. Exposure to poziotinib increased with increase in dose, and pharmacokinetic profiles were similar between males and females in nonclinical species. Poziotinib was widely distributed in tissues, and was concentrated in the uveal tract and eye. Poziotinib was extensively metabolized in the rat following intravenous and oral administration of the drug; 10 metabolites were identified. Metabolites identified *in vitro* were similar to those identified *in vivo*, and in the clinic; M1 (dihydroxy-poziotinib) and M2 (*O*-demethyl-poziotinib) were the major metabolites. Metabolite formation was NADPH-dependent, suggesting a role for cytochrome P450 (CYP450) enzymes. CYP3A4 was the primary enzyme in the formation of M1, and CYP2D6 was the primary enzyme in the formation of M2. Both the M1 and M2 metabolites are pharmacologically active, but M2 is much more potent than M1 **[8]**.

1.1.4.2 Poziotinib Toxicity Studies

The toxicities of single or repeated daily doses of oral poziotinib were assessed in rats and dogs. In the 13-week toxicity study, rats tolerated poziotinib up to a daily dose of 0.45 mg/kg. Adverse toxicological effects included an increase in the incidence of skin lesions (degeneration/atrophy, erosion/ulcer, epidermal hyperplasia, exudates), stomach toxicity (histopathological epithelial hyperplasia, hyperkeratosis, inflammation and erosion/ulcer) and increased neutrophil counts secondary to inflammation. The NOAEL for the 13-week study was 0.15 mg/kg/day. The MTD for the study was 0.45 mg/kg/day, based on reductions in mean body weight in males (-18.7%) and females (-7.1%).

In the 13-week toxicity study, dogs tolerated up to 0.15 mg/kg/day. The NOAEL following dose reduction was 0.075 mg/kg/day. The MTD following dose reduction was 0.15 mg/kg/day, based on reductions in body weight (13.2% and 13.9%) and food consumption (75.8% and 85.0%) in males and females, respectively. The major target organs were skin (hyperplasia, ulcer, and inflammation), gastrointestinal tract (inflammation, attenuation of luminal epithelium), eye (atrophy of the corneal epithelium), and lymphoid organ (lymphocyte depletion/necrosis). In regard to cardiovascular effects (electrocardiogram [ECG], blood pressure, heart rate, and QT), there were no changes up to 0.15 mg/kg/day of poziotinib in the 13-week dog toxicity study.

Poziotinib and its M1 and M2 metabolites were not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or in the Chinese hamster ovary chromosome aberration assay; and, were not clastogenic in an *in vivo* rat bone marrow micronucleus test at doses of up to 1000 mg/kg in males and 500 mg/kg in females. Poziotinib was evaluated in an embryo-fetal study in rats and rabbits. Effects of poziotinib on embryo-fetal development were limited and restricted to high doses. High-dose poziotinib exposure was associated with a reduction in the mean number of viable fetuses and this was correlated with increased post implantation loss and resorptions. Neither the rat nor the rabbit showed evidence of teratogenicity. Poziotinib did not show any evidence of skin irritation in male New Zealand White rabbits or any evidence of phototoxicity to BALB/c 3T3 clone A31 cells.

The toxicological findings in animal studies have been entirely consistent with the adverse events reported in human clinical trials. The most frequent adverse events reported in human clinical trials conducted in South Korea to date include diarrhea, stomatitis, rash, decreased

appetite, and pruritus. These toxicological effects observed in rats, dogs and humans with poziotinib mirror those observed with other EGFR inhibitors **[9-12]**, suggesting that poziotinib toxicity is a class effect of EGFR tyrosine kinase inhibition. Since the poziotinib metabolite M2 exhibits *in vitro* EGFR inhibitory activity nearly identical to poziotinib (IC_{50} values = 5.6 nM and 5.4 nM, respectively), one cannot exclude the possibility that *in vivo* poziotinib EGFR inhibitory activity is due to systemic levels of both poziotinib and M2. As the formation of M2 is dependent on the variable activity of the human polymorphic CYP2D6 enzyme, accounting for poziotinib and M2 may be the most accurate estimate of TKI activity and hence toxicity. The mean safety margin at the NOAEL in dogs in the 13-week toxicity study, compared to humans at the MTD of 24 mg/day, was 0.8-fold using poziotinib exposure alone and 2.1-fold using poziotinib + M2 exposure.

These values are in line with the Phase 1 studies completed in South Korea, in which patients were treated with poziotinib doses ranging from 0.5 mg to 32 mg (**HM-PHI-101**). The dose-limiting toxicity (DLT) in these clinical trials was observed at 32 mg, and 24 mg was the MTD for the intermittent (14 days on treatment and 7 days off) dosing schedule. Taken together, these data support the planned and ongoing clinical trials utilizing doses of poziotinib up to 24 mg/day.

1.1.5 Poziotinib Clinical Studies

To date, the clinical development program for poziotinib has been conducted in Korea and comprises of 3 completed and 6 ongoing clinical studies in patients with advanced cancers.

- Two completed Phase 1 studies conducted in patients with advanced cancers (solid tumors)
- One completed Phase 1b/2 study conducted in patients with advanced gastric cancer
- Six ongoing Phase 2 studies conducted in patients in various malignancies, including one Phase 2 study being performed in patients with breast cancer

To date, more than 200 patients have received poziotinib monotherapy in open-label clinical trials at doses ranging from 0.5 mg to 32 mg on an intermittent dosing schedule and from 12 mg to 24 mg on a continuous dosing schedule, or as combination therapy with trastuzumab and paclitaxel. Clinical activity was observed in patients on poziotinib monotherapy and in combination with other anti-cancer agents, as defined by objective responses or prolonged stabilization of disease. Clinical benefit has been observed in patients with several solid tumors.

Poziotinib monotherapy utilizing an oral dose of 16 mg/day on either an intermittent (2 weeks on, 1 week off) or continuous dosing regimen can induce partial response or disease stabilization in patients with several advanced solid tumor types (**HM-PH1-102**). For the cancer indications being investigated, the patients experienced adverse events (AEs) that were either expected for the underlying malignancies or commonly seen with other HER2-targeted therapies (e.g., diarrhea, rash, and stomatitis).

Despite the fact that most patients treated in poziotinib clinical trials have had advanced and heavily pre-treated disease, the safety profile described for poziotinib in these trials and the anti-tumor activity noted suggests a favorable benefit-risk ratio and provides justification for the continued development of poziotinib for the treatment of multiple EGFR- or HER2-driven solid tumor indications.

The most commonly reported (≥50%) treatment-emergent AEs in all three studies were diarrhea, rash, stomatitis, decreased appetite, paronychia and pruritus (**Table 1**). The most commonly reported treatment-related AEs (≥50% incidence in any 24-mg/day cohort) in **HM-PHI-101** (2 cohorts, 24 mg/day and 24 mg/day) and **HM-PHI-102** (1 cohort) were as follows:

- Diarrhea (100%, 100%, 100%)
- Stomatitis (100%, 100%, 67%)
- Rash (100%, 100%, 67%)
- Pruritus (83%, 92%, 0%)
- Palmar-plantar erythrodysesthesia syndrome (33%, 58%, 0%)
- Decreased appetite (17%, 42%, 100%)
- Rhinorrhea (33%, 75%, 33%)
- Paronychia (67%, 25%, 33%)

Many of these most commonly reported treatment-related AEs in the 24-mg/day cohorts were also reported at an incidence of ≥50% incidence in **NOV120101-202** (16 mg/day continuous), ie, diarrhea (95%), stomatitis (59%), rash (77%), pruritus (64%), and paronychia (54%).

The most commonly reported Grade 3 TEAEs (≥25% incidence in any 24-mg/day cohort) in **HM-PHI-101** (2 cohorts, 24 mg/day and 24 mg/day) and **HM-PHI-102** (1 cohort) were as follows:

- Diarrhea (33%, 25%, 33%)
- Nausea (0%, 8%, 33%)
- Decreased appetite (0%, 8%, 33%)
- Hemoglobin decreased (0%, 0%, 33%)

Different from the most commonly reported Grade 3 TEAEs in the 24-mg/day cohorts, Grade 3 TEAEs reported at an incidence of ≥25% in **NOV120101-202** (16-mg/day continuous dosing) were rash (59%) and mucosal inflammation (26%). Refer to poziotinib IB for complete details.

Table 1 Most Common Treatment-Emergent Adverse Events (≥30% in Group Total for each Study) in Descending Order by Preferred Term (Safety Population) - Phase 1 and Phase 2 Completed Studies with Poziotinib (Doses ≥12 mg/day)

Preferred Term	Number (%) Patients		
	HM-PHI-101 [a] N=55	HM-PHI-102 [a] N=20	NOV120101-202 N=39
Any Adverse Event	**55 (100)**	**20 (100)**	**39 (100)**
Diarrhea	48 (87)	20 (100)	36 (92)
Rash	47 (86)	13 (65)	30 (77)
Stomatitis	42 (76)	16 (80)	23 (59)
Decreased Appetite	34 (62)	13 (65)	21 (54)

Preferred Term	Number (%) Patients		
	HM-PHI-101 [a] N=55	HM-PHI-102 [a] N=20	NOV120101-202 N=39
Paronychia	13 (24)	13 (65)	21 (54)
Pruritus	33 (60)	11 (55)	25 (64)
Mucosal Inflammation	13 (24)	6 (30)	18 (46)
Rhinorrhea	17 (31)	8 (40)	4 (10)
Dry skin	6 (11)	6 (30)	15 (38)
Fatigue	21 (38)	3 (15)	15 (38)
PPE Syndrome	18 (33)	3 (15)	3 (8)
Acne	18 (33)	0	0
Vomiting	16 (29)	6 (30)	4 (10)
Dermatitis Acneiform	2 (4)	6 (30)	5 (13)

PPE = palmar-plantar erythrodysesthesia syndrome.

(a) Includes all patients and all doses.

Note: Adverse events are listed by decreasing order of highest percent in any study.

MedDRA version: 14.0 was used for Studies **HM-PHI-101 and HM-PH1-102**; MedDRA version 17.0 was used for **NOV120101-202.**

Source: Poziotinib IB Table 9.

1.2 Rationale for the Current Study

HER2-targeted approaches have revolutionized the treatment and outcomes associated with HER2-overexpressing breast cancer. However, *de novo* and acquired resistance to HER2-directed approaches remains a clinical challenge, and many metastatic breast cancer patients continue to progress or relapse, despite having initially responded to treatment. Several resistance mechanisms have been described, including mutations in other signaling pathways and expression of a truncated form of HER2 **[13]**. Therefore, there remains an unmet need to develop novel treatment approaches for HER2-positive breast cancer that can improve clinical outcomes, particularly in the context of strategies to overcome resistance to HER2-targeted therapy.

Poziotinib is an orally administered, irreversible pan-HER inhibitor with activity against HER1, (ErbB1; EGFR), HER2 (ErbB2), and HER4 (ErbB4), as well as HER receptor mutations. The clinical results and safety profile of poziotinib to date in various studies involving patients with relapsed or refractory solid tumors as either a single agent or as combination therapy, have been very promising. These data support the expectation that poziotinib will be efficacious and well tolerated in HER2-positive metastatic breast cancer patients.

In Phase 1 studies, the MTD of poziotinib was determined to be 18 mg for continuous daily dosing and 24 mg for intermittent dosing (14 days on treatment, 7 days off treatment). The most commonly occurring toxicities included diarrhea, rash, and stomatitis, which is consistent with the known toxicity profile of other EGFR inhibitors. For monoclonal antibody EGFR-targeted therapies, such as cetuximab or panitumumab, rates of Grade 2 diarrhea are up to 21% and for Grade 3 diarrhea (i.e., greater than 7 stools per day or requiring intravenous fluids) between 1% to 2% **[14-17]**. For small-molecule EGFR tyrosine kinase inhibitors like erlotinib, gefitinib, and

lapatinib, however, diarrhea is substantially more common, occurring in up to 60% for all grades and with Grade 3 diarrhea occurring in about 6% to 9% of patients **[15]**.

Although diarrhea is common with EGFR inhibitor treatment and can significantly impact patients' quality of life, evidence suggests that diarrhea is also an indicator that EGFR TKIs are hitting their target **[18]**. In one study of gefitinib in NSCLC, the presence of diarrhea was identified as one of the independent predictors of a partial response, and the absence of diarrhea was one of the predictors of progressive disease **[19]**. In another study of gefitinib and erlotinib in patients with recurrent and metastatic squamous cell carcinoma of the head and neck, EGFR TKI–induced diarrhea was associated with clinical benefit and also an association with more favorable overall survival **[20]**. In afatinib lung cancer trials, a trend toward a higher rate of progression-free survival was observed in patients who had Grade 2 or greater diarrhea in the first 28 days of treatment with afatinib compared with patients who experienced no AEs **[21]**.

Currently, prophylactic loperamide is often given to prevent diarrhea with other EGFR-directed therapies **[22]**. In addition, based on our experience from a recently completed Phase 2 breast cancer study, it is estimated that the average body size of US patients will be larger than that of the average Korean patient. Therefore, to address the expected issues with acute diarrhea in this study, prophylactic loperamide will be administered with the 24 mg starting dose of poziotinib **(Section 5.4.10.1)**, which was not required in the Korean studies. In addition, intermittent dosing rather than continuous dosing will be used to also help address the more chronic toxicities of rash and stomatitis. Supportive care for mucositis/stomatitis will also be provided, aiming to control symptoms for all patients during the study.

In Phase 1 studies, 18 mg/day was the maximum tolerated dose for continuous dosing, and 16 mg/day was the recommended dose for continuous dosing. Based on the tolerability of poziotinib in patients in this study so far and the previous data, two additional cohorts with lower doses and continuous dosing are being added to this protocol amendment. No new patients will be enrolled into the original 24 mg per day with intermittent dosing cohort (**Cohort 1**) and new patients will be enrolled into **Cohort 2** (16 mg/day, continuous dosing). If patients are unable to tolerate the dosing regimen in **Cohort 2**, new patients will be enrolled into **Cohort 3** (12 mg/day, continuous dosing). These changes are being made in order to improve patient tolerability while maintaining consistent drug exposure.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To establish the dosing schedule for poziotinib to be used in the clinical development program
- To evaluate the **Objective Response Rate (ORR)** of poziotinib in patients with HER2-positive metastatic breast cancer (MBC)

2.2 Secondary Objectives

- To assess the safety and tolerability of poziotinib in patients with HER2-positive MBC
- To evaluate the pharmacokinetics of poziotinib in patients with HER2-positive MBC
- To evaluate other efficacy variables of poziotinib in patients with HER2-positive MBC, including the following:

- **Progression-Free Survival** (**PFS**)
- **Disease Control Rate** (**DCR**)
- **Time to Progression** (**TTP**)

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a Phase 2, open-label, multicenter study to establish the dose regimen and evaluate the preliminary efficacy and the safety / tolerability of poziotinib in approximately 75 patients with HER2-positive MBC who have received at least two prior HER2-directed treatment regimens including trastuzumab and T-DM1.

The **Screening** period (**Day -30 to Day -1**) lasts up to approximately 30 days prior to **Cycle 1, Day 1**. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to undergoing any study procedures.

Each treatment cycle is 21 calendar days in duration. Eligible patients will be enrolled into each dose cohort as described below. In Amendment 1, in addition to the original 24 mg cohort (**Cohort 1**), two additional treatment cohorts were added.

- **Cohort 1:** 24 mg (three 8-mg tablets once daily) for 2 weeks, rest 1 week (ENROLLMENT COMPLETE)
- **Cohort 2:** 16 mg (two 8-mg tablets once daily) continuous dosing
- **Cohort 3:** 12 mg (one 8-mg tablet and two 2-mg tablet once daily) continuous dosing

Patient enrollment in **Cohort 1** is complete. New patients will begin enrollment into **Cohort 2**. Rules for safety review and enrollment for **Cohort 2** and **Cohort 3** follow:

Cohort 2:

- Rate of Grade 3 or greater AEs of special interest (ie, diarrhea, skin rash, stomatitis) that are identified during Safety Data Review after the first 6 patients and again after 12 patients have completed **Cycle 1**:
  - **>33%**: Stop **Cohort 2** (≥3 of 6 or ≥5 of 12 patients with Grade 3 or above AE of special interest) and begin **Cohort 3**
  - **≤33%**: Keep enrolling **Cohort 2** until 30 patients are enrolled and treated and no additional patients will be enrolled.

Cohort 3 - only if Cohort 2 is stopped due to toxicity:

- Rate of Grade 3 or greater AEs of special interest (ie, diarrhea, skin rash, stomatitis) are identified during Safety Data Review after the first 6 patients and again after 12 patients have completed **Cycle 1**:
- **>33%:** End enrollment in **Cohort 3**
- **≤33%:** Keep enrolling **Cohort 3** until 20 patients are enrolled and treated

Toxicity will be assessed based on the grade of the adverse events using CTCAE version 4.03.

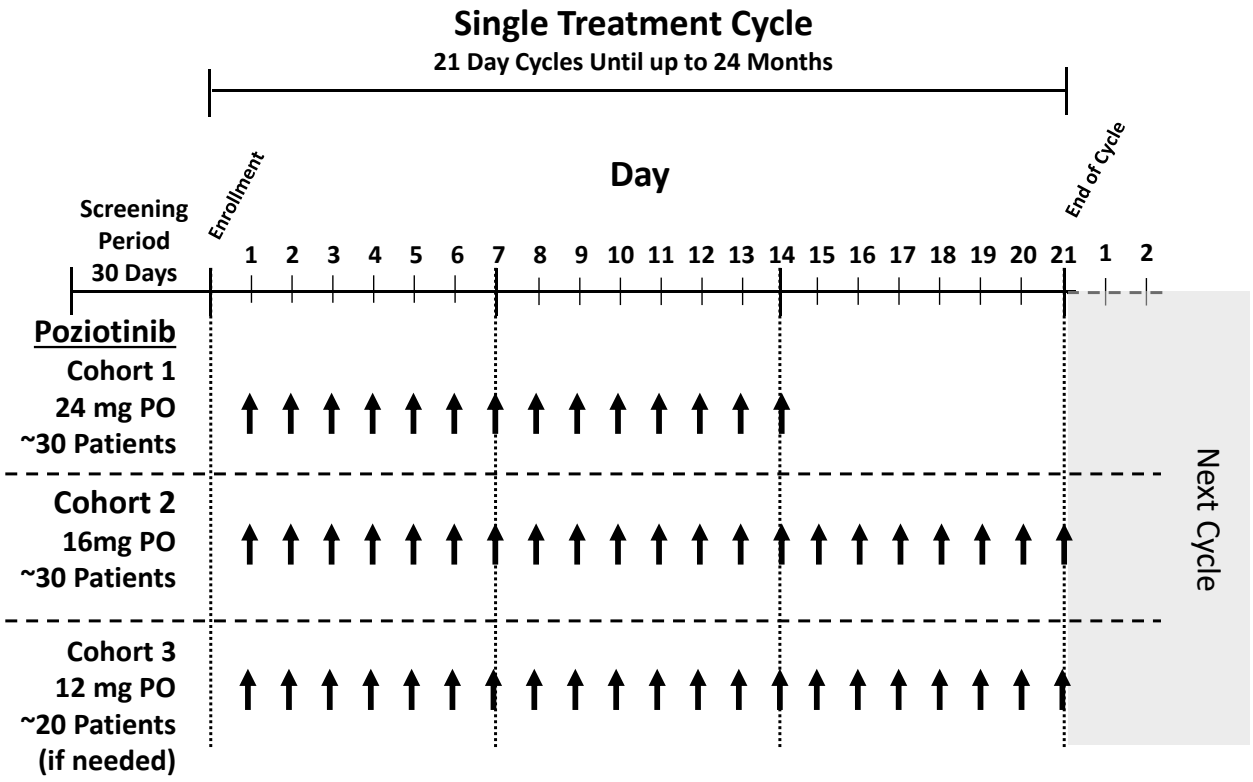
All treatments will be taken orally, once daily (QD) at approximately the same time each morning. On **Day 1** of each cycle, the patient's absolute neutrophil count (ANC) must be

≥1.0×10^9/L and platelet count must be ≥100×10^9/L before administering poziotinib. For **Cycle 1** and **Cycle 2** only, the ANC and platelet count should also be confirmed prior to the dose on **Day 8**. **Day 1** of a new cycle is equivalent to **Day 22** of the previous cycle, with a window of ±3 days for the visit. If a visit is delayed during 1 cycle, then all subsequent cycles will be delayed sequentially.

All patients will be treated until disease progression, death, intolerable adverse events, or up to a maximum of 24 months, whichever comes first.

The study design diagram is presented in **Figure 2,** and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

Figure 2 Study Design Diagram



3.2 Study and Treatment Duration

The total duration of the study will be approximately 3 years. The duration of study participation for each patient includes the following segments:

- **Screening Period:** 30 days
- **Treatment Period:** 21 days per cycle for up to 24 months
- **End-of-Treatment Visit:** 35 (±5) days after the last dose of poziotinib

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient, or patient's authorized representative, must be willing and capable of giving written Informed Consent and must be able to adhere to dosing and visit schedules as well as meet all study requirements.
2. Patient has histopathologically confirmed primary breast cancer with metastatic lesions.
3. Patient has confirmed HER2 overexpression or gene-amplified tumor via immunohistochemistry [IHC] with IHC 3+ or IHC 2+ with confirmatory fluorescence *in situ* hybridization [FISH]+.
4. At least two prior HER2-directed therapy regimen(s) for breast cancer, including trastuzumab and trastuzumab emtansine (T-DM1, KADCYLA®).
5. Patient is at least 18, and ≤90 years of age.
6. Patient has adequate hematologic, hepatic, and renal function, as defined by:
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.
   - Platelet count $\geq 100 \times 10^9$/L
   - Hemoglobin ≥9 g/dL
   - Total bilirubin ≤1.5 mg/dL, if hepatic metastases are present, ≤2.5 mg/dL
   - Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), and gamma-glutamyltransferase (GGT) ≤2.5×upper limit of normal (ULN); if hepatic metastases are present ≤5.0×ULN
   - Creatinine ≤2.2 mg/dL or calculated creatinine clearance ≥40 mL/min
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Life expectancy is more than 6 months.
8. Patient has measurable disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).
9. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method, from study entry until at least 30 days after the last dose of poziotinib.
10. Females of childbearing potential must have a negative pregnancy test within 30 days prior to enrollment. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or who are surgically sterilized do not require this test.

4.2 Exclusion Criteria

1. Patient has had previous treatment with poziotinib prior to study participation.
2. Patient has brain metastases that are symptomatic or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids, to control symptoms from brain metastases within 15 days of enrollment.
3. Patient has received anticancer chemotherapy, biologics, immunotherapy, cure-intent radiotherapy, or investigational treatment within 15 days, except for hormone therapy, palliative therapy, or supportive therapy.

4. Patient has a history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association Functional Classification or serious cardiac arrhythmias requiring treatment.
5. Patient has a cardiac ejection fraction <50% by either echocardiogram or multi-gated acquisition (MUGA) scan.
6. Patient has a history of other malignancies within the last 5 years, except for non-melanoma skin cancer or carcinoma *in situ* of the cervix.
7. Patient is confirmed to have clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as a main symptom (ie, acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) Grade 2 or above diarrhea due to other etiologies).
8. Patient is unable to take drugs orally due to disorders or diseases that may affect gastrointestinal functions, such as inflammatory bowel diseases (eg, Crohn's disease, ulcerative colitis) or malabsorption syndrome, or procedures that may affect gastrointestinal functions, such as gastrectomy, enterectomy, or colectomy.
9. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver diseases).
10. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
11. Patient has active bleeding disorders, uses warfarin or other coumadin-derived anticoagulants, has abnormal International Normalized Ratio (INR), or abnormal prothrombin time test within one month prior to the study.
12. Patient is pregnant or breast-feeding.

4.3 Patient Discontinuation/Withdrawal Criteria

Patients can withdraw from participation in this study at any time, for any reason, specified or unspecified, and without prejudice.

All treated patients must be withdrawn from the study at 24 months or for the following reasons:

- Development of an adverse event (AE) that interferes with the patient's participation
- Initiation of non-protocol therapy
- Development of progressive disease (PD)
- Patient withdrawal of informed consent
- Delay of poziotinib administration for >42 days since last study drug administration
- Investigator decision
- Sponsor decision
- Lost to follow-up
- Pregnancy
- Death

The reason for the patient discontinuing study treatment or terminating from the study must be recorded on the case report form (CRF). Patients who discontinue treatment or who are

withdrawn from treatment will return for an **End-of-Treatment Visit** 35 (±5) days after the last dose of poziotinib or prior to beginning a new treatment, whichever is first.

5 STUDY PROCEDURES

The study design diagram is presented in **Figure 2,** and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

5.1 Screening

Informed Consent is to be obtained prior to the start of any protocol-specified assessments or procedures. The procedures and evaluations required for enrollment into the study are summarized below. All potential study patients will be screened and eligibility determined prior to enrollment. The results of any procedures or laboratory assessments performed prior to the signing of Informed Consent as part of the site's routine standard of practice will be allowed for use as a Screening Assessment at the discretion of the Sponsor. This information is to be discussed with the Medical Monitor before the patient is enrolled in the study. All procedures are to be performed as outlined in **Appendix 1** prior to the start of study treatment, unless otherwise noted.

5.2 Patient Assignment

Each patient who signs an Informed Consent Form for participation in this study will be assigned a unique screening number according to the instructions in the study binder.

Confirmation of eligibility is to be received by the investigational site from Spectrum prior to enrollment of a patient. After a patient has signed the ICF, the Investigator or site staff should assign a Patient ID. The Patient ID will include two parts: the site number assigned by Spectrum will be comprised of 5 digits with a 2-digit alphabetic country code [Reference ISO 3166] followed by a 3-digit site specific numeric code and a 3-digit patient sequential number, unique to a site, separated by a hyphen (ie, [redacted]).

A CRF will only be completed for patients who are enrolled and receive a Patient ID.

5.3 Timing of Assessments and Procedures

5.3.1 Screening (Day -30 to Day -1)

The following screening assessments should be performed within 30 days of **Cycle 1, Day 1**. Obtain Informed Consent prior to any study procedures.

- Informed Consent
- Relevant medical history
- Demographic data
- Height and weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment

- Complete blood count (CBC) with 5-part differential and platelets prior to poziotinib administration (may be obtained up to 7 days prior to **Cycle 1**, **Day 1**)
- Prothrombin time/International Normalized Ratio (as needed, and only for those patients who may have bleeding disorders and are using warfarin or other coumadin-derived anticoagulants)
- Serum biochemistry prior to poziotinib administration (may be obtained up to 7 days prior to **Cycle 1**, **Day 1**)
- Pregnancy test (urine beta-human chorionic gonadotropin [β-HCG]) in women of childbearing potential
- Echocardiogram or MUGA scan to evaluate cardiac ejection fraction
- Tumor histopathology report (from local pathologist)
- Tumor assessment (may be obtained prior to signing of IC and may be used for **Screening** purposes as long as it is performed prior to **Cycle 1**, **Day 1**; consultation with the Sponsor is required)
- Hormone-receptor status, including ER, PR and HER2, number of nodes, and stage
- Adverse event assessment using NCI CTCAE, version 4.03, record AEs related to study procedures only
- Concomitant medications

5.3.2 Treatment Period – Cycle 1, Day 1

- Eligibility confirmation
- Patient ID
- Height and weight
- Physical examination
- Vital signs
- ECOG Performance Status assessment
- Pharmacokinetic blood sampling:
  - Sparse PK blood sampling taken pre-dose and at 1 hour and 2 hours (±15 min) post-dose

    OR
  - Intensive PK blood sampling pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose (**if consented**)
- Dispense poziotinib and loperamide
- Adverse event assessment using NCI CTCAE, version 4.03, record AEs related to study procedures only
- CBC with 5-part differential and platelets
- Dispense Patient Diary
- Concomitant medications review

5.3.3 Treatment Period – Cycle 1, Day 8 (±1 Day)

- Complete blood count with 5-part differential and platelets
- Adverse events using NCI CTCAE, Version 4.03, record AEs related to study procedures only
- Patient Diary Collection
- Concomitant medications

5.3.4 Treatment Period – Cycle 1, Day 14 (±3 Days) (Cohort 1 only)

- Sparse PK blood sampling collected pre-dose
- Adverse event assessment using NCI CTCAE, Version 4.03, record AEs related to study procedures only (**Cohorts 2 and 3 by telephone**)
- Concomitant medications (**Cohorts 2 and 3 by telephone**)

5.3.5 Treatment Period – Cycle 2, Day 1

- Weight
- Physical examination
- Vital Signs
- ECOG Performance Status assessment
- Complete blood count with 5-part differential
- Serum biochemistry
- Sparse pharmacokinetic blood sampling taken pre-dose and at 1 hour and 2 hours (±15 min) post-dose
- Dispense poziotinib
- Adverse event assessment using NCI CTCAE, Version 4.03, record AEs related to study procedures only
- Patient Diary Collection
- Concomitant medications

5.3.6 Treatment Period – Cycle 2, Day 8 (±1 Day)

- Complete blood count with 5-part differential and platelets
- Adverse event assessment using NCI CTCAE, Version 4.03, record AEs related to study procedures only
- Patient Diary Collection
- Concomitant medications

5.3.7 Treatment Period – Cycle 3+, Day 1 (up to 24 months)

- Height and weight
- Physical examination
- Vital Signs

- ECOG Assessment
- Tumor assessment (to be performed after **Cycle 2**, and approximately every 6 weeks thereafter)
- Serum biochemistry
- Echocardiogram or MUGA scan to evaluate cardiac ejection fraction (3 months after the first treatment and then every 6 months thereafter, during treatment)
- Sparse pharmacokinetic blood sampling taken pre-dose and at 1 hour and 2 hours (±15 min) post-dose (**Cycle 3** only)
- Dispense poziotinib
- Adverse event assessment using NCI CTCAE, Version 4.03, record AEs related to study procedures only
- Patient Diary Collection
- Concomitant medications

5.3.8 End-of-Treatment Visit (35 [±5] Days Post-Study Treatment)

The **End-of-Treatment Visit** is required 35 (±5) days after the last dose of poziotinib is administered. The following assessments are to be performed at this visit:

- Physical examination
- Vital signs
- ECOG Performance Status assessment
- Tumor assessment (unless the patient has documented disease progression or has undergone a tumor assessment within the previous 6 weeks)
- CBC with 5-part differential and platelets
- Serum biochemistry
- Echocardiogram or MUGA scan to evaluate cardiac ejection fraction
- Adverse event assessment
- Patient Diary Collection
- Concomitant medications

5.4 Description of Study Assessment Parameters

5.4.1 Relevant Medical History

At **Screening**, the patient's relevant medical history will be collected, to include the history of breast cancer, documentation of HER2 genetic confirmation, previous therapy, as well as significant and relevant past diseases and current medications.

5.4.2 Physical Examination

A complete physical examination, including a description of external signs of the neoplastic disease and co-morbidities, will be performed at **Screening** and **Day 1** of each cycle, and at the **End-of-Treatment Visit**. Symptom-directed examinations are required at other visits. Physical examinations are to be completed by a physician or other health professional licensed to perform

such examinations. Findings will be documented in the patient's medical record and on the appropriate CRF pages. Any abnormalities are to be recorded on the AE CRF.

5.4.3 Vital Signs

Vital signs, to include temperature, blood pressure, heart rate, and respiratory rate, are to be recorded at **Screening** and **Day 1** of each cycle and at the **End-of-Treatment Visit**. Heart rate and blood pressure will be recorded before poziotinib administration.

5.4.4 ECOG Performance Status

Patients' Performance Status will be evaluated using criteria as developed by the Eastern Cooperative Oncology Group (**Appendix 2**) at **Screening** and **Day 1** of each cycle and at the **End-of-Treatment Visit**.

5.4.5 Clinical Laboratory Tests

A local laboratory will be used to process all clinical specimens. The following clinical laboratory parameters will be evaluated in this study:

- **Complete Blood Count (CBC):** A CBC, including white blood cells (WBC), with 5-part differential, hemoglobin, and platelets will be performed at **Screening**, **Day 1** and **Day 8** of **Cycle 1** and **Cycle 2**, **Day 1** of subsequent cycles, and at the **End-of-Treatment Visit**. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician before the start of each cycle.
- **Prothrombin Time (PT) and International Normalized Ratio (INR):** Only for patients with active bleeding disorders or use warfarin or other coumadin-derived anticoagulants a PT/INR need to be evaluated at **Screening**.

  Use of warfarin or other coumadin-derived anticoagulants should be avoided during treatment with poziotinib. When it cannot be avoided, regular monitoring of INR is required and prior authorization from study medical monitor is required.
- **Chemistry Panel:** A comprehensive chemistry and electrolytes, including blood urea nitrogen (BUN), AST/SGOT, ALT/SGPT, alkaline phosphatase (ALP), GGT (only at screening), total bilirubin, albumin, calcium, lactate dehydrogenase, sodium, potassium, chloride, phosphate, magnesium, creatinine, uric acid, and glucose, will be performed at **Screening**, **Day 1** of each cycle, and at the **End-of-Treatment Visit**.
  - **Special note for the Day 1 sampling of each cycle:** If possible, blood samples should be drawn on **Day 1** of each cycle (prior to treatment); however, for logistical reasons, it is also acceptable to draw samples for assessment up to 7 days prior to the start of a cycle. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician before the start of each cycle.
- **Pregnancy Test:** A urine β-hCG test will be performed at **Screening** for all women of childbearing potential.

5.4.6 Pharmacokinetics

All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose for sparse PK sampling on **Day 1** of **Cycles 1**, **2**, and **3** and pre-dose on **Day 14** (±3 days) of **Cycle 1** (**Cohort 1** only).

If consented, intensive PK samples will be drawn pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose on **Day 1** of **Cycle 1**. In addition, if a patient presents with a potentially drug-related SAE at any time during the study, PK samples may be collected during the clinic visit for PK analysis.

5.4.7 Cardiac Ejection Fraction

Cardiac ejection fraction will be assessed by either echocardiogram or multi-gated acquisition (MUGA) scan at **Screening**, 3 months after first treatment, then every 6 months thereafter, while the patient is being treated, and at the **End-of-Treatment Visit**.

5.4.8 Tumor Assessment

Tumor assessment must be performed by Investigators using computed tomography (CT) or magnetic resonance imaging (MRI) at **Screening** up to 30 days prior to **Cycle 1**, **Day** 1. Imaging studies performed prior to the signing of Informed Consent as part of the site's routine standard of practice are allowed at the discretion of the Sponsor. This information is to be discussed with the Medical Monitor before the patient is enrolled in the study.

Tumor assessments will be performed every 6 weeks (±14 days) until disease progression, death, intolerable adverse events, or for up to 24 months.

Each subsequent tumor assessments must use the same Baseline radiologic technique, either CT or MRI. Tumor assessments will be made according to RECIST criteria, Version 1.1 **[23]** using appropriate radiologic imaging or other techniques. For radiographic assessment, CT or MRI must be performed at every assessment.

Measurable and non-measurable lesions that will not be followed by radiological methods should be documented appropriately.

5.4.9 Confirmation of Diagnosis of HER2-Positive Breast Cancer

Confirmation of HER2 overexpression or gene-amplified tumor via immunohistochemistry (IHC) with IHC 3+ or IHC 2+ with confirmatory fluorescence *in situ* hybridization (FISH) is required.

5.4.10 Concomitant Medications

All medications administered from **Screening** to the **End-of-Study Visit** will be recorded on the CRF. A concomitant medication is any medication a patient is using from **Day 1** of **Cycle 1** to the **End-of-Study Visit**. The study drugs are not considered concomitant medications.

All concomitant medications recorded at study entry must have a related, ongoing concomitant illness listed under the medical history at the time of patient entry into the trial unless the medication is used for prophylaxis. Patients may continue to use any ongoing medications not prohibited by the protocol.

All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue until 35 (±5) days after the last dose of study drug.

Premedications (such as antiemetics) used for supportive care are allowed as per institutional standards or guidelines.

Endocrine or hormonal therapy for hormonal receptor positive breast cancer is allowed.

Other supportive and palliative therapies may be allowed during the study upon prior authorization from study medical monitor.

5.4.10.1 Premedication and Supportive Treatment

All patients will receive prophylaxis with loperamide. Loperamide will be supplied by Sponsor and is to be taken by all patients on the following schedule:

- **Days 1** to **56**: 4 mg two times a day (bid), or three times a day (tid) if needed
- **Days 56 until end of treatment**: 4 mg taken as needed, but not to exceed 16 mg/24 hours

Patients should also receive prophylactic mouth care to prevent possible mucositis and or stomatitis during poziotinib treatment.

Mucositis/stomatitis should be treated in a supportive manner aiming to control symptoms. Prophylactic methods to reduce or prevent mucositis/stomatitis include:

- Avoidance of spicy, acidic, or irritating foods and alcoholic drinks
- Use of solutions such as saline (diluted solution with salt water and baking soda by dissolving ½ teaspoon of salt and 1 teaspoon of baking soda in approximately 1 liter of water) and using this solution every 4 hours
- Use of Nystatin solution
- Use of Magic Mouthwash (for instance, combination of viscous lidocaine 2% + Mylanta + diphenhydramine elixir + prednisolone solution)

Pre-medications (including, but not limited to antiemetics), as per Institutional standard of care, should be administered before poziotinib on **Day 1**.

5.4.10.2 Uses of Warfarin or Other Coumadin-Derived Anticoagulants

Use of warfarin or other coumadin-derived anticoagulants should be avoided during treatment with poziotinib. When it cannot be avoided, regular monitoring of INR is required and prior authorization from study medical monitor is required.

5.4.10.3 Other Anticancer Therapies

No additional cytotoxic agents, biologic therapy, or immune response modifiers for cure-intent purpose are to be administered to patients until study treatment has been discontinued.

5.4.10.4 Prohibited Therapies or Medications

No other anti-cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or experimental medications, are permitted during the trial. Any disease progression that requires anti-tumor therapy will be cause for discontinuation from the study.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

Study treatment is to be handled and administered according to the study sites' regulations for the handling and administration of cytotoxic anticancer agents.

6.1 Poziotinib

Poziotinib will be supplied by Spectrum.

6.1.1 Poziotinib Composition

The poziotinib drug substance is a hydrochloride salt of poziotinib and is formulated as a tablet for oral administration.

6.1.2 Poziotinib Supply and Labeling

Poziotinib tablets are supplied in 2.0-mg and 8.0-mg dose strengths, and contain 2.0 mg and 8.0 mg of poziotinib hydrochloride salt, respectively.

6.1.3 Poziotinib Administration

Poziotinib is supplied as 8-mg and 2-mg tablets and will be administered orally once daily at approximately the same time each morning according to the schedule for each cohort during each 21-day cycle. If the morning dose is missed, this dose may be administered any time during the day, at least 8 hours prior to the next scheduled dose.

- **Cohort 1**: 24 mg (three 8-mg tablets) for 14 days and then 7 treatment-free rest days
- **Cohort 2**: 16 mg (two 8-mg tablets) once daily continuously
- **Cohort 3**: 12 mg (one 8-mg tablet and two 2-mg tablets) once daily continuously

6.1.4 Poziotinib Storage and Handling

Poziotinib supplies must be stored in a secure, limited-access location under the storage conditions specified on the drug supply label.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

6.1.5 Poziotinib Dose Modifications

- After the first occurrence of an AE Grade ≥3, the dose of poziotinib will be temporarily withheld. Once the event has recovered to Grade ≤1, the treatment can resume at the same dose.
- If the same AE occurs a second time (Grade ≥3), the dose of poziotinib will be reduced.
- No dose reductions below 12 mg/day will be allowed.

An algorithm for poziotinib dose modification is provided in **Table 2**.

Table 2 Poziotinib Dose Modifications

Adverse Event	Grade	1st Occurrence	2nd Occurrence	3rd Occurrence
Diarrhea	Grade ≥3 (Despite adequate anti-diarrheal prophylaxis and/or treatment) Grade ≥2 for ≥48 hours (Despite adequate anti-diarrheal prophylaxis and/or treatment)	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg → 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
Rash	Grade ≥3	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg→ 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
Nausea and/or Vomiting	Grade ≥3 (Despite adequate anti-emetics) Grade ≥2 for ≥48 hours (Despite adequate anti-emetics)	Poziotinib Dose stays the same	Poziotinib Dose Reduced: 24 mg → 16 mg 16 mg → 12 mg 12 mg dose - discontinue treatment	Poziotinib Dose Reduced: 16 mg → 12 mg 12 mg dose - discontinue treatment
LVEF Dysfunction	Grade ≥3	Discontinue Treatment		

6.2 Comparator Treatment

No comparator is used in this study.

7 SAFETY ASSESSMENT

7.1 Safety Measures

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to study drug or clinical significance. The decision to modify the dose of study treatment will be determined by the Investigator based on the decision rules shown in **Section 6.1.5**.

Safety data will also be reviewed on a regular basis by Spectrum's study monitoring team, which includes a Clinical Research Associate (CRA), Medical Monitor, and other personnel from the company or its designee.

Adverse events will be characterized by intensity (severity), causality, and seriousness by the Investigator based on the regulatory definitions included below.

This study will utilize the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 4.03 for AE grading.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A treatment-emergent AE (TEAE) is any AE that occurs from the first dose of study treatment until 35 (±5) days after the last dose of study treatment.

The study will record all AEs according to the information in **Section 7.3**.

Examples of AEs **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.
- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures, ie, invasive procedures.

Abnormal laboratory results are to be recorded as AEs, if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention.
- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- The abnormal laboratory value is predefined as an AE in the protocol or in another document communicated to the Investigator by Spectrum or designee.

Examples of events that **do not** constitute AEs include:

- Medical or surgical procedures (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence does not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease.

The adverse events of special interest identified with poziotinib treatment in this study include diarrhea, skin rash, oral cavity mucositis/stomatitis, fatigue, and vomiting/nausea.

7.3 Guidelines for Recording and Attribution Scoring of Adverse Events

Timely and complete reporting of all AEs is required for all patients. Monitoring and documentation of all AEs allows for identification of potential study-drug or dose-related AEs, and for adherence to regulatory requirements. Please refer to the CRF Completion Guidelines located in the study binder for detailed instructions for AE reporting.

7.3.1 Recording of Adverse Events

All AEs that occur from the first dose of study treatment through 35 (±5) days after the last dose of study treatment is administered are to be recorded on the AE CRF. From the time the study Informed Consent is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded.

The resolution of all AEs must be recorded at the end of the study. The following conventions will be followed when patient completes or discontinues from the study:

- If a patient dies, the date of death should be the date of AE stop for all ongoing AEs at the time of death.
- If a patient discontinues due to an AE(s), the outcome of the AE is to be followed for 35 (±5) days from the date of discontinuation or until the AE has returned to Grade ≤1. The status of the AE and the date of last contact with the patient will be captured. If the AE has not returned to Grade ≤1 by the end of the study, the AE stop date should be left as ongoing.

All AEs will be classified by intensity/severity (**Section 7.3.2**), relationship to study drug (**Section 7.5**), and as serious or nonserious (**Section 7.7**) by the Investigator.

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale, Version 4.03 for AE grading.

7.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values are to be followed up in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (eg, United States [US] Code of Federal Regulations [CFR]).

7.5 Relationship

The Investigator must make a causality assessment and document their opinion as to the relationship of all AEs and SAEs to study treatment (**Table 3**).

Table 3 Investigator Assessment of Adverse Event Causality

Relationship	Description
Not Related	The event is clearly related to factors other than study treatment, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Unlikely Related	The temporal association, patient history and/or circumstances are such that the study drug or treatment is not likely to have had an association with observed event.
Possibly Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and/or follows a known response pattern to study treatment, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Probably Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Definitely Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.

In addition, the event either occurs immediately following study treatment administration, improves on stopping study treatment, reappears on repeat exposure, or there is a positive reaction at the application site.

7.6 Expectedness

For investigational drugs, an AE is judged "expected" if its description agrees in nature and severity with the description of AEs previously noted with the study drug as detailed in the current Investigator's Brochure. An "unexpected" AE is one for which the specificity or severity is neither consistent with the current Investigator's Brochure nor the risk information described in the general investigational plan. The Sponsor will be responsible for assessing the expectedness of AEs.

The most common AEs associated with poziotinib treatment include:

- Diarrhea
- Rash
- Stomatitis
- Fatigue
- Vomiting
- Decreased Appetite
- Dry Skin
- Nausea

7.7 Serious Adverse Events

In the interest of patient care and to allow Spectrum to fulfill all regulatory requirements, any SAE, regardless of causal relationship to study treatment, is to be reported to the Sponsor within 24 hours of knowledge of the event. SAEs are defined (21 CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death.
- Is life-threatening: ie, any event that, in the opinion of the Investigator, poses an immediate risk of death from that event.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs).
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Includes important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in this definition.

Adverse events that do not meet any of the above criteria for serious should be regarded as non-serious.

7.7.1 Serious Adverse Event Reporting

From the time the study Informed Consent is signed through the first dose of study drug administration, only SAEs that are related to study procedures are to be recorded. All SAEs that occur from the first dose of study drug administration through 35 (±5) days after the last dose of study treatment are to be reported to Spectrum within 24 hours of knowledge of the event.

SAEs (regardless of their relationship to study treatment) are to be reported and the serious adverse event report (SAER) faxed or e-mailed within 24 hours of knowledge of the event to:

Spectrum Pharmaceuticals, Inc.
Primary Contact: Pharmacovigilance Department
Fax: [redacted]
E-mail: [redacted]

Spectrum may request additional information from the Investigator to ensure the timely completion of accurate safety reports. Safety data that are critical to the reportability of an SAE, such as causality assessment and serious criteria, should be included in the initial faxed or e-mailed SAER. If omitted, a timely response to drug safety data queries received from Spectrum or designee is expected.

The Investigator is to take all appropriate therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE are to be recorded in the concomitant medication section of the patient's CRF.

SAEs that are study-treatment related will be followed until resolution or until they have returned to Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Additionally, the SAE is to be entered in the AE section of the CRF. Follow-up SAERs need to be submitted to Spectrum within 24 hours, once additional information regarding the event becomes available (eg, final diagnosis is made, laboratory or test results, event course, outcome, etc).

The Sponsor or its designee will be responsible for reporting SAEs to the regulatory authorities in accordance with applicable expedited reporting regulatory guidelines. The Investigator is responsible for submitting SAEs to his/her Institutional Review Board (IRB)/Ethics Committee (EC). Copies of each SAER, and documentation of IRB/EC notification and acknowledgement of receipt, will be kept in the Site's Regulatory Binder.

7.7.2 Exclusions to Serious Adverse Event Reporting Requirements

The following are not considered SAEs:

- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital, hospitalization for diagnostic tests such as CT scans).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to first study treatment administration that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease.

7.8 Reproductive Risks

No adequate and well-controlled studies of poziotinib have been conducted in pregnant women. The effect of poziotinib on fertility and fetal development have not been studied in pregnant women. Poziotinib is not recommended for use during pregnancy.

Any pregnancy involving a study patient or a patient's partner that occur from the first dose of study treatment through 30 days after the last dose of study treatment is to be reported to the Sponsor within 24 hours after the Investigator has gained knowledge of the event via fax or e-mail (see contact information in **Section 7.7.1**). Pregnancies should be followed up until outcome and follow-up information regarding the outcome of the pregnancy should be faxed or e-mailed to Spectrum's Pharmacovigilance Department.

All patients who become pregnant during participation in this study are to be withdrawn from the study.

8 STATISTICAL PLAN

This section contains a brief overview of the statistical analyses planned for this study. A formal statistical analysis plan (SAP), providing full technical details, will be finalized prior to database lock.

8.1 Sample Size

Other important treatments for HER2-positive MBC include T-DM1, lapatinib-capecitabine combination, and neratinib. Published ORRs reported for these regimens are 43.6%, 30.8%, and 24%, respectively **[22, 24-25]**. The purpose of this study is to evaluate the safety and efficacy of poziotinib and identify the optimal dose for future clinical development. No statistical hypothesis testing will be performed.

The enrollment into **Cohort 1** is now complete. A total of 32 patients have received treatment of poziotinib in **Cohort 1**. A total of 30 patients are expected to be enrolled and treated in **Cohort 2**. If the enrollment in **Cohort 2** is stopped due to toxicity, new patients will be enrolled into **Cohort 3**. A total of 20 patients will be enrolled in **Cohort 3**.

8.2 Method of Treatment Assignment

This study is not randomized. Patients will be enrolled sequentially.

8.3 Analysis Populations

Two analysis populations have been defined as follows:

- The **Evaluable Population (EP)** consists of all patients who are enrolled, complete at least one cycle of poziotinib treatment, and have at least one post-baseline tumor response evaluation using RECIST, Version 1.1.
- The **Safety Analysis Population (SAF)** includes all patients who signed informed consent, enrolled, and received at least one dose of study treatment. All demographics, Baseline characteristics, and safety data will be analyzed using the **SAF** population.

8.4 General Statistical Methods

The Sponsor's Biostatistics and Data Management (BDM) group will be responsible for data management and statistical analysis of this study. All statistical analyses will be performed using SAS for Windows (version 9.3 or higher). Patient data listings and tabular presentations of results will be provided. Further details of the criteria and conduct of the statistical analyses will be included in the SAP for this study.

8.5 Efficacy Analyses

8.5.1 Primary Endpoint

The primary efficacy variables, as described below, will be summarized and analyzed descriptively, along with 95% CI, for each cohort.

- **Objective Response Rate** (**ORR**) will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, version 1.1 **[23]** and is defined as the best response [Complete Response (**CR**) + Partial Response (**PR**)] recorded from the start of the study until the end of study in patients who received at least 1 dose of poziotinib. The ORR will be based on the EP.

8.5.2 Secondary Endpoints

- **Safety, including adverse events and pharmacokinetics**
  - **Safety and adverse events:** Safety will be assessed by reported/elicited AEs, laboratory assessments including hematology and biochemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.
  - **Pharmacokinetics:** All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose for sparse PK sampling on **Day 1** of **Cycles 1**, **2**, and **3** and pre-dose on **Day 14** (±3 days) of **Cycle 1** (**Cohort 1** only). If consented, intensive PK samples will be drawn pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose on **Day 1** of **Cycle 1**. In addition, if a patient presents with a potentially drug-related SAE, PK samples may be collected during the clinic visit for PK analysis.
- **PFS** is defined as the number of days from the treatment start date to the date of documented disease progression or death due to any cause. Disease progression will be determined by RECIST Version 1.1.
- **DCR,** including CR, PR, and Stable Disease (SD), will be assessed using RECIST, version 1.1 and defined as the proportion of subjects who achieve CR, PR, and SD by the best response from the first dose of poziotinib to the end of study.
- **TTP** is defined as the period of time from the first dose of study drug to tumor progression, which excludes death without tumor progression, by the end of study.

The secondary efficacy variables of **PFS**, **DCR**, and **TTP** will be analyzed descriptively, for each cohort.

8.6 Safety Analysis

The overall incidence of treatment-emergent AEs (TEAE) (ie, AEs occurring from the time the first dose of the study drug until 35 (±5) days after the last dose) and the proportion of patients who discontinue because of a TEAE are the primary safety outcome measures. The number and percent of patients with new-onset TEAEs will be summarized by the MedDRA (version 17) system-organ-class (SOC) level and Preferred Term for all treated patients, for each cohort. The summary of TEAEs will be presented in the following categories:

- Number and percentage of patients with any TEAEs by SOC and Preferred Term.
- Number and percentage of patients with any SAEs by SOC and Preferred Term.
- Number and percentage of patients with related TEAEs by SOC and Preferred Term.
- Number and percentage of patients with TEAEs causing discontinuation of the study by Body System and Preferred Term.

In addition, the number and percent of patients with TEAEs by grade will be summarized. Adverse events reported prior to treatment but after IC will be provided in a listing.

Finally, the number of completed cycles will also be summarized and analyzed descriptively.

8.7 Clinical Laboratory Evaluations

Key laboratory parameters will be summarized using shift tables, which display a cross-tabulation of the Baseline grade versus the highest on-study grade for each laboratory parameter, for each cohort.

All laboratory abnormalities will be classified according to NCI CTCAE, Version 4.03 and summarized by worst grade severity and by treatment.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator Responsibilities

The study will be monitored by employees or representatives of Spectrum. CRAs will monitor each site on a periodic basis and perform verification of source documentation for each patient as well as other routine compliance reviews. The Sponsor's Medical Monitor and Pharmacovigilance Department will review safety data and be responsible for ensuring timely reporting of expedited SAERs to regulatory agencies and Investigators.

9.1.1 Good Clinical Practice

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site. The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. By signing the US Form FDA 1572, "Statement of Investigator", the Investigator commits to adhere to applicable sections of the US CFR parts 50 "Protection of Human Patients", 54 "Financial Disclosure by Clinical Investigators", 56 "Institutional Review Boards", and 312 subpart D "Responsibilities of Sponsors and Investigators". All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

9.1.2 Institutional Review Board/Ethics Committee Approval

The Investigator shall assure that the IRB/EC will provide initial and continuing review of the study. Prior to screening and enrollment of study patients, documented IRB/EC approval of the protocol, ICF and any patient materials must be obtained and provided to Spectrum or its designee.

9.1.3 Informed Consent

The Investigator is responsible for preparing the written Informed Consent document for this study. The Sponsor or its designee will provide the Investigator with an Informed Consent template. The Investigator may rearrange or reword the contents of the template, or may add other elements or language, provided the meaning and content are not changed or deleted. The Sponsor or designee is to review and approve the Informed Consent document that is used by the Investigator for this study prior to IRB/EC submission.

Written Informed Consent will be obtained from all patients participating in this study before any procedures are conducted, in accordance with ICH GCP and current regulatory requirements. The case history for each patient is to document that the Informed Consent process was obtained prior to participation in the study. The original Informed Consent document will be kept in the patient's record, and a copy will be provided to the patient.

9.1.4 Study Files and Retention of Records

The Investigator is to retain all study records until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product as per 21 CFR 312.62 and ICH GCP E6 4.9.5 and 5.5.12. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained. If the Investigator relocates, or for any reason desires to dispose of the records, the study records may be transferred to another institution, another investigator, or to the Sponsor upon written agreement between the Investigator and the Sponsor.

9.2 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the Investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by the Sponsor access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

9.2.1 Case Report Forms

At scheduled monitoring visits, CRFs will be verified against source documentation and submitted as final data. Any subsequent changes to the CRFs are to be performed in accordance with the Sponsor's standard operating procedures for editing and clarifying CRFs. Data entry will be performed by the sites using an electronic data capture (EDC) system. Comment fields on the CRFs will be used as a means of clarification and communication between the Investigator and the Sponsor; however, comments entered in these fields will not be edited or clarified.

9.2.2 Drug Accountability

In accordance with all applicable regulatory requirements, the Investigator or designated site staff is to maintain study treatment accountability records throughout the course of the study. This person(s) will document the amount of poziotinib administered to patients. The CRA will review inventory and accountability documentation during monitoring visits.

The Investigator will not supply investigational study drugs to other investigators not listed on the US Form FDA 1572 or equivalent. Investigational study drug use, other than as directed by this protocol, is not allowed.

All unused vials of poziotinib are to be accounted for at the site and maintained in a secured, locked storage area with access limited to authorized study personnel only. Used poziotinib vials/bottles will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused vials of poziotinib may be destroyed at the site, following verification of accountability by a Spectrum representative.

9.3 Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.4 Sponsor Responsibilities

9.4.1 Safety Monitoring

The clinical drug safety of study treatment will be continuously evaluated by the study Medical Monitor or designee on an ongoing basis during the course of this clinical study. All SAEs related to study treatment in this study and all other ongoing clinical studies with study treatment will be processed in compliance with current regulatory guidelines by the Sponsor's Pharmacovigilance Department. This processing will include a formal assessment of each SAE by drug safety. In addition, a cumulative review of all SAEs from all sources will be assessed periodically.

9.5 Joint Investigator/Sponsor Responsibilities

9.5.1 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor is to have direct access to the patient's source documentation in order to verify the data recorded in the CRFs. The CRA is responsible for routine review of the CRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor is to have access to any patient records needed to verify the entries on the CRFs, as well as access to all other study-related documentation and materials. The Investigator agrees to provide the monitor with sufficient time and facilities to conduct monitoring, and to cooperate with the monitor to ensure that any problems detected in the course of these monitoring/auditing visits are resolved.

9.5.2 Termination of the Study

For reasonable cause, either the Investigator or the Spectrum may terminate the Investigator's participation in this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement (CTA). In addition, the Sponsor may terminate the study at any time upon immediate notice for any reason, including but not limited to, Spectrum's belief that termination is necessary for the safety of patients.

9.5.3 Publication Policy

To coordinate the dissemination of data from this study, the Sponsor encourages the formation of a publication committee consisting of the principal investigator and appropriate Spectrum staff. The committee is expected to solicit input and assistance from other investigators and Sponsor staff as appropriate. Membership on the committee (both for investigators and Sponsor staff) does not guarantee authorship – the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirements for Manuscript Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on the following; authors should meet all three conditions:
    1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
    2. Drafting the article or revising it critically for important intellectual content

3. Final approval of the version to be published.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.
- All publications (eg, manuscripts, abstracts, oral/slide presentations, books chapters) based on this study must be submitted to the Sponsor for corporate review.

9.6 Confidentiality

All information provided to the Investigator by the Sponsor, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. Upon request by a regulatory authority such as the US FDA and other regulatory authorities worldwide, the Investigator/institution is to make available for direct access all requested study-related records or reports generated as a result of a patient's participation in this study. This information may be related in confidence to the IRB/EC or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to the Sponsor, or in confidence to the IRB/EC or similar committee, except if required by law.

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APPENDIX 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Screening	Treatment Period[a] (Each Cycle=21 [±3] Days) up to 24 Months						End-of-Treatment Visit
		Cycle 1			Cycle 2		Cycle 3+	
	Day -30 to Day-1	Day 1	Day 8±1	Day 14±3	Day 1	Day 8±1	Day 1	35 (±5) Days After Last Dose[b]
Informed Consent	x							
Relevant Medical History	x							
Demographic Data	x							
Height and Weight	x	x			x		x	x
Physical examination [c]	x	x			x		x	x
Vital signs	x	x			x		x	x
ECOG Performance Status	x	x			x		x	x
Pregnancy test (urine) [d]	x							
Tumor Receptor Status (ER, PR, HER2) and Stage	x							
Tumor Assessment [e]	x						x	x
CBC with 5-part differential and platelets [f]	x	x [f]	x		x	x	x	x
Serum Chemistry [g]	x	x [g]			x		x	x
Cardiac Ejection Fraction [h]	x							x
PK Samples [i]		x		x [i]	x		x	
Dispense Poziotinib and Loperamide[j]		x			x		x	
Adverse event assessment	x [k]	x	x	x	x	x	x	x
Dispense and Collect Patient Diary		x	x		x	x	x	x
Concomitant medications review	x	x	x	x	x	x	x	x

a) Each cycle is comprised of 21 days. **Day 1** of a new cycle is applicable to **Day 22** of the previous cycle, with a window period of ± 3 days. If a visit is delayed during 1 cycle, the subsequent schedules will be delayed sequentially.

b) An **End-of-Treatment Visit** will be performed 35 (±5) days after the last dose of poziotinib. An End of Study page will be recorded at that time.

c) A complete physical examination is required at **Screening**, **Day 1** of each Cycle, and at the **End-of-Treatment Visit**. Symptom-directed exams are required at other visits.

d) Pregnancy test (urine β-HCG) in women of child-bearing potential.

e) Tumor assessment will be performed at **Screening** and every 6 weeks (± 14 days) until disease progression, death, or intolerable adverse events, whichever comes earlier. Imaging studies performed prior to the signing of Informed Consent as part of the site's routine standard of practice are allowed at the discretion of the Sponsor.

f) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to poziotinib administration on **Day 1** of each cycle, at which time, the patient's absolute neutrophil count must be $\geq 1.0\times10^9$/L and platelet count must be $\geq 100\times10^9$/L before administering the next dose of poziotinib. In addition, a CBC is to be performed on **Day 8** of **Cycles 1** and **2**.

g) Blood for chemistry is to be collected within 7 days prior to poziotinib administration on **Day 1** of each Cycle.

h) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan and will be monitored at Screening, 3 months after first treatment, then every 6 months thereafter, while the patient is treated, and at the **End-of-Treatment Visit**.

i) For all cohorts, patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose for sparse pharmacokinetic (PK) sampling on **Day 1** of **Cycles 1**, **2**, and **3** and pre-dose on **Day 14** of **Cycle 1** (**Cohort 1** only). For patients in **Cohort 2** and **Cohort 3**, if consented, intensive PK samples will be drawn pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24 hours post-dose on **Day 1** of **Cycle 1**. In addition, if a patient presents with a potentially drug-related serious adverse event (SAE), PK samples may be collected during the visit for PK analysis.

j) Poziotinib and loperamide will be dispensed on **Day 1** of each cycle. Patients will take poziotinib orally once daily at approximately the same time each morning according to the schedule for each cohort during each 21-day cycle.

k) Adverse event assessment during **Screening** will utilize National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) and record only study-related SAEs.

APPENDIX 2 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.