Title: PRX-115, a Novel PEGylated Uricase: Focus on Plasma levels, Urate Responses and PK-PD Relations Following Single High-Dose Administrations

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BACKGROUND

Uncontrolled gout remains associated with a significant unmet medical need despite the availability of urate-lowering therapies. PRX-115 is a novel recombinant PEGylated uricase produced using a proprietary plant cell-based expression technology. It has been developed to provide sustained plasma urate reduction while potentially decreasing immunogenicity and enabling extended dosing intervals.

A first-in-human (FIH) single ascending dose (SAD) study demonstrated that PRX-115 was generally well tolerated and produced prolonged reductions in plasma urate following a single intravenous administration[1]. The present analysis focuses on the pharmacokinetic (PK) and pharmacodynamic (PD) responses in the higher dose cohorts (18 mg, 24 mg and 36 mg), evaluating the relationship between sustained drug exposure and prolonged urate lowering effect.

METHODS

A randomized, double-blind, placebo-controlled, first-in-human SAD Phase 1 study (NCT05745727) evaluated the safety, tolerability, PK, PD and immunogenicity of PRX-115 following a single intravenous infusion in adults with elevated plasma urate.

Sixty-four participants were enrolled into eight sequential dose cohorts and randomized in a 3:1 ratio to receive PRX-115 (n=48) or placebo (n=16). PRX-115 was administered as a single IV infusion at doses ranging from 1 to 36 mg, with six active-treated participants and two placebo-treated participants per cohort. Participants were followed for 85 days (12 weeks) after dosing.

This analysis focuses on the higher dose cohorts (18, 24 and 36 mg). Individual plasma PRX-115 concentrations, plasma urate reduction and PK-PD relationships were evaluated over the 12-week follow-up period.

RESULTS

Pharmacokinetics

PRX-115 exposure increased with increasing dose, with peak plasma concentrations generally observed at the end of infusion.

At dose levels of 18 mg, 24 mg and 36 mg, measurable PRX-115 plasma concentrations persisted for up to 85 days following administration in an increasing number of participants as dose increased, demonstrating prolonged systemic exposure after a single infusion.

The individual PK profiles demonstrate clear dose-dependent increases in both exposure and persistence of circulating PRX-115 (Figure 1).

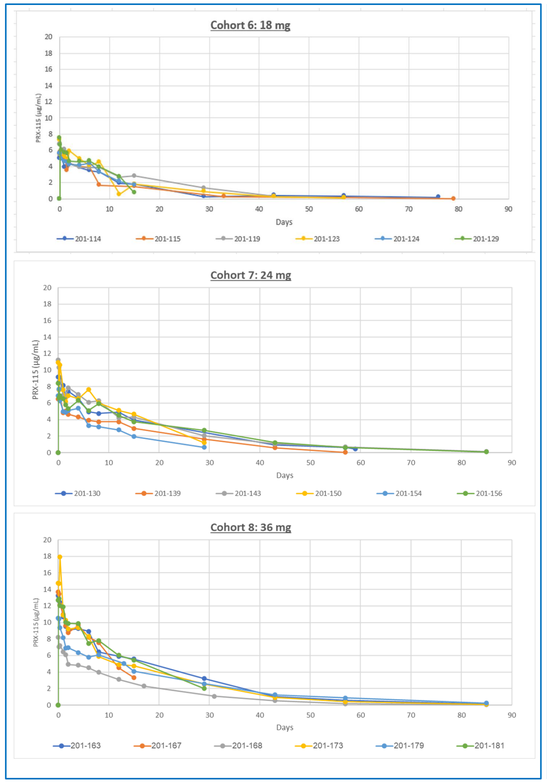


Figure 1: Individual PRX-115 plasma concentrations (18 mg, 24 mg and 36 mg cohorts)

Pharmacodynamics

PRX-115 induced rapid, profound reductions in plasma urate levels across the higher-dose cohorts following a single intravenous infusion. The extent and duration of urate lowering effect increased with dose, demonstrating a clear dose-response relationship. Participants receiving a single administration of 24 mg and 36 mg PRX-115 maintained plasma urate below the therapeutic target (<6.0 mg/dL) for up to 12 weeks.

Individual PD profiles demonstrated durable pharmacodynamic activity that closely corresponded with the sustained PRX-115 plasma concentrations (Figure 2).

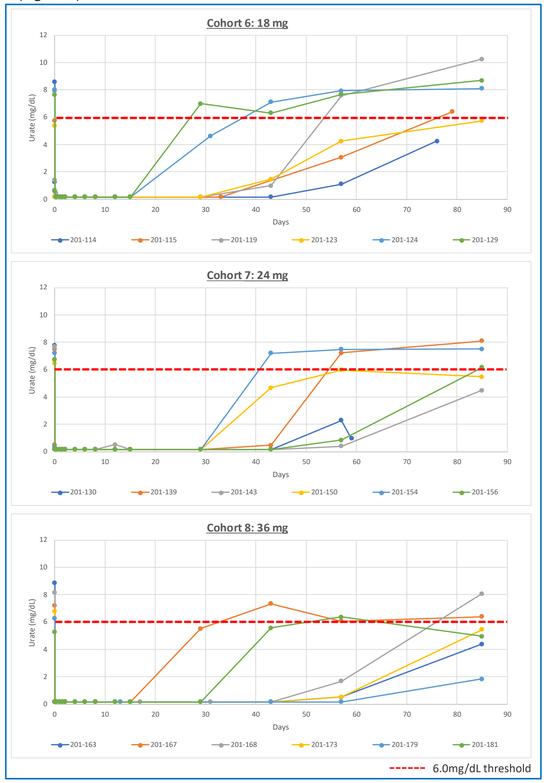


Figure 2: Individual plasma urate concentrations (18 mg, 24 mg and 36 mg cohorts)

Dose-Dependent Urate-Lowering Response

The efficacy of PRX-115, expressed by the reduction of urate and duration of this effect, increased in a dose-dependent manner. At Day 57, the proportion of participants achieving >75% reduction in plasma urate from baseline increased from 16.7% at 18 mg to 33.3% at 24 mg and 66.7% at 36 mg. Among these same participants, the same dose-dependence was observed for achieving plasma urate concentrations <2 mg/dL, further demonstrating greater extent and durability of urate lowering effect at higher PRX-115 doses.

Table 1: Dose-Dependent Reduction in Urate Levels at Day 57 (8 weeks Post-Dose)

Cohort # (dose)*	Mean (SD) Baseline UA (mg/dL)	Number (%) of participants with UA reduction >75% from baseline	Number (%) of participants with UA<2 mg/dL
6 (18 mg)	7.2 (1.3)	1 (16.7 %)	1 (16.7 %)
7 (24 mg)	7.2 (0.5)	2 (33.3 %)	2 (33.3 %)
8 (36 mg)	7.1 (1.3)	4 (66.7 %)	4 (66.7 %)

* Six participants were included in each cohort

PK-PD Relationship

Individual PK and PD profiles demonstrated a clear relationship between sustained PRX-115 plasma exposure and prolonged plasma urate lowering effect.
Participants with prolonged measurable PRX-115 concentrations maintained plasma urate levels below the therapeutic target for extended time periods, whereas declining PRX-115 concentrations were associated with gradual recovery of plasma urate levels.
These findings demonstrate that maintenance of therapeutic PRX-115 exposure is closely associated with sustained pharmacodynamic activity.

CONCLUSIONS

PRX-115 demonstrated prolonged, dose dependent, systemic exposure following a single intravenous administration.

Individual PK and PD analyses demonstrated a clear exposure-response relationship, with sustained PRX-115 concentrations associated with prolonged plasma urate lowering.

A single dose of PRX-115 produced rapid, durable and dose-dependent reductions in plasma urate levels, with the highest dose (36 mg) demonstrating the greatest magnitude and duration of response.

These findings support the continued clinical development of PRX-115 for the treatment of gout and provide the scientific rationale for exploring the optimal dosing regimen for gout patients. (RELEASE study NCT07280156)

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