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Sponsor: Principia Biopharma Inc. **Drug substance(s):** PRN1371	**Study Identifiers:** NCT02608125 **Study code:** PRN1371-001
Title of the study: Phase 1 Open-Label, Multicenter, Dose-Escalation Study of PRN1371, a FGFR1-4 Kinase Inhibitor, in Adult Patients with Advanced Solid Tumors, followed by an Expansion Cohort in Patients with FGFR1, 2, 3, or 4 Genetic Alterations	
Study centers: 7 sites in the US and Spain	
Study period: Date first participant enrolled: 28/Oct/2015 Date last participant completed: 23/Jun/2020 Study Status: *Terminated (focus portfolio on immune-mediated diseases)*	
Phase of development: Phase 1	

Objectives:

The primary objectives of this study were as follows:

Part A

- To investigate the safety and tolerability of PRN1371 in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) of PRN1371

Part B

- To investigate the safety and tolerability of PRN1371 in participants with Metastatic urothelial cell carcinoma (mUC)

The secondary objectives of this study were as follows:

Part A

- To determine the pharmacokinetic (PK) profile of PRN1371
- To evaluate the pharmacodynamic (PD) effects of PRN1371 (serum phosphate and serum fibroblast growth factor 23 [FGF23])
- To evaluate the clinical activity of PRN1371, including clinical response rates, among subsets of patients with solid tumors with FGFR1, 2, 3, or 4 genetic alterations
- To evaluate the effect of a moderate fat meal on the oral bioavailability and PK parameters of PRN1371

Part B

- To determine the applicable PK parameters of PRN1371
- To evaluate the PD effects of PRN1371 (serum phosphate)
- To evaluate the clinical activity of PRN1371, including clinical response rates, among subsets of participants with mUC and FGFR1, 2, 3, or 4 genetic alterations
- To evaluate the effect of a moderate fat meal on PRN1371 PK

Methodology:

Design: This Phase I study utilized a multicenter, open-label, dose-escalation, nonrandomized design. PRN1371-001 was a 2-part Phase I, open-label, multicenter, dose-escalation study in adult patients with advanced solid tumors (Part A), followed by an expansion cohort (Part B).

In Part A, a 3+3 design was used in which the dose of PRN1371 was escalated in successive cohorts of 3 patients per dose level determined by the Cohort Review Committee. The number of dose levels examined in this phase depended on the tolerability of PRN1371. The oral dose of PRN1371 started at 15 mg once daily (QD) and was escalated to 20, 25, and 35 mg QD plus 15 and 25 mg twice daily (BID). The initial evaluation period for Part A consisted of up to three 28-day cycles, in the absence of disease progression. Patients continued on study until they experienced either intolerable toxicity or until the investigator determined they were no longer benefitting from study therapy. Patients with evidence of disease progression at any time during the study were withdrawn from PRN1371 treatment. All patients were followed to disease progression or treatment failure.

In the expansion cohort of this study (Part B), the safety and tolerability, preliminary antitumor activity, pharmacokinetics (PK), and pharmacodynamics (PD) of PRN1371 were evaluated in adult patients with metastatic urothelial cell carcinoma (mUC) pre-identified with fibroblast growth factor receptor (FGFR) genetic alterations (ie, FGFR 1, 2, 3, or 4 gene mutations, fusions, or truncations and other genetic alterations) believed likely to indicate responsiveness to an FGFR inhibitor.

Number of participants:

Enrolled in Part A: 36

Enrolled in Part B: 9

Evaluated:

Efficacy: 45

Safety: 45

Pharmacokinetics Part A: 36 patients for Cycle 1 Day 1, 31 patients for Cycle 1 Day 15

Part B: 9 patients for Cycle 1 Day 1 and Day 15,

Diagnosis and criteria for inclusion:

Part A

- Males and females ≥18 years with metastatic or recurrent disease who failed first-line systemic treatment, and if indicated, failed approved second-line therapy, and for whom no standard therapy options were anticipated to result in a durable remission
- Patient must have had evaluable, progressive, and measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1, and all sites of disease must have been documented
- Life expectancy of at least 12 weeks
- Patients must not have received prior treatment with a highly selective FGFR inhibitor for more than 8 weeks

Part B

- Histological and/or cytological documentation of mUC (ie, cancer of the bladder, renal pelvis, ureter, or urethra). Participants with urothelial carcinoma (transitional cell) with squamous differentiation or mixed cell types are eligible.

Study products

Investigational medicinal product(s):

Part A: PRN1371 was administered orally as immediate-release capsules at dose strengths of 5 mg and 25 mg.

Part B: PRN1371 35 mg QD with the option to reduce the dose if required.

Duration of treatment: The initial evaluation period for Part A consisted of up to three 28-day cycles. Patients were permitted to continue on study until they experienced either intolerable toxicity or until the investigator determined they were no longer benefitting from study therapy.

Criteria for evaluation:

The primary endpoints of this study were as follows:

Part A

- Incidence of dose-limiting toxicities (DLTs) (to determine the MTD and the maximum administered dose [MAD])
- Incidence of treatment-emergent adverse events (TEAEs) for each dose tier, including clinically significant changes in physical examination, laboratory safety tests, electrocardiograms (ECGs), and vital signs
- Clinical response rates (objective response rate [ORR], progression-free survival [PFS], and duration of objective response [DOR] using RECIST criteria)

Part B

- Tolerability of the selected dose in Part B
- Incidence of treatment-emergent adverse events (TEAEs) by dose and regimen, including clinically significant changes in physical examination, laboratory safety tests, electrocardiograms (ECGs), and vital signs
- Overall response rate [ORR, defined as complete response (CR)+PR]
- Clinical benefit rate [CR+PR+stable disease (SD)]
- Progression-free survival [PFS]
- Duration of response [DOR] using Response Evaluation Criteria in Solid Tumors (RECIST) criteria

The secondary endpoints of this study were as follows:

Part A

- Assessment of PK parameters of PRN1371
- Assessment of the timing and extent of changes in serum phosphate and FGF23 at Baseline (Day 1), Cycle 1

Part B

- Assessment of PK parameters of PRN1371
- Serum phosphate at (pre-dose), Cycles 1-2, Days 1 & 15 and Day 1 of all subsequent cycles. Serum FGF23 was not collected

Statistical methods:

Analysis Populations:

Safety population: all enrolled patients who received at least 1 dose of study drug.
Efficacy population: all enrolled patients who received at least 1 dose of study drug.
PK population: all participants who provided adequate plasma concentration data to allow for PK analysis

Efficacy Evaluations:

The efficacy analyses used the Efficacy population. Patient response and disease progression were determined using RECIST guidelines version 1.1. The ORR was defined as the proportion of patients with a confirmed complete response (CR) or partial response to the treatment, based on an overall assessment of both target and nontarget lesions. All patients were followed to disease progression. For each patient, the PFS time was defined as the time from the patient's first dose of PRN1371 to either the patient's disease progression or death, whichever occurred first. The DOR for a patient was defined as the time from the patient's initial objective response (CR or partial response, whichever occurred first) to PRN1371 therapy until disease progression or death, whichever occurred first. Efficacy data were summarized by descriptive statistics by cohort.

Pharmacokinetic Evaluations:

The PK analyses used the PK population. The main absorption and disposition parameters were estimated using non-compartmental analysis, which was performed for all patients with sufficient concentration data from Cycle 1 Day 1 and Cycle 1 Day 15 for calculation of PK parameters. The terminal elimination rate constant (λz) was calculated by linear regression of the log plasma concentration in the apparent terminal elimination phase of the concentration-time profile. The number of points used in λz calculation was determined by visual inspection of the data describing the terminal phase. At least the last 3 time points with measurable values were used in λz calculation. The number of points resulting in the highest adjusted coefficient of determination (Rsq adj) was used. If the Rsq adj value was < 0.8, λz and related parameters (eg, AUCinf, t1/2, CL/F and V/F) were not calculated or reported. Pharmacokinetic parameters were summarized using descriptive statistics.

Pharmacodynamic Evaluations:

The PD analyses used the Safety population. Serum phosphate and FGF23 were summarized by descriptive statistics by cohort and maximum dose level at each time point. Summaries were also presented for the change from baseline for each visit and cohort.

Safety Evaluations:

The safety analyses used the Safety population. Quantitative safety data were summarized by descriptive statistics by cohort and maximum dose level. Summaries, as well as shift tables where appropriate, were also presented for the change from baseline. As appropriate, listings, summary tables, and graphs (individual plots and/or mean plots) by period were provided for safety and tolerability assessment.

Adverse events were mapped according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. The number and percentage of patients with TEAEs was displayed by system organ class (SOC) and preferred term (PT), by cohort, and by maximum dose. TEAEs were reported by number of events and by number of patients. For the total number of patients with TEAEs, at each SOC/PT level, a patient was counted only once if they experienced 1 or more AEs within each SOC/PT at the greatest severity. The same summary was performed for all serious TEAEs, and all TEAEs causing discontinuation of study drug. TEAEs were also summarized by reported relationship (not related or related). TEAEs and serious TEAEs were summarized by greatest reported severity grade per CTCAE version 4.0 for each event PT.

Summary Results:

Patient Disposition:

Part A

A total of 36 patients were screened and enrolled. All 36 enrolled patients (100%) were reported as having completed Cycle 1 (the DLT observation period). Twenty-three patients (63.9%) completed Cycle 2. A total of 11 patients (30.6%) completed the initial evaluation period (Cycles 1 through 3) for Part A of this study.

Part B

All 9 enrolled patients (100%) were reported as having completed Cycle 1, 8 patients (88.9%) completed Cycle 2 and 7 patients (77.8%) completed Cycles 1 through 3 for Part B of this study.

Baseline Demographics:

Part A

Overall, 52.8% of total patients were male. The majority of patients were White (83.3%) and not Hispanic or Latino (83.3%). The median (min, max) age of the Safety population was 58.5 (26, 88) years. Demographics were generally similar among the 6 maximum dose groups. The medical history data were consistent with demographic and disease characteristics in this diseased population and were generally similar among the 6 maximum dose groups. Cancer histories were generally similar among maximum dose groups. For all patients, the median (min, max) time from the original cancer diagnosis to current treatment was 2.79 (0.7, 14.3) years. For all patients, the median (min, max) time from progressive disease to current treatment was 41.5 (7, 534) days. The most frequent sites of primary lesions (≥5% of total patients) were breast (19.4%), bladder (13.9%), liver (8.3%), and colon and parotid gland (5.6% each).

Part B

Overall, the majority of total patients in Part B of this study were male (77.8%), White (88.9%), and not Hispanic or Latino (100%). The median (min, max) age of the Safety Population was 63 (46, 79) years. The 2 CTG patients were aged 48 years and 33 years, and both male, White and not Hispanic or Latino.

The majority of total patients had disease history with locations of primary tumor in the bladder (55.6%) and renal pelvis (44.4%). The median (min, max) years since initial diagnosis in the Safety Population was 2.04 (1.04, 7.00) years. All 9 patients (100%) in Part B of the study had tumor metastases at study enrollment. The majority of total patients had metastases in lung (88.9%), liver (33.3%) and lymph nodes (33.3%)

Efficacy Results:

Part A

No patients had a partial response or CR during Part A of the study; the ORR was 0 at all time points assessed starting on Cycle 3 Day 1. Eleven of 27 (40.7%) treated patients who had tumor response evaluations at Cycle 3 Day 1 had stable disease, including 1 patient from the PRN1371 35 mg QD cohort. The estimated median times (80% confidence interval) of PFS were 62 (54, 62), 52.5 (41, 80), 54.5 (26, 56), 51 (29, 110), 55 (32, 57) 105 (27, 189) days for the 15 mg QD, 20 mg QD, 25 mg QD, 15 mg BID, 35 mg QD, and 25 mg BID cohorts, respectively. No patients met the criteria for DOR.

Part B

No patients experienced CR during Part B of the study at all time points assessed, starting at Cycle 3 Day 1.

An ORR of 22.2% (2/9 patients) was observed at Cycle 3 Day 1; DOR of ORR for the 2 patients was 59 days and 113 days. One of the 2 patients with PR was confirmed with a PR at Cycle 5 Day 1.

CBR of 55.6% (5/9 patients) was observed in the Efficacy Population at Cycle 3 Day 1; 33.3% (3/9 patients) had stable disease.

The 2 patients in the CTG had stable disease throughout Part B of the study at each assessment until 1 CTG patient discontinued due to a final assessment of PD and the other CTG patient transferred to a named patient program.

Pharmacokinetic Results:

Part A

In all subjects, PRN1371 was absorbed rapidly; median values of PRN1371 time of maximum observed plasma concentration (Tmax) ranged from 1.0 to 1.5 hours. Elimination of plasma PRN1371 was rapid; mean values of plasma PRN1371 t1/2 ranged from 1.4 to 2.2 hours. Based on the rapid half-life, accumulation is not expected following either once- or twice daily dosing. Assessment of accumulation ratios with multiple dosing was confounded by small cohort sizes, assessment of food effect, and PK variability. In general, clinically significant accumulation was not observed between Cycle 1 Day 1 and Cycle 1 Day 15. Plasma PRN1371 AUCinf increased proportionally with increasing dose, while maximum observed plasma concentration (Cmax) increased slightly less than proportionally with increasing dose. Renal excretion of unchanged PRN1371 was limited; fe0-8 was

less than 1%. Food effect was evaluated in 5 patients at 25 mg QD or BID, and food did not appear to have a substantial impact on PRN1371 exposures.

Part B

A summary of plasma PRN1371 Plasma (ng/mL) concentrations in patients from Part B of the study are provided in Table 10.

Table 10 Summary of PRN1371 Plasma Concentrations (ng/mL) (PK Population)

	Observed [1]			
Timepoint	n	Mean (SD)	Median	Minimum, Maximum
Cycle 01 Day 1 - 1 Hour Pre-Dose [2]	9	12.56 (37.67)	0.00	0.00 – 113.00
Cycle 01 Day 1 – 1 Hour Post-Dose	9	65.65 (43.69)	64.20	4.51 – 112.00
Cycle 01 Day 8 – Within 8 Hours Post-Dose	7	25.85 (39.32)	1.53	0.00 - 99.90
Cycle 01 Day 15 – 1 Hour Pre-Dose	8	0.95 (2.31)	0.00	0.00 - 6.61
Cycle 01 Day 15 – 1 Hour Post-Dose	9	72.59 (41.43)	87.60	4.60 – 131.00
Cycle 02 Day 1 – 1 Hour Post-Dose	4	107.49 (91.38)	114.00	6.96 – 195.00
Cycle 02 Day 15 – Within 8 Hours Post-Dose	6	27.29 (44.90)	1.58	0.00 – 109.00

Source: Table 14.1.4.3

LLQ=less than limit of quantification; PK population=all patients who had at least one measurable plasma concentration result.

[1] Values reported as '<LLQ' are analyzed as 0 ng/mL.

[2] Subject #204-102 was reported with a concentration level of 113 ng/mL.

Pharmacodynamic Results:

Part A

The FGF23 data were inconsistent, and this endpoint will not be analyzed in Part B of this study. A large consistent increase from Baseline in mean serum phosphate was observed for all 6 cohorts and maximum dose groups on Cycle 1 Day 8 to Cycle 2 Day 15. At most later time points, a smaller mean increase from Baseline was observed for maximum dose groups with enrolled patients.

Part B

Not applicable. The fibroblast growth factor 23 (FGF23) data analyzed in Part A of the study were inconsistent. Based on this finding from Part A, PD analyses for the FGF23 endpoint was not to be analyzed in Part B of the study. FGFR inhibition can result in elevation of serum phosphate. Serum phosphate levels were measured during the study and instances of hyperphosphatemia were observed in 6 patients in Part B. However, due to potentially confounding effects of concomitant use of phosphate binders and protocol described drug interruptions, a formal analysis of phosphate levels was not conducted.

Safety Results:

Part A

Overall, 35 of 36 total patients (97.2%) experienced a TEAE. Sixteen patients (44.4%) experienced a serious TEAE; in 5 patients

(13.9%) in the 3 highest maximum dose groups (15 mg BID, 35 mg QD, and 25 mg BID), the serious TEAEs were considered study drug-related. Sixteen total patients (44.4%) experienced Grade 3 TEAEs, and 2 total patients (5.6%) experienced Grade 4 TEAEs. Five total patients (13.9%) experienced TEAEs that led to study drug discontinuation. No study drug-related deaths occurred during the study.

Treatment-emergent AEs experienced by ≥10% of total patients include hyperphosphataemia (66.7%); constipation (44.4%); nausea (36.1%); dry mouth and fatigue (22.2% each); gastroesophageal reflux disease and vomiting (19.4% each); decreased appetite and diarrhoea (16.7% each); dysgeusia, alopecia, and anaemia (13.9% each); and hyperglycemia, hyponatremia, blood creatinine increased, and back pain (11.1% each).

A total of six patients (16.7%) experienced TEAEs related to study drug,(except as indicated below) in the SOC of eye disorders in the following maximum dose groups:

In the 15 mg QD maximum dose group:

- One patient (25.0%) experienced a TEAE of Grade 1 nonserious subcapsular cataract.

In the 15 mg BID maximum dose group:

- One patient (16.7%) experienced a TEAE of Grade 3 nonserious retinopathy.

In the 35 mg QD maximum dose group:

- One patient (10%) experienced TEAEs of Grade 1 nonserious blepharitis, Grade 1 nonserious xerophthalmia, Grade 2 nonserious right eye cataract (subsequently serious and resolved after surgery post data cut off, Grade 3 serious left eye cataract (resolved after temporarily interrupting PRN1371 dosing and after surgery post data cut off).

In the 25mg BID maximum dose:

- One patient (12.5%) experienced TEAEs of Grade 1 nonserious punctate keratitis (not related), Grade 1 nonserious trichomegaly, and Grade 1 nonserious xerophthalmia.
- One patient (12.5%) experienced the TEAEs of Grade 1 nonserious chorioretinopathy, Grade 1 nonserious dry eye, Grade 1 nonserious retinal detachment, and Grade 1 nonserious retinopathy.
- One patient (12.5%) experienced the TEAEs of Grade 1 nonserious chorioretinopathy, Grade 1 nonserious blurred vision (not related), and Grade 1 and Grade 2 nonserious retinal detachment.

In general, the total number of TEAEs increased with increasing maximum dose beyond what would be proportional to the lower maximum dose groups when taking the higher number of patients into account. In particular, the expected pharmacodynamic effect of hyperphosphataemia occurred in a higher proportion of patients as the dose increased. Events reported in the SOC of eye disorders tended to also occur in a higher proportion of patients in the higher maximum dose groups.

Part B

Overall, 9 patients (100%) experienced a total of 111 treatment-emergent AEs (TEAEs) in Part B of the study. Three patients (33.3%) experienced a serious TEAE.

Hyperphosphataemia was the most commonly reported TEAE (66.7% of total patients), and it was the most common TEAE assessed as related to PRN1371 treatment by the investigators in Part B of the study. The majority of TEAEs (103 out of 111) were Grade 1 or Grade 2; there were 7 Grade 3 TEAEs and 1 Grade 4 TEAE in the study. No deaths occurred during Part B of this study. Four serious TEAEs occurred in 3 patients during Part B; all 4 serious TEAEs were small intestinal obstruction: 2 patients experienced 3 Grade 3 SAEs of small intestinal obstruction and discontinued from the study; 1 patient experienced 1 Grade 4 SAE of small intestinal obstruction with no discontinuation. All SAEs of small intestinal obstruction were assessed (by investigator) as unrelated to PRN1371.

Treatment emergent AEs experienced by ≥3 patients include hyperphosphataemia (6 patients, 66.7%), dry mouth and diarrhea

(each 4 patients, 44.4%), and small intestinal obstruction, nausea, vomiting, pruritus, and fatigue (each 3 patients, 33.3%). The majority of TEAEs (103 of 111) were Grade 1 or Grade 2; there were 7 Grade 3 TEAEs and 1 Grade 4 TEAE in Part B of the study. The most common (≥3 patients) TEAEs assessed as related to PRN1371 in Part B of the study include hyperphosphataemia (Grade 1 [n=4 patients] and Grade 2 [n=2 patients], diarrhea (Grade 1 [n=2 patients], Grade 2 and Grade 3 [each n=1 patient]), dry mouth (Grade 1 [n=3 patients] and Grade 2 [n=1 patient]). No TEAEs leading to death occurred during Part B of this study. Three patients (33.3%) experienced 4 serious TEAEs of small intestinal obstruction. Three patients (33.3%) experienced 5 TEAEs in SOC of special interest, eye disorders: Two patients experienced 1 Grade 1 and 1 Grade 2 TEAE of chorioretinopathy, assessed (by investigator) as related to PRN1371. One patient experienced a Grade 2 TEAE of retinal detachment, assessed (by investigator) as related to PRN1371. One TEAE of photophobia in 1 subject and one TEAE of dry eye in 1 subject were reported, both Grade 1 and assessed (by investigator) as unrelated to PRN1371
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