Official Title: A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)

NCT Number: NCT03318939

Document Date: SA PVersion 1: 18 September 2019

CONFIDENTIAL
STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)
Study Number:	SPI-POZ-202
Study Phase:	Phase 2
Study Drug:	Poziotinib
IND Number:	135,719
Sponsor:	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA, USA
SAP Version / Date:	1.0 / 18 September 2019
Protocol Version / Date:	Amendment 2 / 28 May 2019
Cohorts:	ZENITH20-1, ZENITH20-2, ZENITH20-3, ZENITH20-4

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TABLE OF CONTENTS

List of Tables

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for Cohorts 1-4 (ZENITH20-1, ZENITH20-2, ZENITH20-3, ZENITH20-4) of Study SPI-POZ-202 amendment 2. A separate SAP will be developed for the newly initiated Cohorts 5-7 of the study (ZENITH20-5, ZENITH20-6, ZENITH20-7). The scope of this plan includes all efficacy and safety analyses of poziotinib in patients with non-small cell lung cancer (NSCLC) with EGFR or HER2 (ErBB2) exon 20 insertion mutations. The PK analysis will not be covered in this analysis plan.

1.1 Study Rationale

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 demonstrated that poziotinib may be a good option for patients harboring these mutations. These data support the expectation that poziotinib will be efficacious and well tolerated in solid tumor patients that overexpress EGFR or HER2 or that harbor mutations in EGFR or HER2.

In HER2 overexpressing tumors, clinical activity was shown in a variety of solid tumors in the Phase 1 studies of poziotinib. Additionally, clinical activity has been shown in a Phase 2 study in EGFR-mutant NSCLC at dose of 16 mg once daily (**NOV120101-202**).

In preclinical studies, consistent with reported clinical data, tumors with exon 20 insertions are resistant to first and second generation tyrosine kinase inhibitors. Preclinical models indicate marked sensitivity of both EGFR and HER2 exon 20 insertion mutations to poziotinib **[1].**

Based on the promising clinical data and acceptable safety profile from studies in HER2-overexpressed tumors and the preclinical data suggesting activity against EGFR and HER2 exon 20 insertion mutations, a single-center Phase 2 Investigator Initiated Study (IIS-POZ-001) was started to evaluate poziotinib in the patients with NSCLC and EGFR or HER2 exon 20 insertion mutations. The design of SPI-POZ-202 is similar to the IIS and is intended for further evaluation of the efficacy and safety of poziotinib in this NSCLC patient population.

1.2 Study Objectives

To evaluate NSCLC patients with EGFR or HER2 exon 20 insertion mutations (including duplication mutations) who are treated with poziotinib:

1.2.1 Primary Objective

- **Objective Response Rate (ORR)**

1.2.2 Secondary Objectives

- **Disease Control Rate (DCR)**
- **Duration of Response (DoR)**
- **Safety and tolerability**

1.2.3 Exploratory Objectives

- **Progression-free Survival (PFS)**

- **Quality of Life (QoL)**

2 STUDY OVERVIEW

Patients who are at least 18 years old, have histologically or cytologically confirmed locally advanced NSCLC, are positive for EGFR or HER2 exon 20 insertion mutations (including duplication mutation), have measurable disease as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1 **[2]**), and meet all other inclusion and exclusion study criteria are eligible for this study.

2.1 Study Design and Treatment Plan

This is a Phase 2, open-label, single-arm, multicenter study to evaluate the efficacy and the safety/tolerability of poziotinib in various cohorts. Cohorts 1-4 of the study will enroll up to 174 NSCLC patients previously treated with any systemic therapy (87 patients with EGFR exon 20 insertion mutations and 87 patients with HER2 exon 20 insertion mutations) and up to 140 treatment-naive NSCLC patients (70 patients with EGFR exon 20 insertion mutations and 70 patients with HER2 exon 20 insertion mutations).

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 28 calendar days in duration. There will be four patient cohorts and eligible patients will be enrolled into each cohort in parallel based on EGFR or HER2 exon 20 mutant status and prior treatment status:

- **Cohort 1:** Previously treated patients with EGFR exon 20 insertion mutation positive metastatic NSCLC
- **Cohort 2:** Previously treated patients with HER2 exon 20 insertion mutation positive metastatic NSCLC
- **Cohort 3:** Treatment naïve patients with EGFR exon 20 insertion mutation positive metastatic NSCLC
- **Cohort 4:** Treatment naïve patients with HER2 exon 20 insertion mutation positive metastatic NSCLC

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

Poziotinib will be taken orally, once daily (QD) with food and a glass of water at approximately the same time each morning. On **Day 1** of each 28-day cycle, the patient's absolute neutrophil count (ANC) must be ≥1.5×109/L and platelet count must be ≥100×109/L before administering poziotinib.

All patients will be treated until 24 months of treatment, disease progression, death, intolerable AEs, or other protocol-specified reason for patient withdrawal.

2.2 Study and Treatment Duration

The total duration of the study will be approximately 2 years. However, some patients may receive longer treatment if responding to the treatment. The duration of study participation for each patient, in general, includes the following segments:

- **Screening Period:** up to 30 days
- **Treatment Period:** 28 days per cycle until 24 months of treatment, disease progression, death, intolerable AEs, or other protocol-specified reason for patient withdrawal.
- **Safety Follow-up Visit:** 35 (±5) days after the last dose of poziotinib

2.3 Tumor Assessments

This section provides general description of tumor assessments. All images acquired at baseline and follow-up will be sent to Bioclinica, Inc. for central radiographic review by an Independent Review Committee (IRC) for response evaluation based on RECIST criteria, Version 1.1 **[2]**. Details are found in Bioclinica Independent Review Charter for SPI-POZ-202, including a list of all pre-specified modifications from RECIST 1.1 criteria.

Patient eligibility for enrollment will be based on the scans performed before the patient signed the ICF and review by the Site Principal Investigator. After patient enrolled into the study, baseline tumor assessment is required. All baseline and follow-up tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). The baseline tumor assessment must be performed within 2 weeks prior to, or on **Cycle 1**, **Day 1**. In situation that images are incomplete at baseline evaluation (i.e. missing images from some body sites), the most recently available images of the missing body sites prior to baseline (ie. at Screening) may be sent to Bioclinica as part of baseline evaluation.

For patients with known brain metastases, a baseline brain MRI scan will also be performed to assess the status of brain metastases if present.

Tumor assessments will be performed at

- approximately 4 weeks (**Cycle 2**, **Day 1**) [±7 days], 8 weeks of treatment (**Cycle 3**, **Day** 1 [±14 days]), and approximately every 8 weeks (±14 days) thereafter) [Original Protocol]
- approximately 4 weeks (**Cycle 2**, **Day 1** [up to **Cycle 2**, **Day 7**]), 8 weeks (**Cycle 3**, **Day 1** [up to **Cycle 3**, **Day 7**, with at least 28 days from previous tumor assessment]), and approximately every 8 weeks (±7 days) thereafter [Amendment 1 & 2]

For each patient, subsequent tumor assessment must use the same radiographic technique performed at baseline, either CT, PET/CT, or MRI. Tumor assessments will be made according to RECIST criteria, Version 1.1 **[2]** using appropriate radiographic imaging or other techniques. Patient enrollment and clinical decisions will be based on local imaging review and the efficacy assessments for final analysis will be based on the central imaging review by IRC at Bioclinica.

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

2.3.1 Baseline Tumor Assessments

Consistent with RECIST, at baseline tumor assessment, up to 5 measurable lesions (maximum of 2 lesions per organ) representative of all involved organs will be identified as **target lesions**. Target non-nodal tumor lesions (TLs) should have longest diameter ≥10mm and can be measured reproducibly. Target lymph nodes (LNs) should have short axis ≥15mm. The sum of diameters (SOD), which is the sum of the longest diameter of all target non-nodal lesions and the short axis of all target LNs, will be calculated as the reference baseline value for tumor response evaluation later in the study.

All the other TLs, pathological LNs (short axis ≥10mm), and lesions not measurable by CT or MRI will be identified as **non-target lesions** and the size of these lesions are not recorded for the purpose of follow-up.

2.3.2 Follow-up Tumor Assessments

Target lesions are followed for tumor size, (i.e., longest diameter of TLs and short axis of LNs), and SOD are calculated for response evaluation using RECIST 1.1 criteria. At each tumor assessment, the tumor response of **target lesions** is determined as below.

- **Complete Response (CR)**: Disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal (i.e., decrease in short axis to < 10 mm).
- **Partial Response (PR)**: At least a 30% decrease in SOD of target lesions, taking as reference the baseline SOD. Additionally, progression of target lesions must not be present.
- **Progressive Disease (PD)**: At least a 20% increase in the SOD of target lesions, taking as reference the nadir SOD (or the baseline, if the baseline is the nadir value). In addition to the relative increase of 20% in SOD, the SOD must also demonstrate an absolute increase of ≥ 5 mm.
- **Stable Disease (SD)**: Neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD.
- **Not Evaluable (NE)**: If ≥ one (1) target lesion is classified as NE for a particular time point, the SOD and percent change cannot be accurately determined and the Target Response will be NE for that time point. The only exception is if the SOD of the evaluable target lesions shows a ≥ 20% increase from the nadir SOD and an absolute increase of ≥ 5 mm. In this case, the Target Response will be PD.
- **Not Applicable (NA)**: No target lesions were identified at baseline. Subjects with no target lesions will be evaluated based on the assessment of non-target lesions or the presence of new lesions.

Non-target lesions are assessed qualitatively with present, absent or unequivocal progression and tumor response is determined as below.

- **Complete Response (CR)**: The nontarget lesion has fully resolved. The lymph node must be nonpathological in size (< 10 mm in the short axis).
- **Non-CR/Non-PD**: Persistence of the non-target lesion.
- **Progressive Disease (PD)**: The non-target site of disease has shown unequivocal progression.
- **Not Evaluable (NE)**: Any non-target lesion which was present at baseline, but which subsequently became unevaluable.
- **Not Applicable (NA)**: No non-target lesions identified at baseline.

New lesions are tumor lesions that were not present at baseline. The finding of a new lesion should be unequivocal, and the appearance of new malignant lesions denotes disease progression.

2.3.3 Time Point Response at Each Tumor Assessment

As summarized in **Table 1**, the time point response at each follow-up tumor assessment are determined according to the evaluation of target lesions, non-target lesions, and new lesions.

Table 1 Determination of Time Point Response

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Any but PD	No	
SD	Any but PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	
Any	Any	Yes[1]	
NE	Any but PD	No	NE
NA	CR	No	CR
NA	Non-CR/Non-PD	No	Non-CR/Non-PD
NA	NE or NA	No	NE

[1] If the finding of new lesion is equivocal, it should be confirmed at next scan.

3 STATISTICAL CONSIDERATIONS

This is a Phase 2, open-label, single-arm, multicenter study with seven patient cohorts and this SAP focuses on the first 4 cohorts. Each cohort is an independent study and will be analyzed separately at different time. For Cohorts 1-4 (ZENITH20-1, ZENITH20-2, ZENITH20-3, ZENITH20-4), all statistical summary tables, data listings, and figures will be produced separately with the corresponding clinical study reports. The statistical analyses and clinical study reports may be submitted to the Agency separately for each cohort.

3.1 Randomization

This is a single-arm, non-randomized, independent cohort design study and patients are enrolled into study cohorts based on tumor characteristics.

3.2 Sample Size Determination

There are four patient cohorts and each cohort is considered to be a standalone study with individual primary endpoints and powered for testing hypotheses separately. The original justification for the sample size calculation is provided in the protocol and is described below.

The reported response rate of patients with EGFR exon 20 mutations to gefitinib and erlotinib is low at 5% with a median PFS of 1.5 months. A combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 clinical trials showed that the response rate to afatinib is 8.7%

with a median PFS of 2.7 months in EGFR exon 20 mutant patients. In a pivotal study of crizotinib vs. chemotherapy, the response rate of chemotherapy-treated patients with previously treated ALK-positive NSCLC was 20%.

There is no approved treatment available for EGFR exon 20 insertion mutation NSCLC patients. Unlike other EGFR mutations, patients with EGFR exon 20 insertions rarely respond to gefitinib or erlotinib. A review of 84 patients with exon 20 insertion mutations across different series treated with either gefitinib or erlotinib demonstrated an RR of only 11% with a PFS of 2.4 months (Naidoo et al, 2015). Similarly, treatment with afatinib in this patient population is also associated with a low RR and PFS (8.7% and 2.7 months, respectively; (Yang JC et al, 2015). Overall survival of patients with EGFR exon 20 insertion mutations is similar to that of patients without EGFR-mutant NSCLC but inferior to that of patients with EGFR exon 19 deletion or L858R advanced NSCLC (Oxnard GR et al, 2013).

Patients with HER2 mutated NSCLC treated with lapatinib, a pan HER inhibitor, experienced progressive disease. The most promising data to date have been obtained using irreversible TKIs targeting HER2/3 and EGFR, such as afatinib, neratinib and dacomitinib. Three out of eight HER2 mutant NSCLC patients treated with afatinib achieved a partial response. Dacomitinib demonstrated an overall 13% response rate in the 26 HER2-mutant patients.

3.2.1 Previously Treated Patients - Cohort 1 and Cohort 2

Cohort 1 will enroll EGFR exon 20 insertion mutation positive NSCLC patients who have been previously-treated and **Cohort 2** will enroll patients with previously-treated HER2 exon 20 insertion mutation positive NSCLC. The statistical analysis of primary as well as secondary outcomes will be performed separately for each cohort. Each cohort will be a single-arm and the primary test of hypotheses will be based on a single proportion. Based on the literature and per the FDA reviewed protocol, an observed ORR of 30%, with 17% as the lower bound for 95% CI, is considered to be the clinically meaningful efficacy in our study. Sample size calculation is based on single arm hypothesis testing to reject non-desired ORR of 17% vs. clinically meaningful ORR of 30%. A sample size of 87 patients in each cohort will provide 85% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 17% if the observed ORR is 30% or higher. A sample size of 87 patients in each cohort will also provide 95% CI that contains 30% and rules out 17%, since the lower bound of the CI is above 17%.

3.2.2 Treatment Naïve Patients - Cohort 3 and Cohort 4

Similar to **Cohorts 1** and **2** in previously-treated patients, the study will have 2 additional patient cohorts (**Cohorts 3** and **4**) with no prior treatment for exon 20 mutation positive NSCLC. The statistical analysis of primary as well as secondary endpoints will be performed separately for each cohort. Each cohort will be single-arm and the primary test of hypotheses will be based on a single proportion. Based on the literature and per the FDA reviewed protocol, an ORR of 20% is considered to be the lower threshold of efficacy in our study. Sample size calculation is based on the single arm hypothesis testing to reject non-desired ORR of 20% vs. clinically meaningful ORR of 40% in the study. A sample size of 70 patients in each cohort will be provide 90% power, for a two-sided test with a significant level of 5%, to reject a non-desired ORR of 20% if the observed ORR is 40% or higher. A sample size of 70 patients in each cohort will also provide 95% CI that contains 40% and rules out 20% as the lower bound is above 20%.

3.3 Statistical Principles

3.3.1 General Principles of Analysis

The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.3 or higher. All tables, listings, and figures will be validated and reviewed before being finalized.

In summary tables of continuous variables, the minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median, standard deviation (SD), standard error (SE), and 95% confidence interval (CI) will be presented to one more decimal place than the original data.

In summary tables of categorical variables, count and percentage will be provided. In general, percentage values are to be presented to whole number if sample size ≤100; to one decimal place if sample size is between 100 and 1000; and to two decimal places if sample size is greater than 1000. Any test of comparison performed will be 2-sided at 5% level of significance unless otherwise specified.

3.3.2 Baseline Value

Baseline value will be defined as the most recent non-missing measurements collected prior to the first dose of study treatment. If there is more than one value on or before the date of the first dose of study treatment, the values closest to and prior to (including on) the date of the first dose will be used as the baseline value. Change from baseline will be defined as post-baseline value minus baseline value.

3.3.3 Handling of Missing Data

Missing data will not be imputed. All data will be presented as collected.

3.3.4 Pooling of Data

Data from all sites will be combined for the purpose of data summary and analysis. The number of patients enrolled by study site will be reported. For the primary analysis, data from all exon 20 mutations regardless of the position and designation will also be combined.

3.3.5 Analysis Population

- The **As-Treated Population** will be the primary analysis population and include all patients who receive at least one dose of study medication.
- The **Evaluable Population** consists of all patients who are enrolled, have at least one dose of poziotinib treatment, and is evaluable for tumor response based on RECIST, Version 1.1, by central imaging review. The efficacy data will also be analyzed using the **Evaluable Population**.

  The **Evaluable Population** will exclude patients whose best overall response is NE as well as patients who do not have target lesion at baseline, all based on the central imaging review by IRC at Bioclinica.
- The **Safety Analysis Population** 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 **Safety Analysis Population**.

3.4 Futility Analysis

The study includes a futility analysis to be conducted in each patient cohort when the response rate for the first 20 patients in that cohort is available. A patient cohort will be stopped for futility if the ORR is <10%. No adjustment to multiplicity will be made for the futility analysis.

3.5 Final Analysis

The final analysis will be performed separately for each cohort as if they are independent studies. Although the study is ongoing, the database for a patient cohort will be closed and locked for the final full study analysis separately when all patients in that cohort complete 24-month follow-up or discontinue from the study.

Primary endpoint only and full analysis will be conducted in the timeframe described below. For primary endpoint only analysis, data cutoff, data cleaning and data snapshot will be done before proceeding to analysis.

Primary Endpoint Analysis:

The primary endpoint is the ORR and is evaluated using the response evaluation (RECIST 1.1) data obtained from the IRC at Bioclinica. The timing of the primary endpoint analysis will be determined by taking into consideration the length of follow up, best overall response and possibility to confirm the responses in the primary analysis population and not necessarily at the completion of 24-month follow-up or discontinuation in all patients.

Data will be incomplete to have a full analysis of secondary endpoints such as DCR, DOR, PFS and QoL at the time of the primary endpoint analysis and will be truncated.

Full Cohort analysis:

Once all patients in a cohort complete the study or discontinue, the final database lock will be completed, and the final study analysis will be performed. At this time, all secondary endpoints and safety analysis will be performed.

4 PATIENTS CHARACTERISTICS

Patient characteristics will be summarized for **Safety Analysis Population**. Corresponding patient data listings will be provided.

4.1 Patient Disposition

The number of patients in the **Safety Analysis Population** and the reasons for study discontinuation will be summarized with count and percentage. Reasons for patient discontinuation include

- Development of an 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 >28 days since last poziotinib administration
- Investigator decision

- Sponsor decision
- Lost to follow-up
- Pregnancy
- Death

Summary of enrollment by site will also be presented.

4.2 Protocol Deviations

The following important protocol deviations will be summarized with count and percentage.

- Patients entered the study even though they did not satisfy the entry criteria.
- Patients developed withdrawal criteria during the study but were not withdrawn.

- All protocol deviations will be provided in patient data listings.

4.3 Baseline Characteristics

Demographics including age, gender, ethnicity, race, and age groups (<65 and 65+; <75 and 75+) and other baseline disease characteristics will be summarized using descriptive statistics.

Baseline characteristics include BMI, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, ECG assessment, cardiac ejection fraction, lung cancer histopathology, staging, mutation type, and prior cancer therapy (EGFR/HER2 therapy, immunotherapy, Tyrosine-kinase inhibitor therapy, chemotherapy, surgery, and radiation therapy).

4.4 Medical History

Medical history information will only be provided in patient data listings.

4.5 Concomitant Medication

A concomitant medication is any medication that was taken either on the day of or after the administration of the first dose of poziotinib through the end of the study. This includes medications that started prior to the initiation of the first dose of poziotinib if the patient continues using it.

For all concomitant medications, count and percentage of patients will be presented by medication class and preferred name coded by the World Health Organization Drug (WHO Drug) dictionary. Patients with more than one medication of the same medication class or preferred name will be counted only once.

5 EFFICACY ANALYSIS

- All primary analysis of efficacy endpoints will be based on the **As-Treated Population** and the central imaging review by IRC at Bioclinica using 2 independent readers and 1 adjudicator paradigm.

5.1 Best Overall Response

For **As-Treated Population**, the best overall response is defined as the best response from the start of study treatment until PD or the last tumor assessment on study. A best overall response of

CR or PR requires confirmation at a subsequent visit that is ≥4 weeks after. One NE response before the confirmed evaluation is allowed. A best overall response of SD can only be made if the subject is on-treatment for ≥6 weeks. **Table 2** summarizes how best overall response is determined. Details are referred to Independent Review Charter.

Table 2 Determination of Confirmed Best Overall Response

Initial Best Response (can start at any visit)	Response at Subsequent Visit	Best Overall Response
CR	CR[1]	CR
PR	PR[2] or unconfirmed CR[2]	PR
PR	SD (not followed by CR/PR)	SD
SD	SD or unconfirmed CR/PR	SD
CR or PR or SD	PD	SD[3] or PD[4]
CR or PR or SD	NE (no additional evaluable visit)	SD[3] or NE[4]
PD	Any	PD
NE	NE (no additional evaluable visit)	NE

[1] Confirmation scan needs to be ≥4 weeks from previous scan, 1 intervening NE is allowed.

[2] Confirmation scan needs to be ≥4 weeks from previous scan, 1 intervening NE/SD is allowed.

[3] If initial CR/PR/SD is ≥6 weeks on-treatment.

[4] If initial CR/PR/SD is <6 weeks on-treatment.

For the **Evaluable Population**, a modified best overall response, which requires confirmation scan to be ≥3 weeks from previous scan, will be applied because the study protocol allows 7 days window for tumor assessment **(Section 2.3)**.

5.2 Primary Endpoint

5.2.1 Objective Response Rate (ORR)

The primary endpoint is ORR and is defined as the proportion of patients whose best overall response is confirmed to be CR or PR from the first dose of poziotinib until the last tumor assessment on study. The unconfirmed ORR, which does not require confirmation scans for CR/PR, will also be provided.

ORR and unconfirmed ORR will be estimated with count, percentage and 95% CI (Clopper-Pearson).

The test of hypothesis of the primary endpoint will be performed using the 95% CI. The prespecified primary endpoint criteria for each cohort is stated in **Section 3.2**.

5.3 Secondary Endpoints

5.3.1 Disease Control Rate (DCR)

DCR is defined as the proportion of patients whose best overall response is CR, PR, or SD from the first dose of poziotinib until the last tumor assessment on study.

DCR will be estimated with count, percentage and 95% CI (Clopper-Pearson).

5.3.2 Duration of Response (DoR)

DoR will be evaluated only for patients who has CR or PR and is defined as the time (in months) from the date that response evaluation criteria are first met for CR or PR (whichever status is recorded first) until the first subsequent date that PD or death is documented. DoR of patients without documented PD or death will be censored at the time of last tumor assessment.

Distribution of DoR will be estimated using the Kaplan-Meier method and the median and quartiles of DoR time and the DoR rate at 3, 6, 9 and 12 months will be reported with corresponding 95% CI.

5.4 Exploratory Endpoints

5.4.1 Progression-Free Survival (PFS)

PFS is defined as the time (in months) from the treatment start date to the first date of documented PD or death. PFS time for patients without documented PD or death will be censored at the date of last tumor assessment or the date of first treatment if there is no post-baseline tumor assessment.

Distribution of PFS time will be estimated using the Kaplan-Meier method. The median and quartiles of PFS time and the PFS rate at 3, 6, 9 and 12 months will be estimated with corresponding 95% CI.

5.4.2 Quality of Life (QoL)

QoL data from the EORTC QLQ-C30 and QLQ-LC13 questionnaire are collected for all enrolled patients at Screening, every imaging/tumor assessment visit, and the Safety Follow-up Visit.

QoL analyses will be based on the **As-Treated Population**. The global health status/QoL, functional scales, symptom scales, and lung cancer related symptoms will be summarized for each evaluation time point using descriptive statistics. Additional analyses although not pre-specified may be conducted for certain items of interest.

5.5 Secondary Analysis

5.5.1 Evaluable Population

Modified ORR as described in **Section 5.1**, unconfirmed ORR, DCR, and PFS will be analyzed for the **Evaluable Population**.

5.5.2 Sensitivity Analyses

Analyses of the primary and secondary outcomes will be performed only for patients who are positive for exon 20 mutations based on the central tissue testing.

5.5.3 Subgroup Analysis

Analyses of the primary and secondary endpoints will be performed for the following subgroups.

a) Per FDA Type C meeting minutes of July 13, 2018, subgroup analysis will be conducted for individual mutation and various clusters of mutations within exon 20 in order to evaluate prognostic implications, which may include
   - individual mutation type with higher counts of patients
   - other meaningful mutation clusters

b) Patient subgroups based on prior therapy for locally advanced or metastatic NSCLC, such as
   - patients who had prior platinum-based chemotherapy
   - patients who had 2 lines of prior treatment, including platinum-based chemotherapy with or without immunotherapy, other tyrosine kinase inhibitor (TKI) or other systemic therapy, for locally advanced or metastatic NSCLC
   - patients who had 3 lines of prior treatment, including platinum-based chemotherapy with or without immunotherapy, other tyrosine kinase inhibitor (TKI) or other systemic therapy, for locally advanced or metastatic NSCLC

5.5.4 Tumor Assessment by Local Review

ORR, DCR, DoR, and PFS based on tumor assessment by local imaging review will be reported separately using statistics described above for the **As-Treated Population** and the **Evaluable Population**. Best overall response and modified best overall response will be determined based on tumor measurement using RECIST v1.1 following **Section 5.1**. The agreement of best overall response between central and local imaging review will be displayed using cross table and evaluated using weighted kappa.

5.5.5 Exploratory Analysis

The effect of treatment exposure on tumor response (PR, SD, and PD only) will be evaluated using a logistic regression model. For this exploratory analysis, it is assumed the tumor response of a subject at a time point depends on average daily dose between last and current tumor assessment time points. The average daily dose from last tumor assessment to current tumor assessment will be calculated as total dose in the period divided by total days in the period. The distribution of average dose for different tumor response (PR, SD, PD) will also be summarized using descriptive statistics.

6 SAFETY ANALYSIS

6.1 Extent of Exposure

The extent of exposure to poziotinib will be summarized with descriptive statistics using the following parameters.

- Duration of treatment: days difference between first dose and last dose of poziotinib + 1.
- Number of cycles treated
- Days of treatment administered
- Duration of treatment: number of days from first dose to last dose of poziotinib, which is calculated as (days difference between first dose and last dose +1).

- Relative dose intensity (RDI): the percentage of planned dose that each patient actually received during the study. The planned dose is defined as the dose that would be given if no doses were missed and no dose reductions were made for the number of cycles (28 days per cycle) for the duration of treatment regardless of the number of cycles actually administered. Thus,

$$\text{RDI} = 100 * \frac{\text{total dose administered}}{(28 * 16) * \left[\text{integer of } \left(\frac{\text{days difference between first dose and last dose}}{28}\right) + 1\right]}$$

- Dose reduction: no reduction and dose reduction to 14mg, 12mg, 10mg and 8mg per cycle and for overall. Temporary dose fluctuation is not considered as dose reduction based on the rules specified in study table shell.

6.2 Pharmacokinetics

The PK analysis will be covered in a separate analysis plan.

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

AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, version 17) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). All AEs will be classified for severity by the Investigator according to the definitions set forth by the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

All AE tables will be presented with number and percentage of patients. AE listings will include patient ID, gender, age, race, AE verbatim term and preferred term, AE start date and end date, AE duration, CTCAE grade, if the AE is SAE or not, relation to study drug, study drug action, outcome, and if treatment is given.

Only treatment-emergent AEs (TEAE), as defined in **Section 6.3.2**, will be summarized in tables. SAEs reported prior to treatment but after informed consent will only be provided in AE listings.

6.3.1 Overall Summary

An overall summary table of TEAEs will be provided. The summary will include any TEAE, TEAE by severity, SAE, TEAE and SAE leading to study drug discontinuation, any treatment-related AE, treatment-related AE by severity, treatment-related SAE, and treatment-related AE leading to study drug discontinuation.

6.3.2 Treatment-Emergent Adverse Events

TEAEs are AEs that occur from the first dose of study treatment until 35 (±5) days after the last dose of study treatment. If it cannot be determined whether an AE is treatment-emergent (based on start date or, if the start date is missing then based on the stop date), then the AE will be considered treatment-emergent.

Summary of TEAEs by MedDRA SOC and PT will be presented with any grade and with Grade 3 or 4. Patients who experience more than one type of AE will be counted under each of the corresponding PTs. Patients who experience different episodes of the same AE will be counted only once under the corresponding PT. Similarly, for determination of MedDRA SOC incidences, patients who experience multiple AEs under the same SOC will be counted only once for that SOC. Listing of all TEAEs will also be provided.

6.3.3 Treatment-Related Adverse Events

Assessment of relatedness to study drug for all AEs will be classified by investigators and reported. “Definitely related”, “probably related” and “possibly related” AEs will be considered as treatment related. An AE will be assigned as treatment-related if the relationship to study drug cannot be determined.

The incidences of treatment-related AEs will be presented by MedDRA SOC and PT with any grade and with Grade 3 or 4.

6.3.4 Serious Adverse Events

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.

Listing of all SAEs will be provided. Treatment-emergent SAEs and treatment-related SAEs will be summarized by MedDRA SOC and PT with any grade and with Grade 3 or 4.

6.3.5 Maximum Severity of Adverse Events

TEAEs and treatment-related AEs will be summarized by MedDRA SOC, PT, and maximum CTCAE severity grade. AEs with a missing severity grade will not be included in these analyses. Patients who experience the same event at more than one severity level will be counted only once under the maximum severity level.

6.3.6 Other Important Adverse Events

AEs leading to death and study drug discontinuation will be presented in separate listings and the incidence will be summarized in the overall summary of TEAE table.

6.3.7 Adverse Events of Special Interest

Summary of TEAEs, treatment-related AEs, and SAEs for diarrhea, rash, and stomatitis by MedDRA SOC and PT will be provided in separate tables with any grade and with Grade 3 or 4. Study day of first incidence for diarrhea, rash, and stomatitis will be summarized using median and range.

6.4 Laboratory Parameters

The laboratory abnormalities will be classified for severity grade according to the NCI CTCAE version 4.03. Key laboratory parameters in hematology and blood chemistry 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. Investigator evaluated clinical significance will be summarized for each parameter at each evaluation time point.

6.5 Vital Sign Data

A summary of raw values and changes from baseline values will be provided at each scheduled time point for the following measurements: body temperature, systolic and diastolic blood pressure, and heart rate. A listing of all values will also be included.

6.6 ECOG Performance Status

Descriptive statistics will be presented for ECOG scores baseline. The number and percentage of patients with shifts from baseline ECOG score (0, 1, or 2) to the worst post-baseline ECOG score (0, 1, 2, 3, or 4) will be summarized.

6.7 Other Safety Data

Other safety data, including physical examination and cardiac assessment, will be provided in the data listings.

7 REFERENCES

1. Yang JC-H, Sequist L, O'Byrne K, Schuler M, Mok T, Geater S, et al. Epidermal growth factor receptor (EGFR)-mediated adverse events (AEs) in patients (pts) with EGFR mutation positive (EGFR M+) non-small cell lung cancer treated with afatinib. European Journal of Cancer. 2013;49:S190.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised Recist Guideline (Version 1.1). Eur J Cancer. 2009;45(2):228-47.