PHYOX: A Safety and Tolerability Study of DCR-PHXC in Primary Hyperoxaluria Types 1 and 2

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Background

Primary Hyperoxaluria (PH) is a family of rare diseases characterized by hepatic overproduction of oxalate due to three distinct genetic mutations. Clinical manifestations include nephrocalcinosis, recurrent kidney stones, progressive renal impairment, and systemic oxalosis.

DCR-PHXC is an investigational RNAi therapeutic targeting the LDHA enzyme, which is involved in the ultimate step of hepatic oxalate production and has the potential to treat all three known genetic forms of PH.

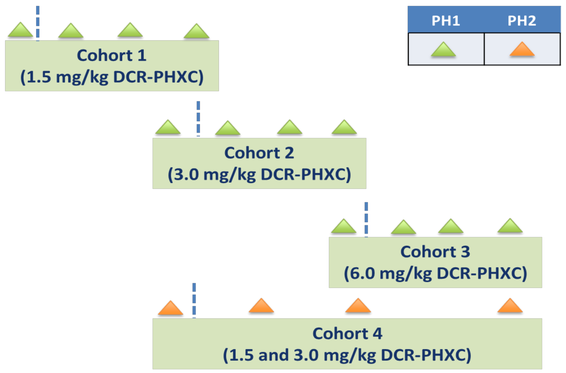
Method

This abstract includes preliminary data from the ongoing PHYOX study (ClinicalTrials.gov: NCT03392896), a two-part, single-ascending dose study conducted in 25 normal healthy volunteers (NHVs, Group A) and 16 PH participants (Group B). Eligible PH participants have genetically-confirmed PH1 or PH2, urinary oxalate (Uox) ≥ 0.7 mmol/24Hr, and eGFR ≥ 30 mL/min/1.73m^2.

Group A is randomized and includes placebo, with five cohorts dosed at 0.3, 1.5, 3.0, 6.0, or 12.0 mg/kg DCR-PHXC or placebo (randomized 3 active: 2 placebo). Group B is open label and has three PH1 cohorts dosed at 1.5, 3.0, or 6.0 mg/kg DCR-PHXC and a fourth PH2-only cohort.

The primary objective is safety and secondary endpoints include change in 24Hr Uox from baseline defined as the mean of two 24Hr urine collections during screening.

Study Design (Group B)



Safety

As of a data cut on 01 October 2018, a total of 25 adult NHV (19 to 55 years old; 44% female) and 12 adult participants with PH1 (n=11) or PH2 (n=1) have been dosed. To date, no severe or serious adverse events have occurred and no clinically significant changes in ECG, vital signs, laboratory, or hematology values have been observed. Five participants (19%) experienced mild or moderate injection site reactions, which all resolved without intervention within 24 to 72hr.

PH Participant Demographics

	1.5 mg/kg DCR-PHXC (n=5)	3.0 mg/kg DCR-PHXC (n=4)	6.0 mg/kg DCR-PHXC (n=3)	All (n=12)
Age Mean (SD)	27.0 (10.4)	29.3 (6.5)	17.3 (3.8)	25.3 (8.8)
Gender Male, n (%)	3 (60.0%)	2 (50.0%)	1 (33.3%)	6 (50.0%)
Female, n (%)	2 (40.0%)	2 (50.0%)	2 (66.7%)	6 (50.0%)
BMI (kg/m^2) Mean (SD)	28.9 (3.9)	22.0 (4.6)	23.4 (3.4)	25.2 (4.9)
Race % White	60.0%	25.0%	66.7%	50.0%
eGFR (mL/min/1.73m^2) Mean (SD)	84.1 (5.9)	78.2 (25.0)	98.0 (25.5)	85.6 (19.1)
Baseline PH Characteristics				
PH Type PH1, n (%)	4 (80.0%)	4 (100%)	3 (100%)	11 (91.7%)
PH2, n (%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Years since PH Diagnosis Mean (SD)	20.4 (9.9)	12.7 (11.1)	14.7 (4.0)	16.7 (8.9)
Number of Stone Events, 6 Months prior to screening n (# events)	1 (1)	2 (3)	1 (1)	4 (5)

Note: Results based on availability of data as of 01 October 2018.

Maximum Postdose Reductions in 24Hr Urinary Oxalate

1.5 mg/kg DCR-PHXC: In PH1 and PH2 participants dosed at 1.5 mg/kg (n=5), the mean maximal 24Hr Uox reduction was 50% (range: 39% to 59%). Per protocol, two participants are still in follow-up as of postdose Day 85 as their 24Hr Uox has not yet returned to within 80% of the lowest baseline 24Hr Uox measurement. **Figure 1** shows mean absolute values for 24Hr Uox over the study period for 1.5 mg/kg (solid blue line). **Figure 2** shows the mean Uox-to-creatinine ratios for 24Hr Uox over the study period for 1.5 mg/kg (solid blue line).

3.0 mg/kg DCR-PHXC: PH1 participants dosed at 3.0 mg/kg (n=4) currently show a mean maximal reduction of 24Hr Uox of 65% (range: 56% to 80%). Three of the participants dosed at 3.0 mg/kg DCR-PHXC are still in follow-up and may not yet have reached maximal 24Hr Uox reductions. **Figure 1** shows mean absolute values for 24Hr Uox over the study period for 3.0 mg/kg (solid yellow line). **Figure 2** shows mean Uox-to-creatinine ratios for 24Hr Uox over the study period for 3.0 mg/kg (solid yellow line).

6.0 mg/kg DCR-PHXC: As of a data cut on 01 October 2018, only one participant has 24Hr Uox results in Cohort 3 at 6.0 mg/kg. The participant has a maximum reduction of 64% as of postdose Day 43.

24Hr Urinary Oxalate Normalization and Near-normalization

In Cohort 1 (1.5 mg/kg), three out of four PH participants' 24Hr Uox values reached near-normalization (< 0.6 and ≥ 0.46 mmol/24Hr) at one or more postdose time points. In Cohort 2 (3.0 mg/kg), three out of four PH participants' 24Hr Uox values have reached normalization (< 0.46 mmol/24Hr) at one or more postdose time points.

Graphical Pharmacodynamic Results

Figure 1. Mean 24Hr Oxalate Over Time, Following Single Administration DCR-PHXC

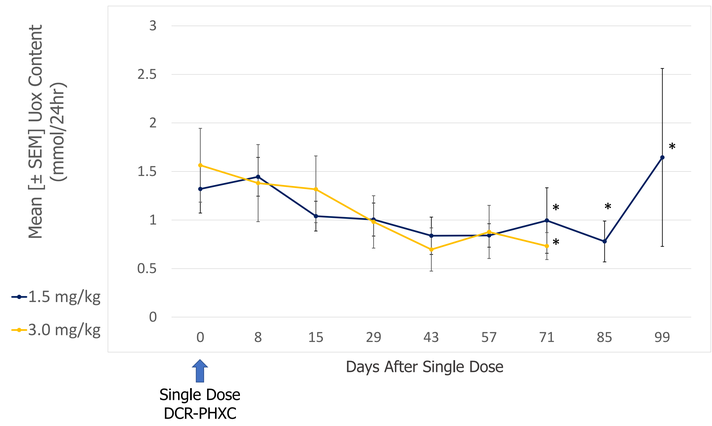
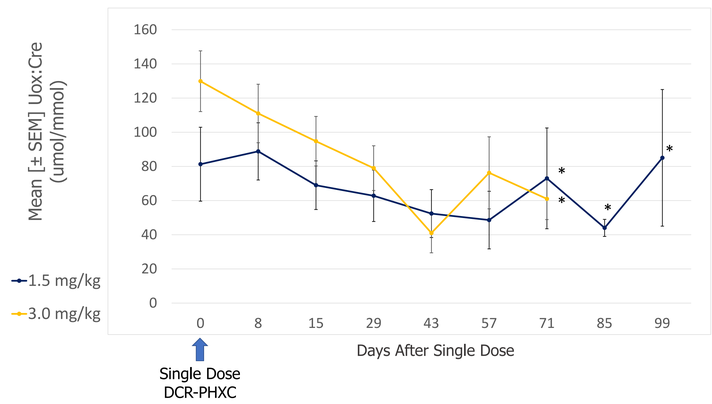


Figure 2. Mean Oxalate-to-Creatinine Ratio Over Time, Following Single Administration DCR-PHXC



Figures 1 and 2 Note: At 1.5 mg/kg, n=5 at all time points, except where * denotes data point where only 3 participants are included. At 3.0 mg/kg, n=4 at all time points, except where * denotes data point where only 3 participants are included. Results based on availability of data as of 01 October 2018.

Summary

Preliminary PHYOX data show DCR-PHXC is safe and well-tolerated in this ongoing study. Observed reduction of 24Hr Uox following a single administration of DCR-PHXC in both PH1 and PH2 participants is a promising sign of DCR-PHXC's potential potency and duration of action. Based on a combination of multiple-dose animal data and single-dose human data, it is anticipated that a multi-dose regimen of DCR-PHXC will show even more pronounced and sustained 24Hr Uox reductions.