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

Bernd Hoppe[1], Pierre Cochat[2], Graham Lipkin[3], Amanda M. Gentile[4], Bob D. Brown[4], Ralf Rosskamp[4], Sally Hulton[5], Jaap W. Groothoff[6], Michelle A. Baum[7]

[1] University Hospital Bonn, Bonn, Germany. [2] Université Claude-Bernard Lyon 1, Lyon, France. [3] Queen Elizabeth Hospital, Birmingham, United Kingdom. [4] Dicerna Pharmaceuticals, Inc., Cambridge, MA, U.S. [5] Birmingham Children's Hospital, Birmingham, United Kingdom. [6] Emma Children's Hospital AMC, Amsterdam, Netherlands. [7] Boston Children's Hospital, Boston, MA, U.S.

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.

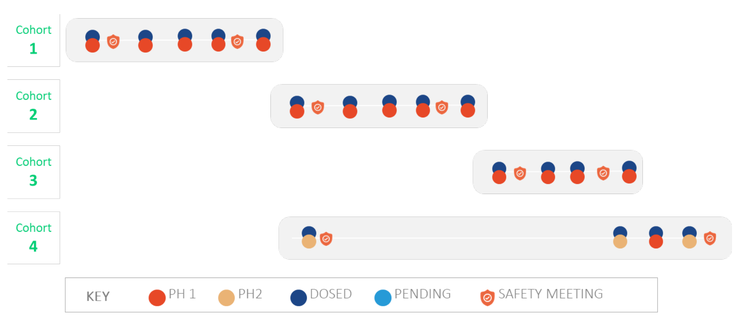
Method

This abstract includes preliminary data from the ongoing PHYOX study (ClinicalTrials.gov: NCT03392896), a two-part, single-ascending dose study conducted in 25 healthy volunteers (HVs, Group A) and 18 participants with PH (Group B). Eligible participants with PH 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 mixed PH1 and PH2 cohort.

The primary objective is safety and tolerability. 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 14 March 2019, a total of 25 adult HV (19 to 55 years old; 44% female) and a total of 18 participants, comprised of 15 adults and 3 adolescents (12-17 years old) with PH1 (n=15) or PH2 (n=3) have been dosed. To date, four serious adverse events have occurred (all assessed as not related to study drug; one mild, two moderate, and one severe). Nine participants out of 33 dosed with DCR-PHXC (27%) experienced mild or moderate injection site reactions, all of which resolved without intervention within 96 hours.

PH Participant Demographics

	1.5 mg/kg DCR-PHXC (n=6)	3.0 mg/kg DCR-PHXC (n=8)	6.0 mg/kg DCR-PHXC (n=4)	All (n=18)
Age Mean (SD)	26.5 (9.4)	25.4 (6.7)	16.5 (3.5)	23.8 (7.9)
Gender Male, n (%)	3 (50.0%)	4 (50.0%)	2 (50.0%)	9 (50.0%)
Female, n (%)	3 (50.0%)	4 (50.0%)	2 (50.0%)	9 (50.0%)
BMI (kg/m^2) Mean (SD)	28.7 (3.5)	22.0 (3.7)	22.8 (3.1)	24.4 (4.6)
Race % White	66.7%	50.0%	50.0%	55.6%
eGFR (mL/min/1.73m^2) Mean (SD)	78.3 (15.1)	83.7 (32.8)	106.6 (27.0)	87.0 (27.6)
Baseline PH Characteristics				
PH Type PH1, n (%)	5 (83.3%)	6 (75.0%)	4 (100%)	15 (83.3%)
PH2, n (%)	1 (16.7%)	2 (25.0%)	0 (0.0%)	3 (16.7%)
Years since PH Diagnosis Mean (SD)	20.5 (8.9)	18.4 (7.8)	12.3 (2.1)	17.7 (7.7)
Number of Stone Events, 6 Months prior to screening n (# events)	0 (0)	1 (1)	1 (1)	2 (2)

Note: Results based on availability of data as of 14 March 2019.

Maximum Postdose Reductions in 24Hr Urinary Oxalate

Summarized here is the efficacy data for the 13 out of 18 dosed subjects in Cohorts 1, 2, and 3 who have completed the Day 57 visit.

Figure 1 shows maximum observed reduction in 24Hr Uox absolute values and maximum percentage reduction from baseline, at any time point post-dose. **Figure 2** shows absolute values for 24Hr Uox for individual participants over the study period for all cohorts.

Cohort Summaries

Cohort 1 (1.5 mg/kg DCR-PHXC): Participants with PH1 dosed at 1.5 mg/kg (n=5) show a mean maximal 24Hr Uox reduction of 51% (range: 28% to 72%). All participants in Cohort 1 have returned to within 80% of the lowest baseline 24Hr Uox measurement and have completed the study.

Cohort 2 (3.0 mg/kg DCR-PHXC): Participants with PH1 dosed at 3.0 mg/kg (n=5) currently show a mean maximal reduction of 24Hr Uox of 71% (range: 62% to 80%). Three participants in Cohort 2 have reached Day 57 and are still in follow-up as their 24Hr Uox has not yet returned to within 80% of the lowest baseline 24Hr Uox.

Cohort 3 (6.0 mg/kg DCR-PHXC): Participants dosed at 6.0 mg/kg (n=3) currently show a mean maximal reduction of 24Hr Uox of 76% (range: 58% to 100%). Two of the participants in Cohort 3 have reached Day 57 and are still in follow-up as their 24Hr Uox has not yet returned to within 80% of the lowest baseline 24Hr Uox.

24Hr Urinary Oxalate Normalization and Near-normalization

In Cohort 1 (1.5 mg/kg), 24Hr Uox values for three out of five participants reached near-normalization (< 0.6 and ≥ 0.46 mmol/24Hr) at one or more postdose time points. In Cohort 2 (3.0 mg/kg), 24Hr Uox values for four out of five participants reached normalization (< 0.46 mmol/24Hr) at one or more postdose time points. In Cohort 3 (6.0 mg/kg), 24Hr Uox values for one out of three participants reached normalization (< 0.46 mmol/24Hr) at one or more postdose time points. Two of the participants dosed at 6.0 mg/kg DCR-PHXC are still in follow-up and may not yet have reached maximal 24Hr Uox reductions.

Graphical Pharmacodynamic Results

Figure 1. Screening to Maximum Observed Reduction in 24Hr Urinary Oxalate

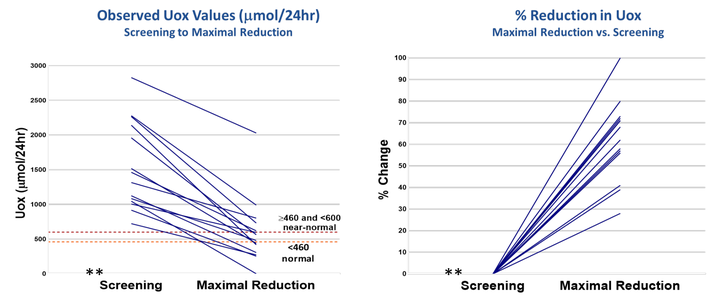
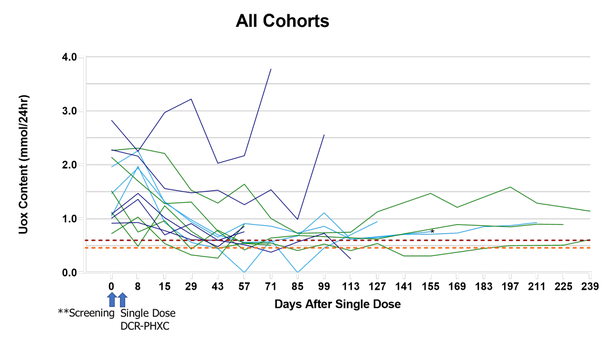
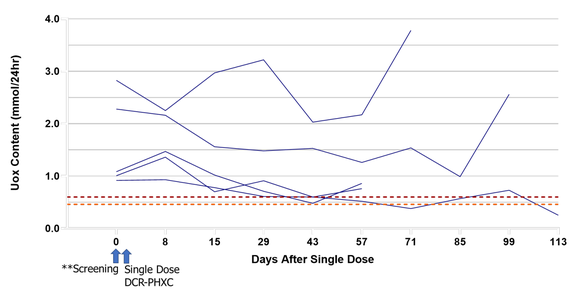
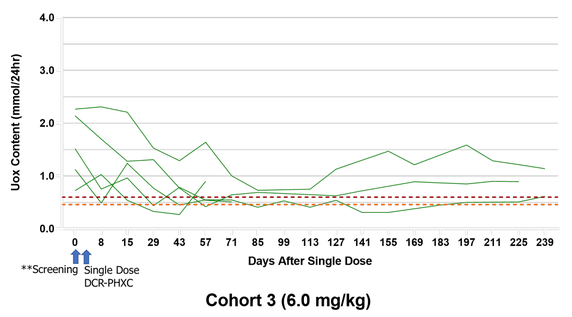
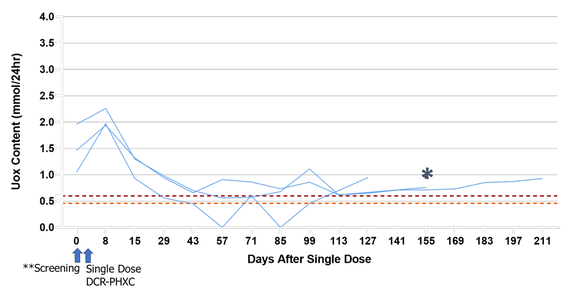


Figure 2. Absolute 24Hr Oxalate Values Over Time, Following Single Administration DCR-PHXC









Note:
* Denotes BSA adjusted for participant < 18 Years old; ** Average of two measurements
Samples with < day 57 measurements not included; Results based on availability of data as of 14 March 2019.

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 participants with PH1 and PH2 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.