PBI-200-101

Protocol Title:	A Phase 1/2 Study of PBI-200 in Subjects with NTRK-Fusion-Positive Advanced or Metastatic Solid Tumors
Indication studied:	Solid tumors
Test Drug:	PBI-200
Study Phase:	1/2
Sponsor Contact:	Nushmia Khokhar, MD Chief Medical Officer Pyramid Biosciences 1200 US Highway 22 East, Suite 2000, #2310 Bridgewater, NJ 08807
Sponsor Signatory:	Nushmia Khokhar, MD Chief Medical Officer +1 (917) 723-0711 nkhokhar@pyramidbio.com
First Patient Enrolled:	21 July 2021
Last Patient Completed:	26 July 2023
Early Study Termination:	30 May 2023
Date of report:	29 January 2024

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline, including the archiving of essential documents.

CONFIDENTIALITY STATEMENT

2. SYNOPSIS

Name of Sponsor/Company: Pyramid Biosciences

Name of Finished Product: PBI-200

Name of Active Ingredient: PBI-200

Title of Study: A Phase 1/2 Study of PBI-200 in Subjects with NTRK-Fusion-Positive Advanced or Metastatic Solid Tumors

Study Centers: 13 study centers enrolled subjects in Australia, France, South Korea, Spain, and the United States

Publications (reference): Not applicable

Studied period (years):	**Phase of development:** 1/2
Date first patient enrolled: 21 July 2021 Date last patient completed: 26 Jul 2023	

Objectives: The planned study objectives are provided in the PBI-200-001 protocol. The objectives for this abbreviated clinical study report (CSR) were as follows:

Phase 1: Dose Escalation

Primary Objectives:

- To determine the safety and tolerability, maximum tolerated dose (MTD), and dose-limiting toxicities (DLTs) of PBI-200 alone and co-administered with ritonavir (PBI-200/ritonavir) in patients with *NTRK*-fusion-positive or neurotrophic tyrosine receptor kinase (*NTRK)*-amplified advanced or metastatic refractory solid tumors or refractory *EWSR1-WT1*-fusion-positive desmoplastic small round cell tumors (DSRCTs).
- To establish the Recommended Phase 2 Dose (RP2D) of PBI-200/ritonavir

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of PBI-200 and metabolite PBI-200-M15
- To evaluate the antitumor activity of PBI-200

Methodology: Study Design

This was a first-in-human, Phase 1/2 open-label, multicenter, dose-escalation, safety, PK, and biomarker study of PBI-200, and PBI-200 co-administered with ritonavir, in patients with *NTRK*-fusion-positive advanced or metastatic solid tumors. Phase 1 also included patients with *NTRK*-amplified advanced or metastatic solid tumors or refractory *EWSR1-WT1*-fusion-positive DSRCTs.

Phase 1 Dose Escalation

Phase 1 was the dose-escalation portion of the study in which the evaluation of safety and tolerability and establishing the RP2D were primary objectives. Patients in Phase 1 with *NTRK*-fusion-positive non-brain primary tumors were previously treated with a TRK inhibitor (e.g., larotrectinib, entrectinib). Patients with *NTRK*-amplified advanced or metastatic solid tumors, *EWSR1-WT1*-fusion-positive DSRCTs or with primary brain tumors may have been treated with a TRK inhibitor, but this was not required (except for patients enrolled in the Republic of Korea).

A 3 + 3 design was utilized. However, because of the rarity of adult patients with NTRK-fusions or amplification in solid tumors or *EWSR1-WT1*-fusion-positive DSRCTs, and in order to minimize the number of patients treated at potentially sub-therapeutic doses, single-patient cohorts were enrolled initially, until a patient had a $\geq$ Grade 2 treatment-related, non-hematologic adverse event (AE) requiring medical or procedural intervention during the DLT period, at which time 2 additional patients were enrolled in that cohort, and a 3 + 3 design was subsequently utilized. In addition, in the absence

of a ≥ Grade 2 treatment-related, non-hematologic AE requiring medical or procedural intervention during the DLT period the Sponsor could decide to expand a single-patient cohort to a 3 + 3 cohort in order to obtain additional safety and/or PK data at that dose level. Enrollment will be sequential to allow for assessment of a sentinel patient in each cohort. Enrollment could proceed after completion of the Cycle 1 Day 8 safety assessment for the sentinel patient.

Dose escalations of up to 100% of the prior dose were permitted until the occurrence of a ≥ Grade 2, treatment-related, non-hematologic AE requiring medical or procedural intervention during the DLT period. Subsequent dose escalations could be no more than 50% of the prior dose. The starting dose of PBI-200 for Cohort 1 was 250 mg administered orally once daily (250 mg QD) in the fasted state, a dose which was less than half the starting dose supported by the GLP nonclinical toxicology studies. If 250 mg QD was not tolerable, dose de-escalation levels between 50 mg and 200 mg (inclusive) could be evaluated. Twice daily (BID) dosing could have been implemented for doses requiring a high pill burden and/or based on PK data, as appropriate, based on assessment of PK parameters and safety by the Safety Review Committee (SRC).

Under the 3 + 3 design, cohorts of at least 3 patients were enrolled at a dose level. If none of the evaluable patients experienced a DLT, the dose was escalated to the next highest dose level. If 1 of the initial patients in a cohort experienced a DLT, up to 3 additional patients were enrolled and treated at the same dose. If none of the additional patients had a DLT (i.e., only 1 of 6 patients in the cohort had a DLT), the dose was escalated to the next highest level. If 2 or more of up to 6 patients at a dose level had DLTs, enrollment to that cohort stopped and the dose was considered to be above the MTD. The dose was then decreased to the previous dose level or to a level intermediate to those previously evaluated. If only 3 patients were enrolled at this previous dose level, 3 additional patients were enrolled and treated to confirm that this was a tolerable dose level. The DLT period for each patient in Phase 1 was 4 weeks (Cycle 1). Patients were considered evaluable for DLTs if they completed Cycle 1, received at least 75% of their assigned daily dose during the DLT period or had a DLT during the DLT period. Study patients who were not evaluable for safety throughout the DLT period for reasons other than PBI-200-related toxicity were replaced in the same dose cohort. In order to ensure that the required number of patients was evaluable for each cohort, additional patients could initially be enrolled (e.g., in a 3+3 cohort, 4 patients could be enrolled initially, rather than 3). Once the required number of patients (following the single patient cohort or 3+3 cohort design) completed the DLT period, a dose escalation decision could be made. For example, if more than 1 patient was enrolled in a single patient cohort, only the first evaluable patient was required to complete the DLT period prior to the dose escalation decision.

Once the required number of patients in a cohort had either received treatment through the DLT period or discontinued treatment due to treatment-related toxicity, the SRC, consisting of a non-Investigator oncologist, the Investigators who have enrolled patients in the current cohort, the study Medical Monitor, and ad hoc members (e.g., other Investigators, a statistician) as needed, reviewed all available safety data, including DLTs, and all available PK data, and made dose-level recommendations. Recommendations could be to open a new cohort at a higher dose level, to expand the current dose level (e.g., to obtain additional safety data prior to deciding on the next dose level), or to dose de-escalate. While the primary basis for the dose level decisions was the occurrence of DLTs, all available safety and PK data, including longer-term safety data from patients treated in lower dose cohorts, were considered. Where the SRC recommended opening a new cohort at a higher dose level, they could also recommend that patients being treated at lower doses dose escalate to the dose level that had just been reviewed and deemed tolerable, as long as the patient was currently not experiencing ≥ Grade 3 treatment-related AEs.

Cohorts that had completed initial enrollment and had undergone review by the SRC could be enrolled (i.e., backfilled) with additional eligible patients. Those patients were not evaluated for DLTs, but any available safety and PK findings were considered during subsequent SRC reviews.

The MTD was the highest dose of PBI-200/ritonavir that was evaluated where ≤ 1 of 6 (or less than 33% of) patients had a DLT. The RP2D was the MTD or a biologically active dose below the MTD (note: if objective responses were demonstrated prior reaching the MTD, the SRC could recommend stopping dose escalation prior to the determination of the MTD). A minimum of 6 patients were enrolled to any dose level being evaluated as the RP2D.

Toxicities which met the criteria for DLT that were observed in patients undergoing intra-patient dose escalation or those enrolled to backfill cohorts, were not considered DLTs, but contributed to overall safety assessment and the SRC's subsequent dose-level recommendations.

Once the RP2D for PBI-200/ritonavir was established, 2 expansion cohorts could have been opened to accrual; however, the study was halted prior to the cohort expansion phase of the study. Planned methodology for Phase 2 is provided in the PBI-200-101 protocol.

Number of Patients (Planned and Analyzed):

Approximately 91 patients were planned for inclusion in this study, as follows:

Phase 1: Approximately 35 patients

Phase 2 Non-Brain Primary Tumor Cohort: Approximately 41 patients

Phase 2 Primary Brain Tumor Cohort: Approximately 15 patients

Due to the Sponsor's decision to halt the study early, a total of 29 patients were enrolled into the Phase 1 Dose Escalation portion of the study.

Diagnosis and Main Criteria for Inclusion:

1. Patient had one of the following solid tumors which had progressed on or following at least one systemic therapy regimen administered for advanced or metastatic disease or for which no approved therapy existed (patients who had received a prior TRK inhibitor may have been eligible after progression or intolerance of therapy):
   - *NTRK*-fusion-positive, locally advanced (i.e., not amenable to surgical resection) or metastatic solid tumor
   - NTRK-gene amplified, locally advanced or metastatic solid tumor (Phase 1 only)
   - EWSR1-WT1-positive DSRCTs (Phase 1 only).
2. Patients with *NTRK*-fusion-positive solid tumors other than primary brain tumors (non-brain primary tumors) must have previously received treatment with a TRK inhibitor, ***unless the patient did not have access to TRK-inhibitor therapy (e.g., no TRK inhibitor was marketed and available to the patient in the patient's country) or unless the Patient was ineligible for marketed TRK-inhibitor therapy (e.g., patient had a resistance mutation).***
3. Patients with *NTRK*-gene-amplified solid tumors, primary brain tumors or *EWSR1-WT1*-positive DSRCTs may have received prior treatment with a TRK inhibitor but this was not required.
4. Patients with brain tumors and brain metastasis must have been neurologically stable. Patients with asymptomatic brain metastases were eligible.
5. Age ≥ 18 years at the time of signing the informed consent form (ICF).
6. Had provided written informed consent.
7. Eastern Cooperative Oncology Group (ECOG) performance score (PS) score of 0 or 1.
8. Acceptable liver, renal, hematologic, and coagulation function.
9. Ability to swallow capsules or tablets and no gastrointestinal issues that may have impacted absorption of oral medication.
10. Women of child-bearing potential must have agreed to use highly effective contraceptive methods and avoid egg donation during the study treatment and for 6 months after the last dose of study treatment.

11. Men of reproductive potential agreed to use highly effective contraceptive methods and avoided sperm donation during the study treatment and for 6 months after the last dose of study treatment. A man was considered to be of child-producing potential unless he had had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy

Investigational Product, Dosage, and Mode of Administration:

PBI-200 is a novel, small molecule, central nervous system penetrant inhibitor of *NTRK1*, *NTRK2*, and *NTRK3*. Three orally administered drug products were used in this study:

- The original dosage form of PBI-200, a micronized solid form (D90 < 10 micron) in hard gelatin capsules (drug in capsule). Supplied in two strengths, 50 mg (size 4) or 200 mg (size 0) capsules.
- A tablet formulation of PBI-200 supplied in two strengths, 50 mg (yellow-coated round tablets) and 200 mg (blue-coated oval tablets).
- Ritonavir, a PK enhancer, manufactured by Abbvie and supplied as white, film-coated, ovaloid 100 mg tablets.

Duration of Treatment: Patients could have continued treatment as long as they were tolerating treatment without disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or Response Assessment in Neuro-oncology (RANO) criteria, as appropriate. Patients with disease progression could have been allowed to continue study treatment if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the Medical Monitor.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable as this was an open-label study.

Criteria for Evaluation:

Safety was evaluated on an ongoing basis throughout the study. Ongoing safety evaluations included physical examination, clinical laboratory tests, vital signs, ECOG PS, and electrocardiograms. AEs were assessed using National Cancer Institute Common Terminology for Classification of Adverse Events v5.0. During the Screening Period, all AEs related to study-mandated procedures and all serious adverse events (SAEs) were recorded. As of Day -2, the first day of study treatment, through the End-of-Treatment (EOT) Visit, all SAEs and AEs were recorded, regardless of causality. After the EOT Visit evaluation, ongoing related SAEs and clinically significant related AEs were followed until either resolution or determination by the Investigator that the event was stable and/or irreversible.

Although planned, assessment of efficacy and biomarkers are not included for this abbreviated CSR. Pharmacokinetic results are described briefly and provided as an appended report.

SUMMARY – CONCLUSIONS

Twenty-eight of the 29 patients comprising the Safety Population reported treatment-emergent adverse events (TEAEs) during the study and 14 patients had a TEAE considered by the investigator to be drug related. The most frequently reported TEAEs overall were alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. There was no dose dependence observed with drug-related TEAEs. All TEAEs reported were ≤ Grade 3 with the exception of a Grade 4 event of ischemic attack and Grade 5 event of acute respiratory distress. Thirteen patients reported serious TEAEs, none of which were considered drug related except for an event of cognitive disorder. Three patients discontinued study treatment due to TEAEs (1 patient due to a drug-related event of ALT increased; 1 patient due to drug-related events of fatigue and cognitive disorder; and 1 patient due to a fatal event of acute respiratory disorder).

Upon careful examination of the emerging data for PBI-200 from the cohorts in Phase 1, the Sponsor decided to halt further development of PBI-200 prior to moving forward to the pivotal Phase 2 cohorts. This decision was unrelated to the safety of PBI-200.
Date of the Report: 29 Jan 2024