FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

September 22, 2022

NDA 215643

Drug name: Poziotinib

Applicant: Spectrum Pharmaceuticals, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the assessment of the benefit:risk profile of poziotinib to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

Include any acronyms or abbreviations used four or more times in the AC BD. Each instance of terms appearing three or fewer times should be spelled out rather than abbreviated.

Acronyms and abbreviations should be spelled out at first use in the Executive Summary, main body (if not spelled out in the Executive Summary), and Appendix (if not spelled out in the Executive Summary or main body). The sample list below includes commonly used acronyms and may be used as a starting point.

AC	Advisory Committee
BD	Briefing Document
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
FDA	Food and Drug Administration
IA	integrated assessment
REMS	risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAP	Statistical Analysis Plan
SD	standard deviation

Executive Summary/Draft Points for Consideration by the Advisory Committee

On November 1, 2021, Spectrum Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for poziotinib (POZENVEO) under the accelerated approval provisions of 21 CFR part 314 subpart H. The Applicant is seeking the following indication:

- POZENVEO is indicated for the treatment of patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring human epidermal growth factor receptor 2 (HER2) exon 20 insertion mutations.

To receive accelerated approval a drug must demonstrate an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit and provide a meaningful advantage over available therapies. For drugs granted accelerated approval, a post-marketing confirmatory trial is required to verify and describe the anticipated clinical benefit. FDA is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss the risk benefit assessment of poziotinib 16 mg once daily (QD).

The FDA has several concerns regarding the totality of evidence supporting this application:

- Low overall response rate (ORR) with minimal duration of response (DOR):
  - ORR 28% (95% CI: 19, 38), with a median DOR of 5.1 months (95% CI: 4.2, 5.5)
- Poorly tolerated safety profile at the current proposed dosage (16 mg QD) with 57% of patients experiencing dose reductions and 85% of patients experiencing grade 3-4 adverse events. The rate of interruptions and dose reductions may be mitigated in patients receiving alternative dosages.
- Inadequate dosage optimization throughout development program. The Applicant is proposing two different doses for accelerated approval (16 mg once daily) and the planned confirmatory trial (8 mg twice daily). Confirmation of benefit will be significantly delayed given that confirmatory trial has not begun enrolling patients.

Poziotinib is an oral tyrosine kinase inhibitor (TKI) that inhibits the activity of epidermal growth factor receptor (EGFR [HER1], HER2, and HER4) kinases. Poziotinib was studied as a single agent in Study SPI-POZ-202 (ZENITH20), an ongoing, global, multicohort, non-randomized, dose finding and activity-estimating study in patients with previously treated locally advanced or metastatic NSCLC harboring EGFR or HER2 exon 20 insertion mutations. Patients received poziotinib at dosages ranging from 10 mg to 16 orally (PO) daily, administered in single or divided doses.

The primary efficacy data supporting this application is derived from patients enrolled in Cohort 2 of ZENITH20 (N=90) with HER2 exon 20 insertion mutations who received at least one prior systemic therapy and received the Applicant's proposed recommended dosage of 16 QD. The ORR was 28% (95% confidence interval [CI]: 19, 38) according to RECIST v1.1 as assessed by blinded independent central review (BICR) with a median DOR of 5.1 months (95% CI: 4.2, 5.5). If granted accelerated approval, this would be the least effective targeted therapy for lung cancer approved to date.

The safety profile of poziotinib at the proposed dosage indicates poor tolerability. A high rate of Grade 3-4 adverse events (AEs) (85%), serious AEs (SAEs) (42%), and treatment interruption/dose reductions (88%) were observed in patients enrolled in ZENITH20 who received 16 mg QD (N=368).

Exposure-Response (E-R) analyses for efficacy conducted by FDA are considered preliminary, based on limited data available at dosages other than 16 mg QD. These analyses for the efficacy comparison do not provide clear support of one dosage over another. With respect to safety, clinical pharmacology based E-R analyses showed that higher average concentration at steady state (Cavg,ss) are associated with greater probability of treatment-emergent adverse events (TEAEs), including Grade 3+ TEAE, diarrhea, stomatitis and TEAEs leading to dose reduction. In order to assess the risk-benefit profile, and potentially improve poziotinib tolerability, while maintaining efficacy, additional data at alternative dosages are needed.

The randomized trial planned to confirm benefit of poziotinib is not well underway, thus uncertainties regarding the benefit of this therapy may take 4-5 years to resolve. Study SPI-POZ-301 is an open-label, randomized, multiregional study of poziotinib 8 mg BID versus single agent chemotherapy (docetaxel) in patients with locally advanced or metastatic NSCLC harboring HER2 Exon 20 mutations who received at least one prior systemic treatment including platinum-based chemotherapy and an immune checkpoint inhibitor. The primary efficacy outcome measure is progression-free survival (PFS). However, as of July 28, 2022, this trial has not yet enrolled any patients and initial results are not anticipated until at least 2026. Furthermore, the selection of poziotinib 8 mg BID as the dosage to be tested in the confirmatory trial is incongruent with the potential approval of a dosage of 16 mg QD and the Applicant's assertion of improved efficacy at a dosage of 16 mg QD.

Purpose/Objective of the AC Meeting

The FDA Division of Oncology 2 is convening this Oncologic Drug Advisory Committee meeting to discuss the following key issues:

Efficacy: The anti-tumor activity of poziotinib is marginal with poor duration of response. It is unclear whether this truly represents an advantage over current available therapies.

Safety: There are high rates of interruptions, dose reductions, and discontinuations at the current proposed dosage. There were also four fatal cases of interstitial lung disease (ILD)/pneumonitis in patients receiving 16 mg daily.

Dosage optimization: The Applicant failed to adequately explore various dosages throughout the development program, resulting in disparate dosages being investigated in the single arm study for accelerated approval and planned confirmatory trial. It remains unclear based on data submitted to FDA if an alternative dosage can maintain efficacy while mitigating toxicities.

Confirmatory trial: Given concerns regarding the totality of evidence supporting this application, the significant delay in confirming benefit with a randomized clinical trial heightens the uncertainty around the risk benefit assessment. The confirmatory trial has

not enrolled any patients to date, and is not expected to report top line results for 4-5 years.

Given the concerns regarding marginal efficacy in the face of high rates of toxicity, poor tolerability, lack of dosage optimization, and significant delay in confirmation of benefit, FDA requests discussion on the overall risk benefit assessment of this application.

Context for Issues to Be Discussed at the AC

Lung cancer is the leading cause of cancer-related mortality in the United States (U.S.) and worldwide. Treatment of NSCLC is guided by both histologic subtype and presence of actionable mutations; NSCLC harboring HER2 alterations is considered a distinct molecular subtype of lung cancer. However, there are no therapies with regular FDA approval specifically targeting this rare molecular subtype; therefore, these patients are treated according to the paradigm for patients with NSCLC without an actionable genomic alteration. In the second-line setting, for which the Applicant is seeking approval, available therapy consists of single-agent chemotherapy, combination chemotherapy including docetaxel and ramucirumab, and anti-PD-1/PD-L1 therapies if not already received. Outcomes with these therapies demonstrate ORRs ranging from approximately 6 to 23% and median DORs of approximately 6 months with chemotherapy and 16 months with anti-PD-(L)1 therapies.

On August 11, 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu) for the treatment of patients with NSCLC whose tumors have activating HER2 (ERBB2) mutations (inclusive of HER2 exon 20 mutations), as detected by an FDA-approved test, and who have received a prior systemic therapy, based on an ORR of 58% (95% CI: 43, 71) and a median DOR of 8.7 months (95% CI: 7.1, not estimable [NE]) in 52 patients who received Enhertu 5.4 mg/kg. The fam-trastuzumab deruxtecan-nxki accelerated approval indication includes the HER2 exon 20 insertion mutation indication sought by the Applicant for poziotinib, and may be considered standard of care for patients with HER2 mutant NSCLC in the second line setting. However, fam-trastuzumab deruxtecan-nxki is not considered available therapy from a regulatory standpoint as it is approved under the provisions of accelerated approval.

Brief Description of Issues for Discussion at the AC

The Division of Oncology 2 seeks the advice of the ODAC regarding the pending NDA for poziotinib on the following issues:

- For accelerated approval, efficacy should demonstrate a meaningful advantage over available therapy. Poziotinib demonstrated limited anti-tumor activity similar to that of available chemotherapy combination therapy and of shorter duration than was observed with immunotherapy in patients who had not previously received an immune checkpoint inhibitor.

- The ORR observed in 90 patients enrolled in Cohort 2 of ZENITH20 who received poziotinib 16 mg QD was 28% (95% CI: 19, 38), with a median DOR of 5.1 months (95% CI: 4.2, 5.5). As of a data cutoff date (DCO) of March 5, 2021, 24% of responders had a response duration of ≥ 6 months. For the subgroup of patients who received both platinum-based chemotherapy and an immune checkpoint inhibitor (N=59), the ORR was 25% (95% CI: 15, 38), with a median DOR of 5.1 months (95% CI: 3.1, 6.6).
- On June 29, 2022, the Applicant submitted updated data from patients enrolled in Cohort 2 based on a DCO date of May 16, 2022. The median DOR was 5.2 months (95% CI: 4.6, 6.2), indicating that there was no improvement in response durability with the additional 14 months of follow-up time.

- Poor tolerability:
  - Treatment with poziotinib 16 mg QD is associated with a high rate of Grade 3-4 AEs, SAEs, and AEs leading to treatment interruption and dose reductions.
  - The high rates of the most commonly observed AEs of diarrhea, mucositis, and rash contributed to the high incidence of interruption and dose reductions.
  - There were three fatal events of ILD/pneumonitis at the 16 mg QD dosage and one fatal event of ILD/pneumonitis at the 8 mg BID dosage.

- Inadequate dosage optimization:
  - The primary efficacy data supporting the proposed indication is derived from patients enrolled in Cohort 2 of study ZENITH20 with HER2 exon 20 insertion mutations who received the proposed recommended dosage of 16 mg QD. Similar ORRs with widely overlapping 95% confidence intervals were observed in patients who received other dosages of poziotinib in ZENITH20, as shown in Table 9 below.
  - FDA performed E-R analyses for effectiveness to correlate ORR with pharmacokinetic metrics, including the Cmax,ss. These exploratory analyses demonstrate that a higher Cmax,ss appears to be associated with a higher ORR. The preliminary E-R analyses also demonstrated that the relationship between ORR and the Cave,ss appears relatively flat over the full dosage range studied. The differences in these E-R analyses for the efficacy comparison of 16 mg QD and other dosages do not clearly support the selection of one dosage over another. These E-R relationships for efficacy are considered preliminary, based on limited data available at dosages other than 16 mg QD, and may alter upon follow-up readouts. These additional data and follow-up readouts will not be available during the current review cycle.
  - FDA performed E-R analyses for safety. These analyses suggest that Cavg,ss was associated with greater probability of significant safety measures including Grade 3+ TEAE, diarrhea, stomatitis and TEAE leading to dose reduction.
  - Given the high rates of interruptions and dose reductions at 16 mg QD, the relative dose intensity was approximately 12 mg per day. At 6 weeks, less than 50% of patients who were still receiving poziotinib remained on 16 mg QD. Of

the patients who remained on poziotinib beyond 24 weeks, most patients received daily dosages of 12 mg or less.
  - Based on the available clinical safety and efficacy data and FDA's E-R analyses, alternative dosages may improve tolerability while providing similar effectiveness.

- Confirmatory trial is not well underway:
  - According to 21 CFR 314 subpart H, further investigation of a drug is required as part of the accelerated approval provisions. Postmarketing studies should be underway at the time of submission of a marketing application for accelerated approval.
  - For accelerated approvals, one or more confirmatory trials conducted with due diligence may be required to confirm the drug's clinical benefit. If these trials don't achieve this goal, are substantially delayed, or are not conducted at all, the marketing authorization for the indication in question may be withdrawn.[1]
  - The proposed confirmatory trial, Study SPI-POZ-301 had not begun enrolling patients as of July 28, 2022 and results are not anticipated until at least 2026.

Draft Points for Consideration

- Discuss the overall risk:benefit of poziotinib 16 mg QD given its lack of efficacy, poor tolerability, and inadequate dosage optimization. The risks of approving a marginal and potential inappropriate dosage in the face of significant delays in confirmation of benefit pose concerns for the FDA when considering the risk benefit assessment.
- Do the benefits of poziotinib outweigh its risks for the treatment of patients with NSCLC with HER2 exon 20 insertion mutations?

Introduction and Background

Background of the Condition/Standard of Clinical Care

Lung cancer is the leading cause of cancer deaths in the U.S. and worldwide. In the U.S. in 2019, 221,097 new cases and 139,601 deaths were reported due to lung cancer[2]. Lung cancer is generally divided into two major histological subtypes: NSCLC and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of all cases of lung cancer and at diagnosis 57% of cases are unresectable (Stage IIIB or Stage IV). Although the outcomes for patients with metastatic NSCLC have improved in the past five years due to the development of immune checkpoint inhibitors, their prognosis remains poor with an estimated median overall survival of approximately 2 years when treated with standard first-line therapy including platinum-based chemotherapy and an immune checkpoint inhibitor[3,4,5,6].

NSCLC is further classified based on histologic subtype (adenocarcinoma versus squamous) and the presence of genomic alterations, which may guide treatment, if present. HER2 alterations in NSCLC can be subdivided into gene mutations, gene alterations, and protein overexpression, with exon 20 insertions being the most frequent gene mutations[7]. These occur in 2-4% of patients with NSCLC; patients with advanced HER2-mutant NSCLC have a median OS of 1.6-1.9 years from the time of diagnosis[8] and are treated according to the same treatment paradigms as patients with advanced NSCLC without actionable genomic alterations.

Approximately 40-50% of patients with advanced NSCLC respond to first-line chemotherapy/immunotherapy combinations, but the majority of patients will progress on or after treatment. Disease progression presents a challenge as response rates (6-23%) and overall survival (9.1-13.8 months) are poor in the second line setting[9,10,11,12].

Fam-trastuzumab-deruxtecan-nski, an antibody-drug conjugate (ADC) targeting HER2 expression, was granted accelerated approval in August 2022 for the treatment of patients with unresectable or metastatic NSCLC whose tumors have activating HER2 mutations based on an ORR of 58% and median DOR of 8.7 months[13].Table 1 provides a summary of FDA-approved second-line or later treatments for patients with HER2 exon 20 insertion mutation positive NSCLC.

Table 1: Approved therapies for patients with NSCLC in the second-line setting

Drug	Indication	Selected efficacy results
Single agent antibody-drug conjugate		
Fam-trastuzumab-deruxtecan-nxki*	Unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations and who have received a prior systemic therapy	ORR 58% (95% CI: 43, 71)
Anti-PD-(L)1 therapies		
Nivolumab	Metastatic NSCLC with progression on or after platinum-based chemotherapy	Squamous NSCLC: ORR 20% (95% CI: 14, 28) Non-squamous NSCLC: ORR 19% (95% CI: 15, 24)
Pembrolizumab	Metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.	ORR 19% (95% CI: 15, 23)
Atezolizumab	Metastatic NSCLC with disease progression during or following platinum-containing chemotherapy	ORR 14% (95% CI: 11, 17)
Single agent chemotherapy		
Docetaxel	Locally advanced or metastatic NSCLC after platinum therapy failure	ORR 6% (95% CI: 2.3, 11.3)
Pemetrexed	Locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	ORR 9% (95% CI: 6, 13)
Combination chemotherapy		
Docetaxel plus ramucirumab	Metastatic NSCLC with disease progression on or after platinum-based chemotherapy	ORR 23% (95% CI: 20, 26)

Source: FDA clinical review. *Fam-trastuzumab-deruxtecan-nxki is under accelerated approval and therefore not considered available therapy per FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics, May 2014

To address the unmet need, poziotinib is being developed for the treatment of patients with previously treated HER2 Exon 20 insertion mutation positive advanced NSCLC. In patients comprising the primary efficacy population of ZENITH20, the observed ORR was 28% and the median DOR was 5.1 months. There was a high rate of Grade 3-4 toxicities (85%), treatment interruptions (83%), dose reductions (58%) and drug discontinuations (18%) at the proposed dosage.

Pertinent Drug Development and Regulatory History

Poziotinib is an irreversible inhibitor of ErbB family of tyrosine kinases including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) resulting in the inhibition of their respective downstream signaling pathways inhibiting cell proliferation. It has a higher affinity for HER2 exon 20 insertions compared to HER2 wild type (WT) but similar to that of EGFR WT receptor as indicated by a lower in vitro IC50 value.

Following repeated once daily oral administration, poziotinib achieved peak plasma concentration (t_{max}) in 1 hour and its elimination half-life was 6.3 hours. Following administration of poziotinib with a meal (908 total calories, with 35% from fat and 45% from carbohydrates), tmax was increased by 2 hours and no clinically significant differences in the exposure (Cmax and AUC) of poziotinib were observed. Poziotinib is metabolized by CYP3A4 and CYP2D6 to inactive metabolites M1 and M2, respectively, and excreted majorly by fecal route.

Table 2 and Table 3 provide summaries of key regulatory interactions and of the studies supporting the NDA. Discussions with the Applicant on dosage optimization and confirmatory trial development were held as early as 2017 and 2020, respectively.

Of note the Applicant did NOT seek Breakthrough Designation status for the HER2 exon 20 insertion mutation indication, a designation reserved for therapies with preliminary evidence of an improvement over currently available therapies, for the HER2 exon 20 insertion mutation indication. This is rare for targeted therapies in NSCLC, but appropriate given the lack of robust data to support such a request.

Table 2: Key regulatory history

Date	Discussion
07/28/2017	Clinical development program for poziotinib was initiated under IND 135719; Study SPI-POZ-202 (ZENITH20) was the IND-initiating trial and was initially comprised of two cohorts in patients with EGFR or HER2 exon 20 insertion mutations. **FDA communicated concerns that the trial as proposed will not identify a dosage that provides the optimal balance of efficacy and safety needed to maximize the chances of a successful outcome in subsequent registration trials designed to demonstrate efficacy and safety.** FDA noted that there is insufficient information to adequately differentiate the risk-benefit profiles of the clinically active dose range (12 mg to 16 mg/day) in the proposed patient population. FDA recommended that the Sponsor also evaluate a lower daily dose than 16 mg/day that is within the efficacious dose range in the proposed trial.
02/14/2020	Submission of a protocol amendment to ZENITH20 that included justification for evaluating additional dosages including 8 mg BID.

11/09/2020	A Type B Pre-NDA meeting was held to discuss the adequacy of the safety and efficacy results from Cohort 2 of ZENITH to support an NDA submission for poziotinib. FDA agreed to the filing of an NDA. **The Applicant proposed a randomized, confirmatory trial to be conducted in the first-line setting comparing poziotinib as a single agent to platinum-based chemotherapy in patients with previously untreated HER2 exon 20 insertion mutant NSCLC. FDA expressed concerns given the lack of evidence for poziotinib's activity in this setting.** The Applicant stated that they would provide FDA with data from treatment naïve patients enrolled in ZENITH20 Cohort 4 which would inform the design of the proposed trial.
02/11/2021	Fast track designation was granted for poziotinib for the treatment of patients with previously treated locally advanced or metastatic NSCLC whose tumors harbor HER2 exon 20 insertion mutations.
07/16/2021	A Type C guidance meeting was held to discuss data from treatment-naïve patients enrolled in Cohort 4 of ZENITH20, whether data from Cohort 5 of ZENITH20 could be provided in the NDA submission to support a BID dosing schedule, and design elements for the proposed confirmatory trial. The Applicant proposed a randomized trial of poziotinib versus docetaxel in patients with previously treated HER2 exon 20 insertion mutation positive NSCLC. FDA agreed with the inclusion of data from Cohort 5 in the NDA and recommended that the Applicant pool all available clinical pharmacokinetic, pharmacodynamic, safety and efficacy data from completed trials and perform integrated dose-response and exposure-response analyses to support clinical dose selection based on an optimum biologic dosage and schedule.
10/01/2021	Spectrum submitted the first portion of the rolling submission for NDA 215643.
11/24/2021	The final components of the NDA containing clinical data were submitted.
12/13/2021	A Type B Pre-phase 3 meeting was held discuss the proposed poziotinib dosing and design of the confirmatory trial, Study SPI-POZ-301. The Applicant proposed a dosage regimen of 16 mg QD for 2 weeks followed by 8 mg BID or 6 mg BID. FDA stated that additional data is needed to determine whether the poziotinib dose is optimized for further evaluation in Study SPI-POZ-301. Specifically, FDA indicated that the Applicant should evaluate the 6 mg BID dose in one or more confirmatory trials, potentially conducted as a run-in phase. However, the Applicant and FDA agreed that the 8 mg BID regimen as the starting dosage was preferable in the confirmatory trial compared to the Applicant's proposal.

01/25/2022	Given FDA's concerns regarding top line efficacy results, lack of dosage optimization, delayed confirmatory trial status, and the safety profile of poziotinib, the review classification was designated as standard.
02/07/2022	A Type B End of Phase 2 (EOP2) meeting was held under IND 135719 to discuss the Applicant's proposals for confirmatory trials of poziotinib to be conducted at the 8 mg BID dosage. FDA requested additional efficacy data from patients enrolled in Cohort 5 of ZENITH20 to further analyze the anti-tumor activity of poziotinib 8 mg BID. FDA expressed concern about the delay in initiation of the confirmatory trial and emphasized the need to begin enrollment as soon as possible.
05/18/2022	A Midcycle Communication meeting was held in which FDA expressed concerns regarding the safety profile of poziotinib, particularly at the 16 mg QD dose, given the high rate of dose reductions and dose interruptions. FDA stated that additional clinical data at a dosage of 8 mg BID and other dosages was necessary to assess the risk-benefit profile. FDA expressed concern about the delayed confirmatory trial status and communicated that based on the ongoing review, uncertainties remain regarding whether the proposed dosage of 16 mg QD is optimized from both the efficacy and safety perspectives.
07/28/2022	A Type B Guidance meeting was held to discuss the adequacy of dosage optimization to support both the proposed dose of 16 mg QD for the current marketing application and the 8 mg BID dose for the confirmatory trial. FDA stated that the proposed dosage of 16 mg QD does not appear adequately justified and that additional clinical data from the ongoing Cohort 5 and proposed confirmatory trial are needed to compare the benefit-risk profiles of the 16 mg QD to alternative dosage regimens. Additionally, FDA asked for an update on the planned confirmatory trial. On the date of the meeting, no patients had been enrolled.
09/08/2022	A Late Cycle Communication meeting was held in which FDA indicated that based on the ongoing review, uncertainties remain regarding whether the proposed dosage of 16 mg QD is optimized from both the efficacy and safety perspectives. FDA stated that additional clinical data from Cohort 5 of ZENITH20 (currently ongoing) and proposed confirmatory trial, Study SPI-POZ-301, are needed to compare the benefit-risk profiles of the 16 mg QD dosage to alternative dosage regimens.

Table 3: Studies supporting the NDA

Study ID/ Status	Patient population	Study design	Poziotinib dosage	Endpoint
Primary efficacy and safety data				
SPI-POZ-202 (ZENITH20) Cohort 2 N=90 Enrollment complete	Locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations	Non-randomized, activity estimating	16 mg QD	ORR
Supportive efficacy and safety data				
SPI-POZ-202 Cohort 5 N=118 Ongoing	Locally advanced or metastatic NSCLC with EGFR or HER2 exon 20 insertion mutations	Non-randomized, activity estimating	16 mg QD (N=22) 8 mg BID (N=18) 12 mg QD (N=23) 6 mg BID (N=20) 10 mg QD (N=35)	ORR
Supportive safety data				
SPI-POZ-202 Cohorts 1, 3, 4, 6, 7 N=253 Ongoing	Locally advanced or metastatic NSCLC with EGFR acquired or activating mutations, EGFR exon 20 insertion mutations, or HER2 exon 20 insertion mutations	Non-randomized, activity estimating	16 mg QD	ORR

Source: FDA clinical review

Data from a total of 482 patients enrolled in ZENITH20 was included in the NDA. Table 4 provides a description of the efficacy and safety analysis populations by study and poziotinib dose.

Table 4: Summary of efficacy and safety populations

Analysis Population	Poziotinib Dose		Overall
	16 mg daily	8 mg BID	
Efficacy	90	0	90
Safety	368	114	482

Source: FDA clinical review

Summary of Issues for the AC

Efficacy Issues

- Issue #1: Limited response rate with poor durability (efficacy issue)
- Issue #2: Poor tolerability at the proposed dosage (safety issue)
- Issue #3: Inadequate dosage optimization for efficacy and safety (efficacy and safety issue)
- Issue #4: Delayed initiation of confirmatory trial (efficacy and safety issue)

Sources of Data for Efficacy

ZENITH20 is an ongoing, multicenter, multi-cohort, open-label, activity-estimating study evaluating the anti-tumor effects, safety, and tolerability of poziotinib in patients with locally advanced or metastatic NSCLC harboring EGFR or HER2 mutations. The primary efficacy outcome measure was ORR by BICR; DOR was a secondary outcome measure. Cohort 2 enrolled patients with previously treated locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations to receive poziotinib 16 mg QD.

Key inclusion criteria:

- Histologically or cytologically confirmed locally advanced or metastatic NSCLC that was not amenable to treatment with curative intent.
- At least one prior systemic treatment for locally advanced or metastatic NSCLC.
- Tissue samples for mutation confirmation if patient had adequate tumor tissue obtained from a biopsy or surgical procedure to enable molecular profiling for retrospective central laboratory confirmation of the mutation. If tissue was not available, the patient must have had biopsy accessible disease and must have been willing to undergo a biopsy to provide an appropriate tissue sample prior to receiving treatment in the study.
- Patient was positive for HER2 mutations based on a documented HER2 exon 20 insertion mutation (including duplication mutations) using a next generation sequencing (NGS) diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples.

- Patients with brain metastases were eligible if the patient's condition was stable, asymptomatic and did not require high dose systemic corticosteroids and anticonvulsant therapy.
- Patient had an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and had a life-expectancy of more than 6 months.

Key exclusion criteria:

- Previous treatment with poziotinib or any other EGFR or HER2 exon 20 insertion mutation selective TKI prior to study participation. The currently approved TKIs (ie, erlotinib, gefitinib, afatinib, osimertinib) were not considered to be exon 20 insertion-selective and were permissible.

Tumor assessments were made according to RECIST v1.1 criteria and occurred at baseline, every 4 weeks for two cycles, and every 8 weeks thereafter until disease progression, death, or protocol-specified reasons for patient withdrawal. Brain MRIs were performed for patients with known brain metastases.

Patients enrolled in Cohort 2 of ZENITH20 provide the primary source of data intended to establish substantial evidence of effectiveness of poziotinib for the treatment of patients with locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations. The primary hypothesis test was based on a single proportion and the sample size calculation was based on single arm hypothesis testing to reject an ORR of 17% versus an ORR of 30%. A sample size of 87 patients provides a 95% CI that includes 30% and exceeds 17% as the lower bound.

Efficacy Summary

Amongst the primary efficacy population of 90 patients with HER2 exon 20 insertion mutation-positive NSCLC whose disease had progressed on at least one prior systemic therapy, the median age was 60 years, with 62% of patients less than 65 years and 11% at least 75 years old. The majority of patients were female (64%). Patients were predominantly White (78%), with 13% Asian and 4% Black or African American patients, and never smokers (66%). A total of 58% of patients had an ECOG performance status of 1. Ninety-six percent of patients had adenocarcinoma histology and 16% had brain metastases at baseline. These demographic and baseline characteristics are reflective of the population of patients with NSCLC with HER2 exon 20 insertion mutations in the U.S.[14], although its association with race and ethnicity has not been well established.

All patients were previously treated with systemic therapy for advanced NSCLC with a median of 2 prior lines of therapy. A total of 39% of patients received at least 3 prior lines of systemic therapy and a majority (97%) of patients received prior platinum-based chemotherapy. Sixty-eight percent of patients received prior platinum-based chemotherapy and an immune

checkpoint inhibitor (CPI) and 28% of patients received prior HER2-targeted therapy. Table 5 provides an overview of the prior lines of treatment.

Table 5: Summary of prior lines of therapy received in the primary efficacy population

Parameter	ZENITH20 Cohort 2 N=90
Lines of Prior Systemic Therapy, n (%)	
1 Line	27 (30)
2 Lines	28 (31)
3+ Lines	35 (39)
Type of Prior Systemic Therapy, n (%)	
Chemotherapy	88 (98)
Platinum-Based Chemotherapy	87 (97)
CPI	61 (68)
TKI-EGFR	12 (13)
HER2-Targeted Therapy	25 (28)
VEGF-Targeted Therapy	14 (16)
Multiple Prior Systemic Therapies, n (%)	
Chemotherapy Only	22 (24)
Chemotherapy, CPI	41 (46)
Chemotherapy, HER2-Targeted Therapy	7 (8)
Chemotherapy, HER2-Targeted Therapy, CPI	18 (20)
CPI only	2 (2.2)

Source: SPI-POZ-202 Clinical Study Report-Cohort 2

A summary of primary efficacy results in the primary efficacy population and in the subgroup of patients who progressed on prior platinum-based chemotherapy and an immune checkpoint inhibitor is provided in Table 6. The ORR and DOR results observed in the primary efficacy population are intended to provide primary evidence of effectiveness of poziotinib in support of its accelerated approval.

Table 6: Primary efficacy results from ZENITH20 Cohort 2

Efficacy parameter	Primary efficacy population N=90	Prior chemo/IO N=59
ORR by BICR, % (95% CI)	28 (19, 38)	25 (15, 38)
Median DOR, mos. (95% CI)	5.1 (4.2, 5.5)	5.1 (3.1, 6.6)
% responders with DOR ≥ 6 mos.	24%	20%

Source: FDA statistical review

Efficacy Issues in Detail

Issue #1: Limited response rate with poor durability

As described above, a limited response rate of 28% with poor durability as demonstrated by a median DOR of 5.1 months, was observed in patients enrolled in Cohort 2 of ZENITH20. Similar anti-tumor activity results were observed in the subgroup of patients who received both platinum-based chemotherapy and an immune checkpoint inhibitor. ORR of large magnitude and long duration is considered to be an endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with $NSCLC_{15,}$ as shown in Table 7. This Table details recently approved targeted agents for NSCLC, in which the accelerated approvals were based upon higher ORRs and/or longer durations of response than were observed with poziotinib.

Table 7: Comparison of results observed with recently approved targeted therapies for NSCLC

Drug name	Target	ORR (%) (95% CI)	mDOR (mos.) (95% CI)	Year of approval
Fam-trastuzumab deruxtecan-nxki	HER2	58 (43, 71)	8.7 (7.1, NE)	2022
Mobocertinib	EGFR exon 20 insertion	28 (20, 37)	17.5 (7.4, 20.3)	2021
Amivantamab	EGFR exon 20 insertion	40 (25, 51)	11.1 (6.9, NE)	2021
Sotorasib	KRAS G12C	36 (28, 45)	10 (1.3, 11.1)	2021
Selpercatinib	RET	64 (54, 73)	17.5 (12, NE)	2020
Lorlatinib	ALK	48 (42, 55)	12.5 (8.4, 23.7)	2018
Osimertinib	EGFR T790M	59 (54, 64)	NR	2015

Sources: ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2022. EXKIVITY [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc.; 2021. RYBREVANT [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2021. LUMAKRAS [package insert]. Thousand Oaks, CA: Amgen Inc.; 2021. RETEVMO [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020. LORBRENA [package insert]. New York, NY: Pfizer Labs; 2018. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.

In order to grant accelerated approval, a drug must demonstrate a meaningful therapeutic benefit over existing treatments. It is not clear that the duration and response rate seen with poziotinib is clearly improved over that of available therapy particularly when considered in the context of its toxicity profile. For patients with HER2 exon 20 insertion mutations who received both prior platinum-based chemotherapy and an immune checkpoint inhibitor, available therapy includes docetaxel in combination with ramucirumab, with a benchmark ORR of 23%[9]. In addition, for the approximately 30% of patients in the primary efficacy population who did not receive prior immunotherapy, this would be considered available therapy, associated with markedly longer DORs of approximately 16-17 months than the 5.1 months observed with poziotinib.

Issue #2: Poor tolerability at the proposed dosage (safety issue)

See discussion under Section 3.2.2.

Issue #3: Inadequate dosage optimization for efficacy and safety

The observed ORR for 12 mg QD, 8 mg BID and 6 mg BID dosages investigated in Cohort 5 of ZENITH20 were similar to that observed in the 16 mg QD cohort given the overlapping

confidence intervals. However, the data are inconclusive due to a limited number of patients who received dosages other than 16 mg QD.

Table 8: Efficacy comparisons at various dosages investigated in patients with previously treated NSCLC harboring HER2 exon 20 insertions

	Cohort 2 Primary	Cohort 5 Exploratory				
Efficacy parameter	16 mg QD N=90	16 mg QD N=10	8 mg BID N=27	12 mg QD N=16	6 mg BID N=15	10 mg QD N=14
ORR, n (%) **95% CI**	25 (28%) (19, 38)	4 (40%) (12, 74)	6 (22%) (9, 42)	4 (25%) (7, 52)	2 (13%) (2, 40)	1 (7%) (2, 34)

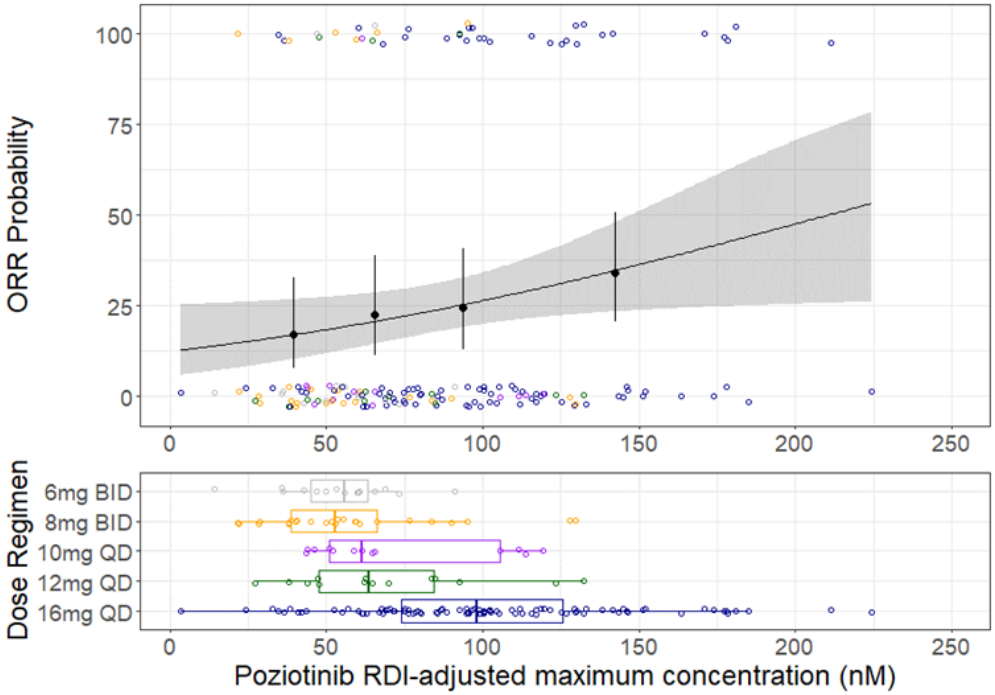
Abbreviations: ORR – Overall Response Rate; QD – Once daily; BID – Twice daily; CI – Confidence Interval.
Source: SPI-POZ-202 Clinical Study Report.

FDA performed independent E-R analyses for efficacy. Efficacy data (cut off: 11/19/2021) consisted of 163 previously treated patients with HER2 exon 20 insertions from Cohort 2 (n=87) and Cohort 5 (n=76) of ZENITH20. The majority of the patients received 16 mg QD (n=96) as a starting dose (vs. n=25 for 8 mg BID, n=14 for 12 mg QD, n=13 for 10 mg QD, and n=15 for 6 mg BID).

E-R analyses revealed that Cmax,ss of poziotinib was associated with greater probability of ORR (Figure 1). For equivalent total daily dosages, administered once daily or twice daily, these exploratory analyses show that a higher Cmax,ss (16 mg once daily) appears associated with a higher probability of achieving ORR, compared to the lower Cmax,ss (8 mg twice daily). However, the relationship between Cavg,ss and ORR was flat over the dosage range evaluated (6 mg BID, 8 mg BID, 10 mg QD, 12 mg QD and 16 mg QD) (Figure 2). These E-R analyses for the efficacy comparison do not clearly support one dosage compared to another and it it uncertain if alternative dosages may maintain efficacy. FDA concludes that these E-R relationships for efficacy are considered preliminary, based on limited data available at dosages other than 16 mg QD and may change upon follow-up readouts, which will not be available during the current review cycle.

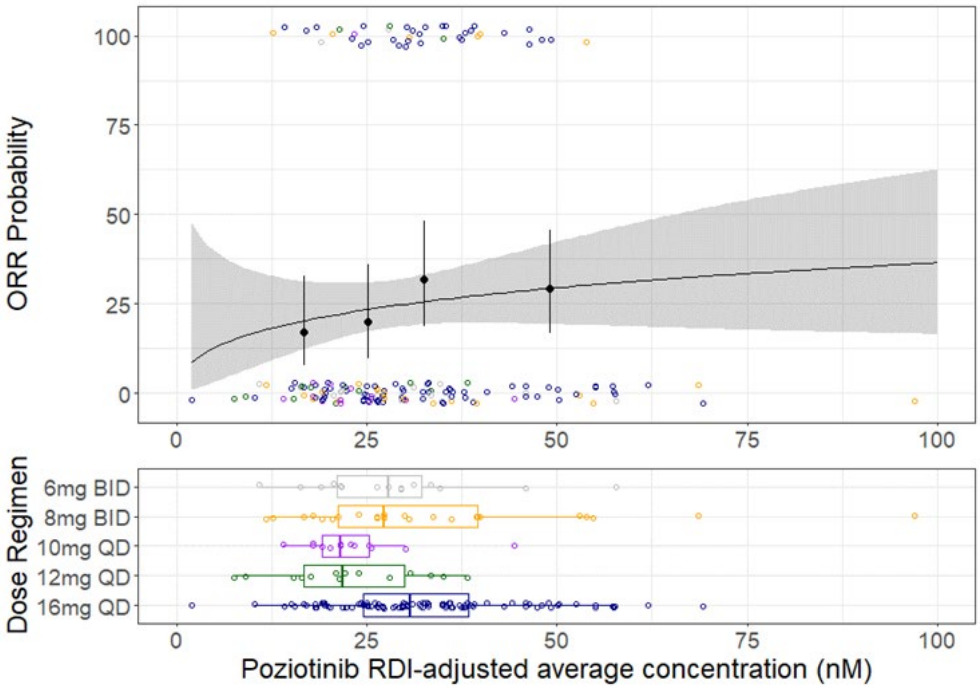
Based on the available clinical safety and efficacy data and FDA's E-R analyses, alternative dosages may improve tolerability while providing similar effectiveness.

Figure 1: Higher Cmax, (as shown for 16 mg once daily regimen) appears associated with a higher probability of achieving ORR



Data source: spi-poz-202-bor-qdbid-d120resp-allexpo-erprthpy.csv (eCTD Sequence 0031), ZENITH20 cohort 2 and 5, data cut off at 11/19/2021, N=163

Figure 2. Association between ORR and average concentration at steady-state appears flat



Data source: spi-poz-202-bor-qdbid-d120resp-allexpo-erprthpy.csv (eCTD Sequence 0031), ZENITH20 cohort 2 and 5, data cut off at 11/19/2021, N=163

Issue #4: Delayed confirmatory trial

According to 21 CFR 314 subpart H, further investigation of a drug is required as part of the accelerated approval provisions. Postmarketing trials should be underway at the time of submission of a marketing application for accelerated approval. Communication between the FDA and the Applicant regarding the potential design for a confirmatory trial began in 2020; however, the study design was not agreed upon until the NDA review was underway and no patients had been enrolled as of July 28, 2022. This delay in initiation and conduct of a confirmatory trial may result in the prolonged exposure of patients to the risk of severe toxicity and marginal efficacy pending results of the randomized study.

To verify the clinical benefit of poziotinib, the Applicant plans to conduct a multiregional, open-label, randomized (2:1) trial of poziotinib 8 mg BID versus docetaxel 75 mg/m^2 in approximately 268 patients with locally advanced or metastatic NSCLC with documentation of HER2 exon 20 insertion mutation in tumor tissue or plasma using an approved next generation sequencing (NGS) diagnostic test who have received at least one prior systemic treatment including platinum-based chemotherapy and an immune checkpoint inhibitor. The primary endpoint is planned to be PFS with OS as a key secondary endpoint. Patients with stable, clinically asymptomatic brain metastases are permitted to enroll. Tumor assessments will be made at baseline and every 6 weeks until disease progression, death, or other protocol-specified reasons for withdrawal from treatment.

Assuming a median PFS of 6 months in the poziotinib arm and 3.5 months in the docetaxel arm, a total of 193 PFS events are needed to provide 95% power to detect a hazard ratio (HR) of 0.58 at a two-sided alpha level of 0.05. The Applicant estimates that with an accrual rate of 2 patients per month for the first year and 8 patients per month thereafter, the primary analysis will occur approximately 47 months after study initiation. No interim analyses are planned.

Assuming a median OS of 9 months in the poziotinib arm and 6 months in the docetaxel arm, a total of 163 OS events are needed to provide 71% power to detect a HR of 0.67 at a two-sided alpha level of 0.05. OS will be tested as part of a hierarchical testing procedure following the analysis of the primary endpoint; no additional analyses of OS are planned.

Safety Issues

- Issue #1: Limited response rate with poor durability (efficacy issue)
- Issue #2: Poor tolerability at the proposed dosage (safety issue)
- Issue #3: Inadequate dosage optimization for efficacy and safety (efficacy and safety issue)
- Issue #4: Delayed initiation of confirmatory trial (efficacy and safety issue)

Sources of Data for Safety

As described in Table 4, the primary safety analysis of poziotinib is based on 368 patients who received poziotinib 16 mg QD in ZENITH20. The safety results in this population are compared with those in patients who received 8 mg BID (N=114) to assess the tolerability of 16 mg QD in the context of an alternative dosage. All safety analyses described in this review are based on the Applicant's 120-day safety update with a DCO date of November 19, 2021.

Safety Summary

An overall summary of safety for poziotinib is provided in Table 9.

Table 9: Overall summary of safety

Safety parameter, %	ZENITH20 16 mg QD (N=368)	ZENITH20 8 mg BID (n=114)
All-causality AEs		
Grade 3-4	79	68
Grade 5	7	1.8
SAEs	42	34
AEs leading to treatment interruption	83	58
AEs leading to dose reduction	57	33
AEs leading to treatment discontinuation	18	18

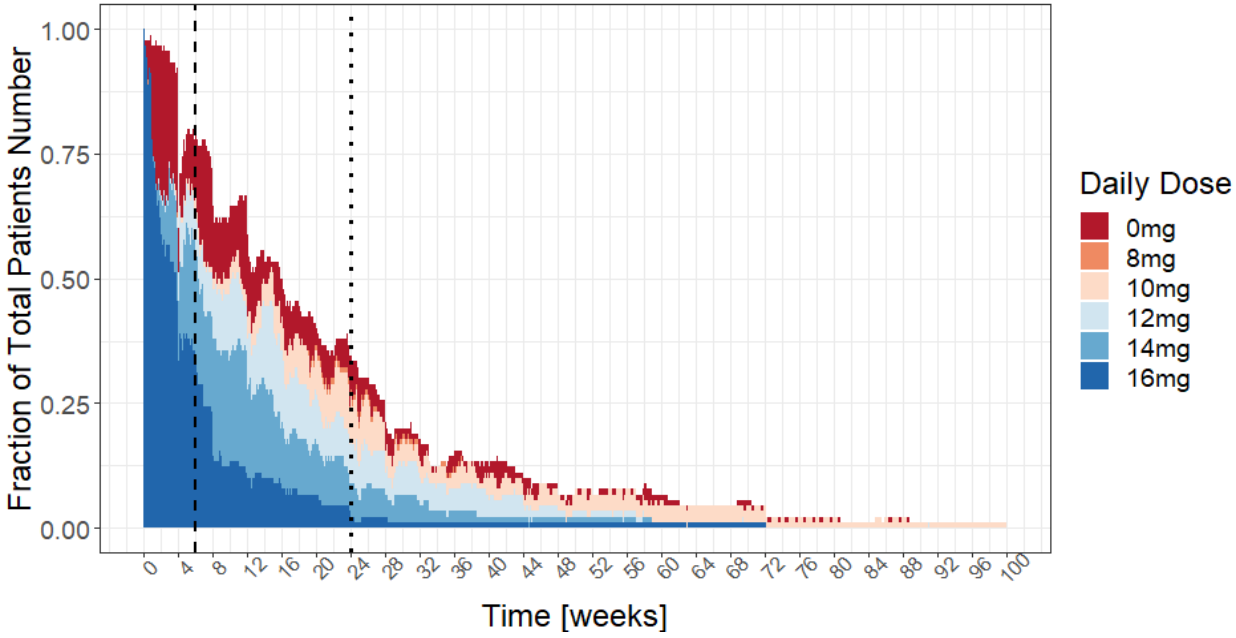
Source: FDA clinical review; adae.jmp

Although patients enrolled at 8 mg BID had a lower incidence of Grade 3-5 AEs and SAEs, there is a marked reduction in AEs leading to treatment interruption and dose reduction by approximately 25%, indicating that the BID dosing schedule may mitigate the tolerability of the treatment.

Given the high rate of dose reductions and interruptions at a dosage of 16 mg QD, the median relative dose intensity (RDI) was 72% or approximately 12 mg per day. The mean time to the first interruption was 29 days, with a duration of approximately 8 days. The poziotinib elimination half-life is 6.3 hours, which would result in no drug in the systemic circulation within less than 2 days following the interruption. It is uncertain whether these early interruptions to manage tolerability may therefore have negative implications on effectiveness.

At 6 weeks following the start of poziotinib, less than 50% of patients enrolled in Cohort 2 who were still receiving poziotinib remained on the starting dosage of 16 mg QD starting dosage (Dashed line, Figure 3). Beyond 24 weeks or 6 months, most patients received daily dosages of 12 mg daily or less (Dotted line, Figure 3). Patients who did not receive a dosage of 16 mg QD due to interruptions are shown in red (Figure 3). Since the fraction of patients receiving the proposed dosage of 16 mg QD decreased rapidly over time, this result suggests the proposed dosing regimen is poorly tolerated.

Figure 3: Poziotinib was poorly tolerated with most patients receiving a reduced dose within one month after treatment initiation at 16 mg QD in ZENITH20 Cohort 2.



Data source: adsl.xpt and ex.xpt (eCTD Sequence 0002), ZENITH20 cohort 2, original submission, N=90

Table 10 provides a summary of the most common events leading to interruption and dose reduction in patients receiving 16 mg QD; rash, mucositis, and diarrhea accounted for the most common reasons for these dosage modifications. As shown in Table 12, these events appear to be at least partially dependent on dosing schedule, with a lower incidence observed in patients who received a dosage of 8 mg BID.

Table 10: Most common AEs (≥ 5%) leading to treatment interruption and dose reduction

Adverse event ZENITH20 16 mg QD; N=368	Treatment interruption, %	Dose reduction, %
Rash (GT)[a]	48	30
Diarrhea (GT)[b]	30	18
Mucositis (GT)[c]	18	10
Nail disorders (GT)[d]	9	5
Fatigue (GT)[e]	8	
Nausea	5	
Pruritus	5	
Vomiting	5	

Source: FDA clinical review; adae.jmp

a: Grouped term rash (GT) includes preferred terms rash, dermatitis acneiform, rash maculo-papular, rash erythematous, rash papular, palmar-plantar erythrodysesthesia syndrome, dermatitis, skin exfoliation, rash morbilliform, rash macular, eczema, erythema multiforme, rash pruritic, rash pustular, dyshidrotic eczema, vulvovaginal rash.

b: Grouped term diarrhea (GT) includes preferred terms diarrhea, enterocolitis, colitis.

c: Grouped term mucositis (GT) includes preferred terms stomatitis, mucosal inflammation, glossitis, cheilitis, mouth ulceration tongue ulceration, aphthous ulcer.

d: Grouped term nail disorder (GT) includes preferred terms paronychia, nail disorder, onychalgia, onychoclasis, onycholysis, nail toxicity, onychomadesis, onychomycosis.

e: Grouped term fatigue (GT) includes preferred terms fatigue, asthenia.

Table 11: Comparison of incidence of select AEs at 16 mg QD and 8 mg BID

Adverse event, %	ZENITH20 16 mg QD n=368	ZENITH20 8 mg BID n=114
Rash (GT)[a]	92	76
Diarrhea (GT)[b]	83	76
Mucositis (GT)[c]	74	63

Source: FDA clinical review, adae.jmp

a: Grouped term rash (GT) includes preferred terms rash, dermatitis acneiform, rash maculo-papular, rash erythematous, rash papular, palmar-plantar erythrodysesthesia syndrome, dermatitis, skin exfoliation, rash morbilliform, rash macular, eczema, erythema multiforme, rash pruritic, rash pustular, dyshidrotic eczema, vulvovaginal rash.

b: Grouped term diarrhea (GT) includes preferred terms diarrhea, enterocolitis, colitis.

c: Grouped term mucositis (GT) includes preferred terms stomatitis, mucosal inflammation, glossitis, cheilitis, mouth ulceration tongue ulceration, aphthous ulcer.

The Applicant states that poziotinib fulfills an unmet need given its improved toxicity profile over currently available therapies, however, there were fatal cases of ILD/pneumonitis observed at a dosage of 16 mg QD.

Interstitial lung disease (ILD)/pneumonitis was considered an AE of special interest (AESI) for poziotinib. According to the ZENITH20 protocol, patients with a history of Grade ≥ 2 pneumonitis were ineligible for the study.

At a dosage of 16 mg QD (N=368), a total of 13 patients (3.5%) experienced an event of ILD/pneumonitis. Of these, 3 events (0.8%) were fatal and an additional 4 events (1.1%) were Grade 3 in severity. For all but one event, the dose was reduced, withdrawn, or treatment was interrupted.

At a dosage of 8 mg BID (N=114), a total of 4 patients (3.5%) experienced an event of ILD/pneumonitis. Of these, one event (0.9%) was fatal, two events (1.8%) were Grade 3 in severity and poziotinib was either withdrawn or interrupted, and one event (0.9%) was Grade 1 in severity and no action with poziotinib was taken.

At a dosage of < 16 mg daily (N=98), a total of 3 patients (3.1%) had an event of ILD/pneumonitis; of these one (1.0%) was fatal and two (2.0%) were Grade 2 in severity.

A summary of the fatal events of ILD/pneumonitis in patients who received a total dose of 16 mg daily is provided in Table 12.

Table 12: Fatal Adverse Events of Pneumonitis in the Overall Safety Population

Cohort/ Starting Dosage	Preferred Term	Study Day	Clinical Summary
3 16 mg QD	Pneumonitis	92	73-year-old male was hospitalized on Day 83 for worsening dyspnea and hypoxia; received oxygen, antibiotics, steroids and non-invasive ventilation. Patient continued to have worsening respiratory insufficiency and died on Day 92. The investigator assessed the event as possibly related to study therapy.
3 16 mg QD	Pneumonitis	176	54-year-old female previously treated for Hodgkin's Lymphoma with MOPP/ABVS and mantle radiotherapy in 1991 was hospitalized on Day 174 due to worsening Grade 3 dyspnea and chest CT showing bilateral interstitial lung disease. Despite management, patient's condition deteriorated rapidly and she died on day 176. The investigator assessed the event as probably related to study therapy.
4a 16 mg QD	Pneumonitis	84	51-year-old male was hospitalized on Day 73 for worsening dyspnea and cough. Chest CT revealed bilateral ground glass lung infiltrates. Patient was treated with oxygen, steroids, antibiotics and

			intubated. Patient's condition deteriorated and progressed to respiratory failure with cardiac arrest and he died on Day 84. The investigator assessed the event as possibly related to study therapy.
7a 8 mg BID	Pneumonitis	13	62-year-old female previously treated with cisplatin and pemetrexed with a chest CT showing right lung consolidation and left lung ground glass opacity prior to initiating poziotinib. On Day 13, patient was hospitalized with worsening hypoxia. She had a chest x-ray which revealed increased interstitial and airspace opacities. She was intubated and treated with antibiotics with minimal response and died on Day 14. The investigator considered the event as unlikely related to study therapy. *FDA assessment: Although the Applicant considers this event to be unlikely due to study therapy, given the patient's pre-existing CT findings, it is not possible to exclude the contribution of poziotinib to either new-onset or worsening drug-related pneumonitis. Therefore, FDA considers the event to be possibly related to poziotinib.*

Source: FDA clinical review; SPI-POZ-202 120 day safety update

Although these analyses are limited by a small number of patients who received 8 mg BID, fewer patients experienced an event of ILD/pneumonitis at 8 mg BID, and the events were less severe in grade overall with one fatality compared to three.

Safety Issues in Detail

Issue #1: Limited response rate with poor durability

See discussion under Section 3.1.3

Issue #2: Poor tolerability at the proposed dosage

See discussion under Section 3.2.2.

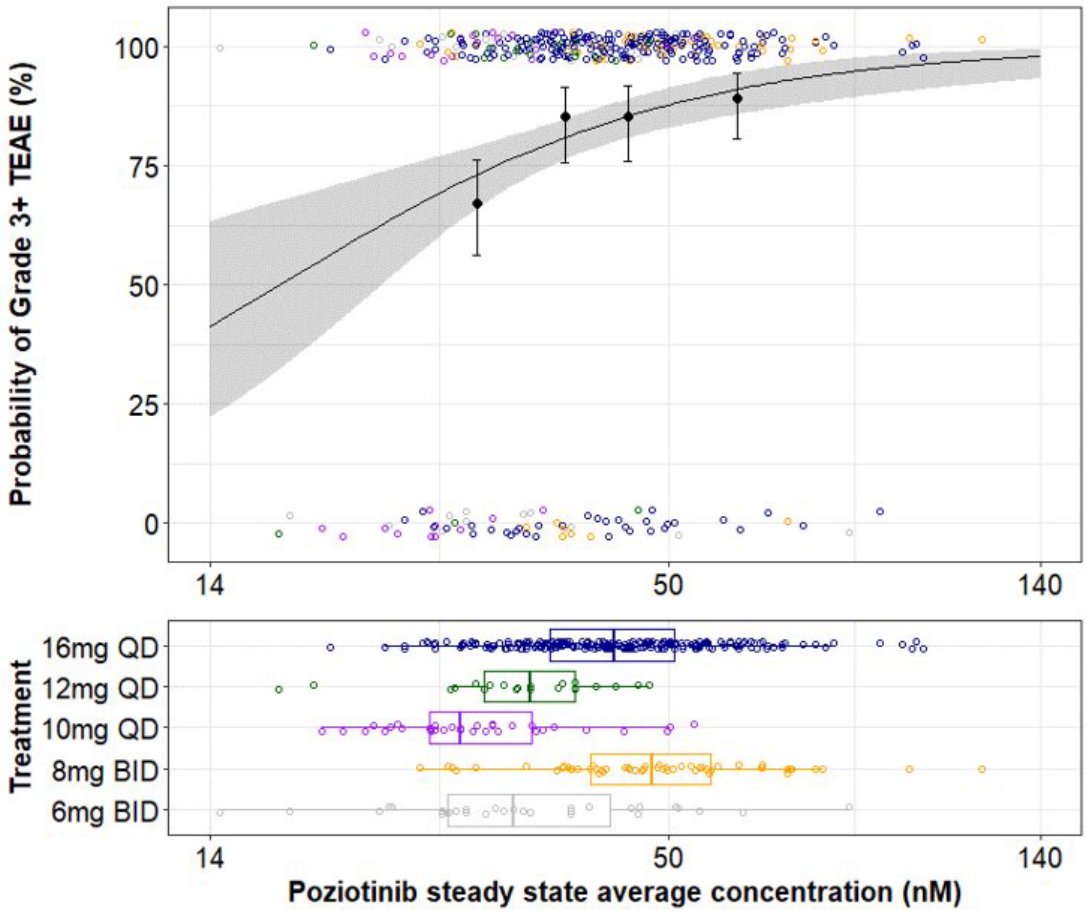
Issue #3: Inadequate dosage optimization for efficacy and safety

FDA performed independent exposure-response analyses for safety.

With respect to E-R analyses for safety, Cavg,ss was correlated with TEAEs including Grade 3+ TEAE, diarrhea, stomatitis and TEAE leading to dose reduction. Therefore, additional data are needed to determine if alternative dosages may lead to better tolerability and benefit-risk.

Safety data (cut off: 05/16/2022) was derived from 361 previously treated patients with EGFR or HER2 exon 20 insertions from ZENITH20 Cohort 1 (n=111), Cohort 2 (n=87), and Cohort 5 (n=163). Most patients received 16 mg QD (n=222) (vs. n=54 for 8 mg BID, n=21 for 12 mg QD, n=33 for 10 mg QD, and n=31 for 6 mg BID). Logistic regressions were performed to correlate measures of poziotinib exposure with significant safety measures, including Grade 3+ TEAEs, Grade 3+ treatment-emergent diarrhea, Grade 3+ treatment-emergent stomatitis, Grade 3+ treatment-emergent rash, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to treatment discontinuation. Figure 4 demonstrates that the higher Cavg,ss was associated with greater probability of Grade 3+ TEAEs.

Figure 4: Greater probability of adverse events with higher average concentration at steady-state following 16mg QD compared to other dosages investigated



Data source: poz-202-tte-safety-20220808-1417-allexpos.csv (eCTD Sequence 0062) and adtte_ir.xpt (eCTD Sequence 0050), ZENITH20 cohort 1, 2 and 5, data cut off at 05/16/2022, N=361

Issue #4: Delayed initiation of confirmatory trial (efficacy and safety issue)

See discussion under Section 3.1.3.

Risk Mitigation

The commercial product intended for use for the poziotinib 16 mg equivalent dose is the free base form of poziotinib 14.8 mg. The Applicant proposes to use tablets in two different dose forms, 7.4 mg and 1.85 mg. This would require dose reductions as shown in Table 13.

Table 13: Dose Reductions based on Proposed Tablet Strength

Dose Reduction	Dose (Orally Once Daily)
First	13.3 mg (seven 1.85 mg tablets)
Second	11.4 mg (six 1.85 mg tablets)
Third	9.5 mg (five 1.85 mg tablets)

Source: FDA chemistry and manufacturing review

To facilitate a dose reduction, patients may have to take a different and greater number of tablets than previously administered. **This may pose a risk of medication error that has not been adequately mitigated.**

Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	HER2 exon 20 insertion mutation positive NSCLC represents 2-4% of all metastatic NSCLC cases. This mutation is associated with female patients who are never smokers. The median overall survival of patients with HER2 exon 20 insertion mutation positive NSCLC is approximately 1.6-1.9 years.	Locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations is a life-threatening condition with poor survival.
Current Treatment Options	• Available first line therapy for patient with metastatic NSCLC with HER2 exon 20 insertion mutations includes the same therapies for the treatment of metastatic NSCLC that does not harbor a targetable mutation. • Second line available therapies for this patient population include immune checkpoint inhibitors and pemetrexed if not already given as part of a first-line regimen, docetaxel with ramucirumab, or docetaxel alone. • Enhertu was granted accelerated approval on 08/11/2022 based on an ORR 58% (95% CI 43, 71) and mDOR 8.7 months (95% CI (7.1, NE).	FDA-approved available treatment options for patients with NSCLC with HER2 exon 20 insertion mutations with progression on or after prior therapy include single agent chemotherapy, combination chemotherapy, or an immune checkpoint inhibitor if not previously received. Enhertu has accelerated approval, with regular approval pending confirmation of benefit based on a randomized trial and is not considered available therapy.
Benefits	• The primary efficacy data supporting this NDA is derived from Cohort 2 of ZENITH20, a global, open label, non-randomized, multicohort trial (N=482), including 90 patients with locally advanced or metastatic HER2 exon 20 insertion mutation positive NSCLC who received poziotinib 16 mg QD and progressed on at least one prior systemic therapy. • The ORR observed in the primary efficacy population was 28% (95% CI: 19, 38), with a median DOR of 5.1 months (95% CI 4.2, 5.5); only 24% of patients had a duration of response of ≥ 6 months. Anti-tumor activity results were similar in the subgroup of patients (N=59) who received prior platinum-based chemotherapy and an immune checkpoint inhibitor. • Oral route of administration may be preferred by patients versus the intravenous route for currently available therapies.	The ORR and DOR results observed in the primary efficacy population enrolled in ZENITH20 supporting this NDA may not provide a meaningful advantage over available therapies and may not be likely to predict clinical benefit. **Points to consider:** Do the anti-tumor activity results observed in ZENITH20 provide an advantage over available therapies?

	Evidence and Uncertainties	Comments to the Advisory Committee
Risks and Risk Management	• ORRs ranging from 7-25% were observed at other dosages investigated in in ZENITH20, with widely overlapping 95% confidence intervals compared to the ORR observed in patients who received 16 mg QD. • There was a higher rate of Grade 3-4 AEs, SAEs, and AEs leading to interruption or dose reduction when compared to other dosages, including 8 mg BID. • Fatal cases of ILD were observed at a dosage of 16 mg QD. • The dosage of 16 mg QD appears to be inadequately optimized for both efficacy and safety. • The confirmatory trial, Study SPI-POZ-301, was not well underway at the time of NDA submission and had not enrolled any patients as of July 28, 2022. Results are not anticipated until at least 2026.	Risks from the 16 mg QD dose appear to be related to the dosage level compared to other tested doses. The confirmatory trial to verify the clinical benefit of poziotinib is not well underway and results are not expected until at least 2026. Furthermore, the dose selected for evaluation in the confirmatory trial is 8 mg BID rather than 16 mg QD. This NDA submission may have been premature given the inadequate dosage optimization when considered in the context of marginal efficacy and high toxicity. **Points to consider:** Do the risks of approving a drug with marginal efficacy, poor tolerability, and lack of dosage optimization outweigh the potential benefits?

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. A benefit-risk assessment for poziotinib requires careful consideration of the evidence and remaining uncertainties about the key benefits of a product (as demonstrated in the development program) and potential key risks, as well as the ability to adequately mitigate such risks. This assessment should consider the significant unmet need for patients with this severe and life-threatening disease.

During the course of our review, FDA identified potential key benefits and risks of poziotinib for the treatment of patients with locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations. The key issues for consideration in the benefit-risk assessment of poziotinib include the presumed clinical benefits of the approval of a targeted therapy for a rare patient population, the inadequate dosage optimization in the context of marginal efficacy and high toxicity, and the acceptable tradeoffs between the benefits and risks to patients.

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