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.

Presented here are 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/1.73m².

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.

**Method**

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

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Note: Results based on availability of data as of 01 May 2019.

**PH Participant Demographics (Group B)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose Level</th>
<th>N</th>
<th>Day 57 Reached</th>
<th>Max Reduction Mean (range)</th>
<th>Max Uox Reduction Mean (range)</th>
<th>Reduction (≥ 0.6 mmol/24Hr)</th>
<th>Normalization (≥ 0.6 mmol/24Hr)</th>
<th>Follow-up (Month)</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH1</td>
<td>1.5 mg/kg</td>
<td>5</td>
<td>5</td>
<td>42 (28-59%)</td>
<td>57.0 (43 - 81)</td>
<td>2 (42)</td>
<td>1 (2)</td>
<td>Ongoing</td>
<td>10.0 (3-14)</td>
</tr>
<tr>
<td></td>
<td>3.0 mg/kg</td>
<td>6</td>
<td>6</td>
<td>71 (62-89%)</td>
<td>66.5 (59 - 291)</td>
<td>1 (37)</td>
<td>1 (27)</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0 mg/kg</td>
<td>4</td>
<td>4</td>
<td>64 (55-100%)</td>
<td>67.5 (41 - 111)</td>
<td>2 (60)</td>
<td>1 (33)</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>PH2</td>
<td>Mixed dose</td>
<td>3</td>
<td>3</td>
<td>42 (22-67%)</td>
<td>47.7 (29 - 77)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>Ongoing</td>
<td></td>
</tr>
</tbody>
</table>

**PH1 participants**: Participants dosed at 1.5, 3.0 and 6.0 mg/kg DCR-PHXC showed a 48% (range 28-59%), 71% (range 62-89%) and 66% (range 35-100%) mean maximum reduction of 24Hr Uox, respectively; with either Normalization or Near-normalization achieved in 60%, 84% and 75% of the participants, respectively.

**PH2 participants** (1.5 and 3.0 mg/kg DCR-PHXC) (Fig 1d): Participants with PH2 in this mixed dose Cohort (n=3) currently show a mean maximal reduction of 24Hr Uox of 42% (range: 22% to 66%).

**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.