Official Title: An Open-Label Extension Study to Allow Continued Dosing and/or Follow-up of Patients who have had Previous Exposure to Poziotinib

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TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

Study Title:	**An Open-Label Extension Study to Allow Continued Dosing and/or Follow-up of Patients who have had Previous Exposure to Poziotinib**
Study Number:	SPI-POZ-501
Study Phase:	Phase 2 Long-Term Extension
Study Drug:	poziotinib
IND Number:	127,487
Sponsor(s):	Spectrum Pharmaceuticals, Inc. Global Corporate Office 11500 S. Eastern Ave, Suite 240 Henderson, NV 89052 USA Spectrum Pharmaceuticals, Inc. Research and Development Office 157 Technology Drive Irvine, CA 92618 USA
Protocol Version/Date:	Amendment 1/27 Nov 2019

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 applicable 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The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or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 this protocol. You will not disclose any of the information to others without prior written authorization from Spectrum Pharmaceuticals, Inc. except to the extent necessary to obtain Informed Consent from those persons to whom the investigational drug may be administered.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-POZ-501

An Open-Label Extension Study to Allow Continued Dosing and/or Follow-up of Patients who have had Previous Exposure to Poziotinib

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 drug, 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 conduct of this study. I will discuss this material with them to assure that they are fully informed regarding the investigational drug and the conduct of the study.

I will perform the study according to the specifications outlined in this 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 from the IRB/EC 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 this study will be released without prior written consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by the applicable territory's regulatory authority (e.g., FDA).

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: An Open-Label Extension Study to Allow Continued Dosing and/or Follow-up of Patients who have had Previous Exposure to Poziotinib

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: Poziotinib

Study Centers: This study will be conducted at sites that have participated in poziotinib studies

Duration of Study: Open-ended until patient discontinuation	**Clinical Phase:** Phase 2 Long-Term Extension

Objectives:

Primary Objective

- To continue to monitor patients who appear to derive clinical benefit from poziotinib

Secondary Objective(s)

- To evaluate the efficacy of poziotinib in patients
- To evaluate the safety of poziotinib in patients

Exploratory Objective

- Overall survival of patients receiving long-term treatment with poziotinib

Study Design and Treatment Plan:

This is an open-label extension study (Extension Study) designed to allow patients who have had previous exposure to poziotinib to continue to receive poziotinib treatment and/or are still receiving clinical benefit from treatment, as judged by the Investigator or treating physician. Patients must begin treatment in this study within 28 days after their last dose of study drug.

This extension protocol is intended to provide the clinical benefit of poziotinib to patients who are responding to treatment. The additional treatment is optional and voluntary.

Patients who wish to participate in the extension study must provide written Informed Consent. Treatment will begin after the patient has completed the End-of-Study (EOS) or End-of-Treatment (EOT) Visit in an Original Study. Assessments obtained at the EOS or EOT visit in an Original Study will serve as Baseline data for the extension study.

Patients will continue to receive poziotinib treatment at the last dose received or at the standard starting dose of 16 mg poziotinib, once daily. Poziotinib dose modifications will be allowed under the treating physician's discretion after consultation and approval from Spectrum.

Safety will continue to be followed during the extended treatment according to Standard of Care (SOC). Efficacy of continued poziotinib treatment will also be followed to the extent that it is evaluated according to the Institution's SOC, but at least every 2 cycles.

A patient may receive treatment as long as the patient is deriving clinical benefit, as judged by the investigator or treating physician (case-by-case decision with approval of Spectrum), death, withdrawal of consent, unacceptable toxicity, the patient is lost to follow-up, poziotinib receives commercial approval in their country of residence, or development of poziotinib is terminated by the Sponsor, whichever occurs first. There will be an EOS Visit 35 (±5) days after the last dose of poziotinib.

Planned Number of Patients: This study is open to all patients who have had previous exposure to poziotinib and are receiving clinical benefit from treatment, as judged by the Investigator or treating physician.

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

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient has had previous exposure to poziotinib and is still receiving clinical benefit from treatment, as judged by the Investigator or treating physician.
2. Patient must have completed the End-of-Treatment or End-of-Study Visit if enrolled in a previous (original) poziotinib study.
3. Investigator or treating physician opinion indicates that extended therapy with poziotinib is clinically appropriate for the patient and the patient is suitable for this Study.
4. Patient agrees to continue study treatment.
5. Patient must provide written Informed Consent, must be able to adhere to dosing and visit schedules, and meet protocol-defined study requirements.
6. 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.

Exclusion Criteria

1. Patient has any ongoing adverse event that hasn't improved to Grade ≤1 and could impact the patient's tolerability to poziotinib.
2. Patient has an active uncontrolled infection, bleeding disorder, underlying medical condition, or other serious illness that would impair the ability of the patient to receive poziotinib.
3. Patient has any medical or non-medical condition that may not be suitable for poziotinib treatment, as determined by the Investigator or treating physician.
4. Patient's last dose of poziotinib was more than 28 days prior to Day 1 of the study.
5. Patient is pregnant or breastfeeding.

Test Product, Dose, and Route of Administration:

Patients will continue to receive poziotinib treatment at the last dose received or at the standard starting dose of 16 mg poziotinib, once daily. Poziotinib is supplied as 8-mg tablets and 2-mg tablets. Poziotinib will be taken by the patient orally, once daily with food and a glass of water at approximately the same time each day. If a dose is missed, it may be taken any time during the day preferably with food, but at least 8 hours prior to the next scheduled dose.

Poziotinib Dose Modification Recommendations

Dose modifications may be made at the discretion of the Investigator in response to drug toxicity using the dosing recommendations specified in an Original Study Protocol or on dosing recommendations specified in this protocol. Dose reductions below 8 mg are not recommended in the study.

Efficacy Assessments:

Efficacy assessment will be dependent on the assessment used in the original study and may include the overall response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free-survival (PFS). In addition to previous protocol-specified endpoints, an explorative analysis of overall survival may be conducted. Efficacy will be assessed based on Investigator's reported outcomes per standard of care (SOC) but tumor assessment (imaging) must be performed at least every 2 Cycles.

Safety Assessments:

Evaluation of safety will include assessment of treatment-related adverse events (AEs), AEs that result in modification or discontinuation of study treatment, all serious adverse events (SAEs), and all deaths. The frequency and schedule are based on either SOC or the institutional requirement. Study required tests for safety will be performed at Baseline Visit and at least once every 2 cycles thereafter. The Safety Follow-up/End-of-Study evaluations will be performed 35 (±5) days after the last dose of poziotinib treatment.

Adverse events and SAEs will be recorded from the time Informed Consent for this extension study protocol is signed until 35 (±5) days after the last dose of poziotinib is administered.

Statistical Methods:

Depending on the statistical methods defined in the previous study for efficacy assessment, the data from the current study will be combined with the data from the corresponding previous study to update the statistical analysis of the respective endpoints. In addition, if appropriate, the analysis of overall survival will be conducted using product-limit method to provide median survival and 95% confidence interval (CI).

Data will be listed by patient. If sufficient data are collected, summary descriptive statistics may be presented; however, no inferential statistics will be performed.

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SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Treatment Period [a]			Safety Follow-up /End-of-Study Visit
	Cycle 1, Day 1 (Baseline)	Every 2 Weeks-Phone Visit [b]	At Least Every 2 Cycles	35 (±5) Days After Last Dose
Informed Consent [c]	x			
Physical Examination	x		x	x
Vital signs	x		x	x
ECOG Performance Status	x		x	x
Pregnancy Test (urine) [d]	x			
Tumor Assessment	x [e]		x [f]	x
CBC with 5-part Differential and Platelets	x		x	x
Serum Chemistry	x		x	x
Collect/Dispense Poziotinib [g]	x		x	
Adverse Event Assessment	x	x	x	x
Concomitant Medications	x	x	x	x

a) The length of each treatment cycle is defined in the patient's original study protocol
b) The Investigator will contact the patient by telephone every 2 weeks between visits for adverse event assessment. If a significant AE is reported by phone, the patient should return to the site for evaluation.
c) A new Informed Consent Form must be signed for this extension study
d) Urine pregnancy test (β-HCG) in women of child-bearing potential.
e) The Screening tumor assessment can be based on the last scan from an original study or standard of care.
f) All tumor assessments during the treatment period will be per standard of care, or at least every two cycles.
g) Patients will return any unused poziotinib that will be counted and recorded at the site. A new 2-cycle supply of poziotinib will be dispensed on Day 1 of every other cycle. Patients will take poziotinib orally once daily with food and a glass of water at approximately the same time each morning according to the schedule of the original protocol.

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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
AE	Adverse event
CFR	Code of Federal Regulations
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DOR	Duration of Response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOS	End-of-Study
EOT	End-of-Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
NCI	National Cancer Institute
NOS	Not otherwise specified
ORR	Overall response rate
PFS	Progression-free survival
PPI	Proton-pump inhibitor
SAE	Serious adverse event
SAER	Serious adverse event report
SOC	Standard of Care
TEAE	Treatment-emergent adverse event
US	United States

1 INTRODUCTION

1.1 Background

This long-term extension study (Extension Study, SPI-POZ-501) is intended to provide continued dosing and/or follow-up in patients who have had previous exposure to poziotinib and are receiving clinical benefit as judged by the study Investigator or treating physician.

1.1.1 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. Blockade of EGFR receptors in turn, leads to inhibition of the proliferation of tumor cells that overexpress these receptors.

It is well established that several solid tumor malignancies are associated with a mutation in or overexpression of members of the EGFR and HER2 receptor families **[1]**. EGFR and HER2 mutation positive malignancies may include:

- Breast Cancer
- Gastrointestinal Cancer
  - Gastroesophageal Cancer
  - Colorectal Cancer
  - Biliary Tract Cancer
- Head and Neck Cancer
- Genitourinary Cancer (except bladder)
  - Endometrial Cancer
  - Cervical Cancer
  - Ovarian Cancer
- Bladder Cancer
- Solid Tumors NOS
- Patients enrolled in this study may have any of the above malignancies and were studied in the Original Study.

1.1.1.1 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 Studies 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.

1.2 Rationale for the Current Study

The purpose of this extension study is to allow patients who have had previous exposure to poziotinib to continue to receive poziotinib dosing and/or follow-up until the criteria for patient discontinuation are met.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To continue to monitor patients who appear to derive clinical benefit from poziotinib

2.2 Secondary Objectives

- To evaluate the efficacy of poziotinib in patients
- To evaluate the safety of poziotinib in patients

2.3 Exploratory Objective

- To evaluate overall survival of patients receiving long-term treatment with poziotinib

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is an open-label extension study (Extension Study) designed to allow patients who have had previous exposure to poziotinib to continue to receive poziotinib treatment and are still receiving clinical benefit from treatment, as judged by the Investigator or treating physician. Patients must begin treatment in this study within 28 days after their last dose of study drug.

This extension protocol is intended to provide the clinical benefit of poziotinib to patients who are responding to treatment. The additional treatment is optional and voluntary.

Patients who wish to participate in the extension study must provide written Informed Consent. Treatment will begin after the patient has completed the End-of-Study (EOS) or End-of-Treatment (EOT) Visit in an Original Study. Assessments obtained at the EOS or EOT visit in the Original Study will serve as Baseline evaluations in this extension study.

Patients will continue to receive poziotinib treatment at the last dose received or at the standard starting dose of 16 mg poziotinib, once daily. Poziotinib dose modifications will be allowed under the treating physician's discretion after consultation and approval from Spectrum.

Safety will continue to be followed during the extended treatment according to Standard of Care (SOC). Efficacy of continued poziotinib treatment will also be followed to the extent that it is evaluated according to the Institution's SOC, but at least every 2 cycles.

A patient may receive treatment as long as the patient is deriving clinical benefit, as judged by the Investigator or treating physician (case-by-case decision with approval of Spectrum), death, withdrawal of consent, unacceptable toxicity, the patient is lost to follow-up, poziotinib receives commercial approval in their country of residence, or development of poziotinib is terminated by the Sponsor, whichever occurs first. There will be an EOS Visit 35 (±5) days after the last dose of poziotinib.

3.2 Study and Treatment Duration

All patients who receive at least one dose of study treatment in this Extension Study will be followed for up to 35 (±5) days after their last dose of poziotinib or until all treatment-related AEs have resolved or returned to Baseline/Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient has had previous exposure to poziotinib and is still receiving clinical benefit from treatment, as judged by the Investigator or treating physician. .
2. Patient must have completed the End-of-Treatment or End-of-Study Visit if enrolled in a previous (original) poziotinib study.
3. Investigator or treating physician opinion indicates that extended therapy with poziotinib is clinically appropriate for the patient and the patient is suitable for this Study.
4. Patient agrees to continue study treatment.
5. Patient must provide written Informed Consent, must be able to adhere to dosing and visit schedules, and meet protocol-defined study requirements.
6. 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.

4.2 Exclusion Criteria

1. Patient has any ongoing adverse event that hasn't improved to Grade ≤1 and could impact the patient's tolerability to poziotinib.
2. Patient has an active uncontrolled infection, bleeding disorder, underlying medical condition, or other serious illness that would impair the ability of the patient to receive poziotinib.
3. Patient has any medical or non-medical condition that may not be suitable for poziotinib treatment, as determined by the Investigator or treating physician.
4. Patient's last dose of poziotinib was more than 28 days prior to Day 1 of the study.
5. Patient is pregnant or breastfeeding.

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.

Patients must be withdrawn from study drug treatment for the following reasons:

- Initiation of another anti-malignancy therapy with curative intent
- Development of progressive disease
- Lack of clinical benefit with continued treatment
- Development of a serious adverse event (SAE)/adverse event (AE), illness, condition, or procedural complication that may interfere with the patient's participation
- Patient decision
- Patient is lost to follow-up
- Investigator decision
- Sponsor decision
- 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 have a telephonic or in person Safety Follow-up Visit 35 (±5) days after the last dose of poziotinib. If death is recorded as the reason for study discontinuation, the case of death should be recorded on the CRF.

5 STUDY PROCEDURES

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 original study to which the patient was enrolled or 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 extension study will continue to be identified by the patient number in the original protocol. The Patient ID will include additional prefix component of Study ID to correctly identify in case of duplicate IDs across studies. The format will be XXX-YYYYY-ZZZ where XXX will be original study number, YYYYY will be site ID and ZZZ will be the patient number. For example, if a patient US001-001 from the SPI-POZ-201 study is enrolled in this protocol, the Patient ID will be [redacted].

5.2.1 Timing of Assessments and Procedures

5.2.2 Screening/Cycle 1, Day 1

Obtain Informed Consent prior to any study procedures. The Baseline Visit will be the EOT or EOS Visit of an Original Study the patient participated in (Original Study protocol). Assessments made at the last assessment (EOT or EOS Visit) of the Original Study will serve as Baseline data for the Extension Study.

- Informed Consent
- Height and weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Pregnancy test (beta human chorionic gonadotropin [β-HCG]) in women of childbearing potential
- Tumor assessment
- Baseline brain MRI scan for patients with known brain metastases

- Complete blood count (CBC) with 5-part differential
- Serum chemistry
- Dispense poziotinib
- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications

5.2.3 Treatment Period Assessments

During the poziotinib treatment period of the Extension Study, patients should be followed and monitored by the investigator or treating physician according to their institutional SOC. In addition, the patient must be contacted every 2 weeks to assess safety and must have a site visit at least every 2 cycles.

5.2.3.1 Telephone Visit – Every 2 Weeks

- Adverse event assessment using NCI CTCAE, version 5.0
- Concomitant medications

5.2.3.2 Site Visit – Every 2 Cycles

- Weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Tumor assessment (per standard of care)
- Complete blood count (CBC) with 5-part differential
- Serum chemistry
- Dispense/collect poziotinib
- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications

5.2.4 Safety Follow-up Visit

The Safety Follow-up Visit will occur 35 (±5) days after the last dose of Poziotinib is administered. The following assessments are to be performed:

- Weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Tumor assessment
- Complete blood count (CBC) with 5-part differential
- Serum chemistry
- Adverse event assessment using NCI CTCAE, Version 5.0

- Concomitant medications
- During the Safety Follow up visit, patient's survival status will be recorded. Patients may not be followed until mortality event in this study. Patients will be discontinued from the study if one of the criteria listed in **Section 4.3** is met.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

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 Supply and Labeling

Poziotinib tablets are supplied in 2.0-mg and 8.0-mg dose strengths. Patients will be dispensed a 2-month supply of poziotinib at each scheduled visit.

6.1.3 Poziotinib Administration

Poziotinib will be taken by the patient orally, once daily with food and a glass of water at approximately the same time each day. Patients will continue to receive poziotinib treatment at the last dose received or at the standard starting dose of 16 mg poziotinib, once daily. If a dose is missed, it may be taken any time during the day preferably with food, at least 8 hours prior to the next scheduled dose.

6.1.4 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.

6.2 Comparator Treatment

No comparator will be used in this study.

6.3 Blinding of Study Treatments

This is an open-label study.

6.4 Poziotinib Dose Delays and Modifications

Dose modifications may be made at the discretion of the Investigator in response to drug toxicity using the dosing recommendations specified an Original Study Protocol or on dosing recommendations specified in **Table 1**. Dose reductions below 8 mg are not recommended in the Study.

Table 1 Recommended Dosing Modifications

Related Adverse Event	Grade	Occurrence			
		1	2	3	4
Diarrhea	Grade ≥3 (Despite adequate anti-diarrhea management)	Stop poziotinib treatment until AE Grade ≤1 and then continue treatment at the same dose or Poziotinib Dose Reduced: 16 mg → 14 mg 12 mg → 10 mg 10 mg → 8 mg [a]	Poziotinib Dose Reduced: 16 mg → 14 mg or 14 mg → 12 mg 12 mg → 10 mg [a] 10 mg → 8 mg [a]	Poziotinib Dose Reduced: 14 mg → 12 mg or 12 mg → 10 mg [a] 10 mg → 8 mg [a]	Poziotinib Dose Reduced: 12 mg → 10 mg [a] 10 mg → 8 mg [a]
	Grade ≥2 for ≥48 hours (Despite adequate diarrhea management)				
Rash	Grade ≥3				
Fatigue	Grade ≥3				
Mucositis/ Stomatitis	Grade ≥3 (Despite adequate management)				
Nausea and/or Vomiting	Grade ≥3 (Despite adequate anti-emetics)				
	Grade ≥2 for ≥48 hours (Despite adequate anti-emetics)				
LVEF Dysfunction	Grade ≥3	Discontinue Treatment			

a) Dose reduction below 8 mg are not recommended.

6.5 Concomitant Medications

All medications administered from Baseline to the Safety Follow-up Visit will be recorded on the CRF. A concomitant medication is any medication a patient is using while being treated with poziotinib. 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 study. patients may continue to use any ongoing medications not prohibited by the protocol.

All prescription and over-the-counter medications at study entry as well as any new medications started during the study must be documented on the CRF and in the source documents. The documentation should continue until the Safety Follow-up Visit 35 (±5) days after the last dose of poziotinib). Premedications (such as antiemetics) used for supportive care are allowed as per institutional standards or guidelines and Investigator discretion. Other supportive and palliative therapies may be allowed during the study per SOC.

6.5.1 Possible Drug Interactions

Poziotinib is a substrate for cytochrome P450 (CYP) 3A4 and 2D6 enzymes. Patients may be taking medications that are strong inhibitors or inducers of these two enzymes (**Table 2**). The plasma concentration of poziotinib could be different in these patients. The Investigator should try to substitute a medication that is not a strong inhibitor/inducer of these enzymes, if possible. If there is not an available substitute for a medication that a patient is taking or the patient is not

willing to change medications, the Investigator must monitor the patient closely for possible AEs or changes in response.

Poziotinib is also a moderate inhibitor of CYP2C8 and CYP2D6, so patients who take medications that are sensitive substrates for these two enzymes (**Table 2**) should be followed closely for possible changes in the patient's response to these medications. Patients should be advised that grapefruit juice and St. John's Wort should be avoided during the study treatment.

Table 2 Examples of Important Clinical Inhibitors/Inducers/Substrates for P450 Enzymes Involved in the Metabolism of Poziotinib

CYP	Strong Inhibitor	Strong Inducer	Sensitive Substrate
2D6	Bupropion, Fluoxetine, Paroxetine, Quinidine, Terbinafine	None	Atomoxetine, Desipramine, Dextromethorphan, Eliglustat, Nebivolol, Nortriptyline, Perphenazine, Tolterodine, Venlafaxine
3A4	Boceprevir, Cobicistat, Conivaptan, Danoprevir and Ritonavir, Elvitegravir and Ritonavir, Grapefruit Juice, Indinavir and Ritonavir, Itraconazole, Ketoconazole, Lopinavir and Ritonavir, Paritaprevir and Ritonavir and (Ombitasvir and/or Dasabuvir), Posaconazole, Ritonavir, Saquinavir and Ritonavir, Telaprevir, Tipranavir and Ritonavir, Troleandomycin, Voriconazole	Carbamazepine, Enzalutamide, Mitotane, Phenytoin, Rifampin, St. John's Wort	Not Applicable
2C8	Not Applicable	Not Applicable	Repaglinide

Source:https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

6.5.2 Premedication and Supportive Treatment

6.5.2.1 Diarrhea Management

Loperamide is recommended for diarrhea management. Diarrhea should be monitored very closely. Diarrhea can be managed per standard of care as determined by the Investigator, Institutional Guidelines, or considering the algorithm in **Appendix 2**.

6.5.2.2 Mucositis Management

Mucositis/stomatitis can 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)

6.5.2.3 Rash Management

Rash may be managed according to the algorithm in **Appendix 3** and/or per standard of care as determined by the Investigator or Institutional Guidelines.

6.5.3 Uses of Warfarin or Other Coumadin-Derived Anticoagulants

Warfarin or other coumadin-derived anticoagulants should be used cautiously during treatment with poziotinib. When it cannot be avoided, regular monitoring of INR is required or followed with institutional SOC.

6.5.4 Other Anticancer Therapies

No additional cytotoxic agents, biologic therapy, or immune response modifiers for curative-intent purposes are allowed prior to discontinuation of poziotinib treatment.

7 SAFETY ASSESSMENT

7.1 Safety Measurements

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.

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 5.0 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. The study will record all treatment-emergent adverse events (TEAEs), which are defined as new AEs occurring from the time of the ICF for this extension study until 35 (±5) days after the last dose of study treatment or worsening of AEs from prior to the first dose of Poziotinib.

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.

All laboratory assessments are based on the study sites and their laboratories. 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.
- The abnormal laboratory value is ≥Grade 3 based on CTCAE Version 5.0.

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.

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

Any AE (related or unrelated) that occurs from the time the study Informed Consent is obtained until at least 35 (±5) days after the last dose of study drug administration.

Any AE that occurs from informed consent through 35 (±5) days after the last dose of study treatment is administered is to be recorded on the AE CRF.

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 will be the date of AE stop for all ongoing AEs at the time of death.

- If a patient discontinues study drug due to an AE(s), the outcome of the AE is to be followed until the AE has returned to Grade ≤1 or to baseline conditions for the patient.
- If the AE has not returned to Grade ≤1 or to baseline conditions for the patient 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 non-serious (**Section 7.7**) by the Investigator.

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale Version 5.0 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.

In addition, whether 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 should also be considered in the causality assessment.

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. Spectrum will be responsible for assessing the expectedness of AEs.

7.7 Serious Adverse Events

In the interest of patient care and to allow Spectrum to fulfill all regulatory requirements, any serious adverse event (SAE), regardless of causal relationship to study treatment, is to be reported to Spectrum 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 at the time of 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 will be regarded as not serious.

7.7.1 Serious Adverse Event Reporting

All SAEs that occur from the time the study Informed Consent is obtained and through 35 (±5) days after last dose of study drug administration or 35 (±5) days after the date of patient early discontinuation 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: +1 (949) 861-6599
E-mail: drugsafety@sppirx.com

The Investigator is to take all appropriate therapeutic measures necessary for resolution of SAEs. 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 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).

Spectrum or 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 local 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 and death due to progressive disease

7.8 Reproductive Risks

No adequate and well-controlled studies 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.

Females of childbearing potential will continue to follow the approved, medically accepted birth control regimen (eg, abstinence, birth control pills, intrauterine device, condoms, implants) or agree to abstain from heterosexual intercourse while participating in the study and for 30 days following the last dose of study treatment, as described in the original clinical study protocol.

Males who are sexually active are to agree to practice a medically acceptable barrier method contraceptive regimen while receiving study treatment and for 30 days after the last dose of study treatment is administered.

Pregnancies involving a study patient or a patient's partner, that occur from the first dose of study treatment through 30 days after last dose of study drug administration or 30 days after the date of patient early discontinuation, will be reported 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.

Pregnancies involving a study patient or a patient's partner that occur while the patient is receiving study treatment, or within 30 days of the last dose of study treatment, will be brought to the attention of the treating physician immediately and reported to Spectrum on the Pregnancy Report Form.

8 STATISTICAL PLAN

8.1 Sample Size

This study is open to all patients who have had previous exposure to poziotinib .

8.2 Method of Treatment Assignment, Randomization, and/or Stratification

Not applicable.

8.3 General Statistical Methods

Data will be listed by patient. If sufficient data are collected, summary descriptive statistics may be presented; however, no inferential statistics will be performed.

8.4 Efficacy Assessments

Efficacy assessment will be dependent on the assessment used in the Original Study and may include overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and progression-free-survival (PFS). In addition to previous protocol-specified endpoints, an explorative analysis of overall survival may be conducted. Efficacy will be assessed based on Investigator's reported outcomes per standard of care (SOC) but tumor assessment (imaging) must be performed at least every 2 Cycles. The overall survival data may be truncated as the patients may not be followed until mortality event, patients will be discontinued from the study if one of the criteria listed in **Section 4.3** is met.

8.5 Safety Assessments

Evaluation of safety will include assessment of treatment-related adverse events (AEs), AEs that result in modification or discontinuation of study treatment, all SAEs, and all deaths. Patients should be contacted every 2 weeks by telephone to assess adverse event and collect concomitant medication information. Patients will have a site visit every 2 cycles for assessment of reported/elicited AEs, laboratory assessments including hematology and chemistry, vital signs, and a physical examination.

Adverse events (AE) and serious adverse events (SAE) will be recorded from the time Informed Consent for this Extension Study is signed until 35 (±5) days after the last dose of poziotinib is administered.

8.6 Statistical Methods

Data will be listed by patient. If sufficient data are collected, summary descriptive statistics may be presented; however, no inferential statistics will be performed.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator Responsibilities

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 will ensure that the method of obtaining and documenting the Informed Consent complies with ICH-GCP and all applicable regulatory requirement(s). Informed Consent must be obtained before study procedures are performed, unless performed as standard of care. The subject's source documents shall document the informed consent process and that Informed Consent was obtained prior to study participation. A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed ICFs must remain in each patient's study file and must be available for verification at any time.

9.1.4 Study Files and Retention of Records

The Investigator will retain all study records until at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Spectrum. 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 Spectrum upon written agreement between the Investigator and Spectrum.

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 Spectrum 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 Spectrum's standard operating procedures for editing and clarifying CRFs. Data entry will be performed by the sites using an electronic data capture (EDC) system.

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 the study drug 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 bottles 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 bottles will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused bottles 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 Study Monitoring

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 study site monitoring will be risk-based and may not be 100% of the source document verification. A monitoring plan will be developed prior to the start of the monitoring. Spectrum'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.

9.4.2 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 Spectrum'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.

9.5.2 Termination of the Study

For reasonable cause, either the Investigator or Spectrum may terminate the Investigator's participation in this study. In addition, Spectrum Pharmaceuticals Inc. 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, Spectrum 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 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; and
    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 including case reports, manuscripts, abstracts, oral/slide presentations, books chapters based on this study must be submitted to Spectrum within 30 days (but no less than 10 days) prior to submission or publication for corporate review.

9.6 Confidentiality

All information provided to the Investigator by Spectrum, 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 Spectrum, or in confidence to the IRB/EC or similar committee, except if required by law.

10 REFERENCES

1. Roskoski R, Jr. ErbB/HER protein-tyrosine kinases: Structures and small molecule inhibitors. Pharmacological research. 2014;87:42-59.

Appendix 1 Schedule of Assessments and Procedures

Assessment	Treatment Period [a]			Safety Follow-up /End-of-Study Visit
	Cycle 1, Day 1 (Baseline)	Every 2 Weeks-Phone Visit [b]	At Least Every 2 Cycles	35 (±5) Days After Last Dose
Informed Consent [c]	x			
Physical Examination	x		x	x
Vital signs	x		x	x
ECOG Performance Status	x		x	x
Pregnancy Test (urine) [d]	x			
Tumor Assessment	x [e]		x [f]	x
CBC with 5-part Differential and Platelets	x		x	x
Serum Chemistry	x		x	x
Collect/Dispense Poziotinib [g]	x		x	
Adverse Event Assessment	x	x	x	x
Concomitant Medications	x	x	x	x

a) The length of each treatment cycle is defined in the patient's original study protocol
b) The Investigator will contact the patient by telephone every 2 weeks between visits for adverse event assessment. If a significant AE is reported by phone, the patient should return to the site for evaluation.
c) A new Informed Consent Form must be signed for this extension study
d) Urine pregnancy test (β-HCG) in women of child-bearing potential.
e) The Screening tumor assessment can be based on the last scan from an original study or standard of care.
f) All tumor assessments during the treatment period will be per standard of care, or at least every two cycles.
g) Patients will return any unused poziotinib that will be counted and recorded at the site. A new 2-cycle supply of poziotinib will be dispensed on Day 1 of every other cycle. Patients will take poziotinib orally once daily with food and a glass of water at approximately the same time each morning according to the schedule of the original protocol.

APPENDIX 2 RECOMMENDATIONS FOR DIARRHEA MANAGEMENT

RECOMMENDATIONS FOR DIARRHEA MANAGEMENT

For diarrhea management, the following interventions may be used based on the severity of the condition.

DIARRHEA SEVERITY	INTERVENTION
Start Diarrhea Prophylaxis *(CTCAE grade 0) Initiation of Pozionitib Treatment	- Start prophylactic therapy with Loperamide** 4mg orally twice daily when Poziotinib is initiated and continue for first 2 cycles - If patient becomes constipated, modify/discontinue Loperamide therapy appropriately - Upon development of diarrhea other etiologies including GI infection and inflammatory disorders must be ruled out. If Poziotinib related diarrhea is considered → follow the suggested approach per CTCAE severity as below:
Mild Diarrhea *(CTCAE Grade 1) Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool - Start Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - Continue Poziotinib at the current dose level
Moderate Diarrhea *(CTCAE Grade 2) Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool - Continue Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - Consider starting Cholestyramine 4 g orally, once or a twice day (30 minutes prior to the meals), continue till improvement of diarrhea to Grade 1 or a resolution OR Budesonide orally 9 mg daily for 4 weeks - Continue Poziotinib at the current dose level
Severe Diarrhea *(CTCAE Grade 3)	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool

Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL		- Continue Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - If started then continue Cholestyramine OR Budesonide (if started) - Consider Octreotide SubQ: 100 to 150 mcg every 8 hours; may increase to 500 to 1500 mcg IV or SubQ every 8 hours - Hold Poziotinib for one week and restart at the lower dose - Upon resolution or diarrhea improvement to ≤ Grade 1, Poziotinib dose escalation may be allowed after approval from the Sponsor

Gastrointestinal disorders	*GRADE				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Definition of Diarrhea: A disorder characterized by frequent and watery bowel movements

**** The maximum daily dose of Loperamide is 16 mg**

Version 1,

Dec, 12. 2017

APPENDIX 3 Rash Management Recommendations

RECOMMENDATIONS FOR ACNEIFORM RASH MANAGEMENT

For rash management, at the treating investigator's discretion, the following interventions may be used based on the severity of the rash.

RASH SEVERITY	INTERVENTION
Start Prophylaxis for Rash *(CTCAE grade 0) Initiation of Poziotinib Treatment	- Start prophylactic treatment on initiation of Poziotinib therapy with Doxycycline 100 mg orally (or alternatively use Minocycline 100 mg orally) twice per day - **Upon occurrence of rash:** Change/modify treatment per severity of the rash as following:
Mild Rash *(CTCAE Grade 1) Generally localized Minimally symptomatic No impact on ADL^ No sign of infection	- Continue all Grade 0 measures - **For face/body folds** - Start topical Hydrocortisone 2.5% cream or ointment (class VII topical steroid) twice daily on the affected areas - **For body** - Start topical Triamcinolone 0.1% cream or ointment (class IV topical steroid) twice daily on the affected skin area - Continue Poziotinib at the current dose level
Moderate Rash *(CTCAE Grade 2) Generalized Mild symptoms (for example, pruritus, tenderness) Minimal impact on ADL No sign of superinfection	- **For face/body folds** - Change Hydrocortisone to Triamcinolone 0.1% cream or ointment (class IV topical steroid) twice daily and add topical Clindamycin cream 1% twice daily on the affected skin area - **For body** - Change triamcinolone to Clobetasol or betamethasone 0.05% cream or ointment (class 1 topical steroid) twice daily and add topical Clindamycin cream 1% twice daily on the affected skin area - Consider obtaining culture and changing antibiotic based on sensitivity or change to a broad spectrum antibiotic otherwise continue Doxycycline 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day - Continue Poziotinib at the current dose level
Severe Rash *(CTCAE Grade 3) Generalized Severe symptoms (for example, pruritus, tenderness) Potential for superinfection	- Continue all Grade 2 - Hold Poziotinib for one week and restart at the current dose with prednisone or next lower dose upon discussion with sponsor - Start Prednisone 10-20 mgs daily and continue till improvement of rash to grade 1 or less - Obtain a dermatology consult - Upon resolution of rash to ≤ Grade 1, Pozionitib dose escalation may be attempted after approval from the Sponsor

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***CTCAE Severity Grading of Rash:**

Skin and subcutaneous tissue disorders **GRADE**

Adverse Event	1	2	3	4	5
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death

Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.

*CTCAE v4.03

**Topical steroids;

- Hydrocortisone → Low potency

- Triamcinolone → Medium potency

Clobetasol/betamethasone → high potency

*** In Grade 3 severe case, consider initiation of acitretin 10 mg daily after checking fasting lipids, LFTs, and confirming that patient does not have child bearing potential and is not pregnant. This needs an approval from the Sponsor prior to its use.

^ADL: activities of daily living

http://www.aafp.org/afp/2009/0115/p135.pdf

- Hirsh, V. Managing treatment-related adverse events associated with egfr tyrosine kinase inhibitors in advanced non-small-cell lung cancer. Current Oncology.18.3.126-138