Cover Page for Protocol

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Official title of study:	A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (Subcutaneous Use) in Patients With Primary Hyperoxaluria
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Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (subcutaneous use) in Patients with Primary Hyperoxaluria

"PHYOX2"

Protocol Number: DCR-PHXC-201

Product:	DCR-PHXC
Sponsor:	Dicerna Pharmaceuticals, Inc. 33 Hayden Avenue Lexington, MA 02421 US (617) 621-8097
EudraCT Number:	2018-003098-91
NCT Number:	NCT03847909
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Redacted protocol
Includes redaction of personal identifiable information only.

[redacted]

Sponsor Signature Page

A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (subcutaneous use) in Patients with Primary Hyperoxaluria

Protocol Number: DCR-PHXC-201

Version: 5.0 US

Date: 13-Aug-2020

[redacted] [redacted]

Date

Dicerna Pharmaceuticals, Inc

[redacted] [redacted]

Date

Dicerna Pharmaceuticals, Inc

[redacted] [redacted]

Date

Dicerna Pharmaceuticals, Inc

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Sponsor Medical Monitor	[redacted] email: [redacted]

Protocol Update Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (v 5.0 US)	13-Aug-2020
Amendment 2 (v 4.0 US)	12-Mar-2020
Amendment 1 (v 3.0 US) Original protocol for use in the United States	30-Apr-2019
Administrative Update (v 2.0)	16-Nov-2018
Original Protocol	24-Oct-2018

Amendment 3 (version 5.0), 13-Aug-2020

The 12 March 2020 version of the protocol was updated to include the dose of DCR-PHXC to be administered in children aged 6 to 11 years. An appendix detailing measures to be undertaken during the COVID-19 pandemic was added. A tabular summary of changes is located in Section **10.7**.

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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Protocol Title: A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (subcutaneous use) in Patients with Primary Hyperoxaluria

Short Title: PHYOX2

1.1.1. Overall Design

This is a 6-month randomized, placebo-controlled, double-blind study of DCR-PHXC in patients with primary hyperoxaluria (PH1 and PH2). Potential participants are screened over an up-to-6-week period prior to randomization to DCR-PHXC or placebo.

Disclosure statement: This is a parallel-group treatment study that is participant-, Investigator-, and Sponsor blinded.

Number of arms: 2

Number of participants: Approximately 40 participants will be screened to achieve 36 evaluable participants.

Intervention groups and duration of participation: Eligible participants will be randomized in a 2 to 1 (DCR-PHXC to placebo) ratio. Following the up-to-35-day screening period, participants will return to the clinic for interim visits through Day 180. Note: an extra 7 days will be allowed for participants who are required to repeat screening 24-hour urine collections or for repeat of initially unanalyzable screening laboratory assessment samples. The total time on study for each participant is approximately 7 months.

Study Duration: Approximately 18 months from first participant, first visit to last participant, last visit. After completion of the study, eligible participants will be offered the opportunity to enroll into a long-term open-label extension study (DCR-PHXC-301).

Data Safety Monitoring Committee (DSMC): A DSMC will be convened to provide periodic review of the efficacy and safety data. The DSMC will consist of 3 voting members, who are independent of the study team and Sponsor.

At a minimum, the DSMC will meet prior to the first participant being enrolled, when the first 5 participants have been enrolled and have completed the Day 30 visit, when the first 3 adolescent participants (aged 12-17 years) have been enrolled in the DCR-PHXC arm and have completed the Day 60 visit, and periodically thereafter, depending on enrollment.

Following completion of Modeling and Simulation (M&S) of pharmacokinetic (PK) and pharmacodynamic (PD) data and determination of the dose for 6- to 11-year-old children, the DSMC affirmed that the overall risk-benefit balance remained positive and approved the enrollment of 6- to 11-year old children.

Complete details regarding the constitution and responsibilities of the DSMC are specified in the committee charter.

Statistical Overview: This is a superiority study. The primary endpoint for the study is the area under the curve (AUC) from Day 90 to Day 180, based on percent change from baseline in

24-hour urinary oxalate (Uox). For the primary endpoint, the null hypothesis to be tested is: H_0: AUC_a=AUC_p against the 1-sided alternative hypothesis H_A: $AUC_a > AUC_p$, where AUC_a is the area under the curve for the active arm and AUC_p is the area under the curve for the placebo arm. The AUC is calculated based on the percent change from baseline in 24-hour Uox.

The group sequential design, with prespecified alpha spending for the interim analysis and final analysis, will be utilized and no futility boundaries will be utilized. The primary hypothesis tested is a 1-sided superiority hypothesis at the significance level alpha of 0.025. An analysis of covariance (ANCOVA) model, with the baseline Uox, age category, and eGFR category as the covariates will be used for the analysis.

The AUC of 24-hour Uox in the placebo arm is assumed to be 0, as Uox values may oscillate up and down from baseline due to measurement variability. The AUC of 24-hour Uox in the active arm is assumed to be 3600, based on a 40% decrease over the 90 days. The effect size is assumed to be 1.2.

Under these assumptions, the sample size of 36 patients (24 in the active arm and 12 in the placebo arm) will yield a power of approximately 94%. All calculations were performed using [redacted].

An interim analysis to reassess sample size may be performed after two-thirds of participants have completed the study. A minimal fraction of alpha (.0001) will be spent at the interim analysis, as the trial will not be stopped based on the results from the interim analysis. The final analysis will use an alpha of 0.0249 for the primary endpoint, in order to preserve an overall type I error at the 1-sided 0.025 level.

1.1.2. Study Rationale

DCR-PHXC consists of the drug substance (DCR-L1360), a synthetic double-stranded (hybridized duplex) ribonucleic acid (RNA) oligonucleotide conjugated to *N*-acetyl-D-galactosamine (GalNAc) amino-sugar residues, as a sterile solution in water for injection (WFI). DCR-PHXC is designed to selectively reduce *LDHA* messenger ribonucleic acid (mRNA) and lactate dehydrogenase (LDH) activity in the liver, and subsequently decrease liver oxalate production. DCR-PHXC is being developed as a treatment for PH, an ultra-rare autosomal recessive disease characterized by excessive production of oxalate in the liver.

The proposed study is designed to evaluate the efficacy, safety, tolerability, and PK of DCR-PHXC versus placebo in patients with PH1 and PH2.

1.1.3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden in patients with PH	AUC from Day 90 to Day 180, based on percent change from Baseline in 24-hour Uox
Key Secondary	
To identify the proportion of participants with normalized or near-normalized Uox	The proportion of participants with a 24-hour Uox level < 0.46 mmol/24 hours or ≥ 0.46 to < 0.60 mmol/24 hours (adjusted per 1.73 m2 BSA in participants aged < 18 years) on at least 2 consecutive visits, beginning with Day 90
Secondary	
1. To evaluate the effect of DCR-PHXC on stone burden in patients with PH	1. Percent change in the summed surface area and number of kidney stones identified via kidney ultrasound from Baseline to Day 180
2. To evaluate the effect of DCR-PHXC on plasma oxalate in patients with PH	2. Percent change in plasma oxalate from Baseline to Day 180 (for adults only)
3. To evaluate the effect of DCR-PHXC on eGFR	3. Rate of change in eGFR from Baseline to Day 180
4. To assess the safety of DCR-PHXC in patients with PH	4. AE and SAE; change from Baseline in 12-lead ECG, physical examination findings, vital signs, and clinical laboratory tests
5. To characterize the PK of DCR-PHXC in patients with PH	5. Population and individual PK parameters for DCR-PHXC
Tertiary/Exploratory	
1. To evaluate the effect of DCR-PHXC on stone events in patients with PH	1. Number of stone events over a 6-month period
2. To assess the efficacy of DCR-PHXC in reducing Uox burden over 6 months in patients with PH	2. AUC of 24-hour Uox from Day 1 to Day 180, based on percent change from Baseline
3. To assess the efficacy of DCR-PHXC in reducing Uox at month 6 in patients with PH	3. Percent change in 24-hour Uox from Baseline to Day 180
4. To evaluate the effect of DCR-PHXC on urinary oxalate-to-creatinine ratio in patients with PH	4. AUC of 24-hour urinary oxalate-to-creatinine ratio from Day 90 to Day 180, based on percent change from Baseline
5. To evaluate the effect of DCR-PHXC on QoL Assessments in patients with PH	5. Change from Baseline to Day 180 in the SF-36 and EQ-5D-5L in adults; and in the PedsQL™ in children
6. To evaluate the relationship between Uox spot urine and 24-hour urine measurement in patients with PH	6. Uox in spot urine and 24-hour urine

Abbreviations: AE: adverse events; AUC: area under the curve; BSA: body surface area; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; PedsQL: Pediatric Quality of Life Inventory; PH: primary hyperoxaluria (types 1 and 2); PK: pharmacokinetic; QoL: quality of life; SAE: serious adverse events; SF-36: Short Form 36 Health Survey; Uox: urinary oxalate

1.1.4. Study Population

Male and female patients, at least 6 years of age, with genetically confirmed Type 1 or Type 2 primary hyperoxaluria (PH1, PH2).

Key inclusion criteria include:

- 24-hour Uox excretion ≥ 0.7 mmol (adjusted per 1.73 m^2 body surface area [BSA] in participants < 18 years of age) in both collections performed in the screening period. Of the first 24 participants enrolled, at least 12 (50%) must have at least one 24-hour Uox excretion ≥ 1.6 mmol (adjusted per 1.73 m^2 BSA in participants aged < 18 years).
- Less than 20% variation between the two 24-hour urinary creatinine excretion (mmol/24 hr/kg) values derived from the two 24-hour urine collections in the screening period.
- Estimated GFR at screening ≥ 30 mL/min normalized to 1.73 m^2 BSA calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in participants aged ≥ 18 years (Levey & Stevens, 2010), or the multivariate equation by Schwartz in participants aged 6 to 17 years (Schwartz et al., 2012).

Key exclusion criteria include:

- Renal or hepatic transplantation (prior or planned within the study period)
- Current dialysis or anticipated requirement for dialysis during the study period
- Plasma oxalate > 30 µmol/L
- Documented evidence of clinical manifestations of systemic oxalosis (including pre-existing retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations)
- Liver function test (LFT) abnormalities: Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 times upper limit of normal (ULN) for age and gender

1.1.5. Sites and Facilities

The study will be conducted at approximately 35 sites in North America, Europe, Asia-Pacific and the Middle East.

1.1.6. Description of Study Intervention

DCR-PHXC is a synthetic ribonucleic acid interference (RNAi) drug that consists of a double-stranded oligonucleotide conjugated to GalNAc ligands. DCR-PHXC is a colorless to pale yellow, preservative-free, sterile solution of DCR-L1360 (the drug substance) at a concentration of 170 mg/mL in WFI.

DCR-PHXC is to be stored at 2°C to 8°C (inclusive).

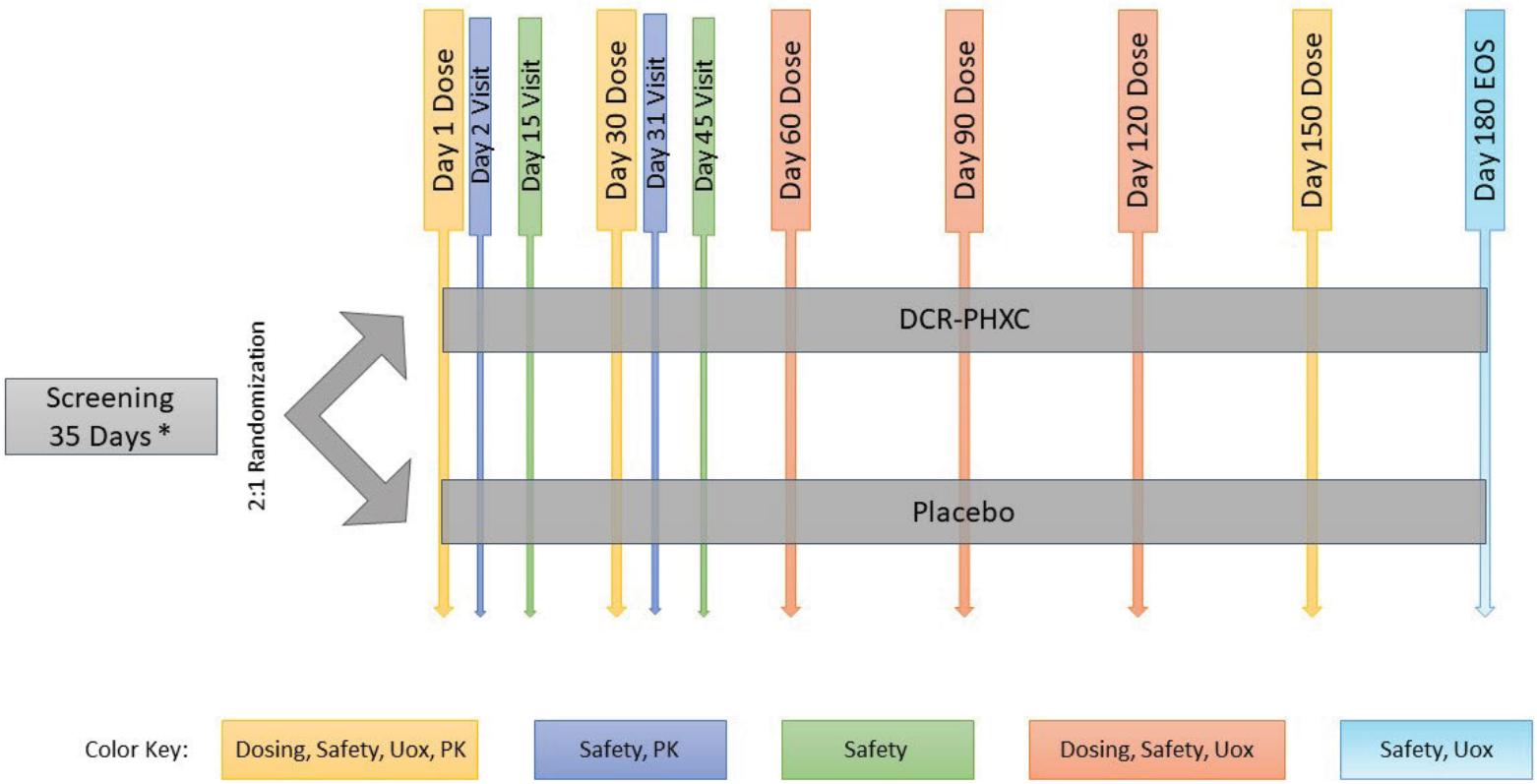
DCR-PHXC is administered monthly as a SC injection into the abdomen or thigh.

The dose of DCR-PHXC in adults and in adolescents (12-17 years old) weighing at least 50 kg will be 170 mg. For adults and adolescents weighing less than 50 kg, the dose will be 136 mg. In

children aged 6 to 11 years of age, the dose of DCR-PHXC will be 3.5 mg/kg, with an upper limit of 136 mg.

The placebo comparator is a sterile, preservative-free normal saline 0.9% solution for SC injection, which is of similar osmolality to the DCR-PHXC formulation. Placebo will be administered as a SC injection in the thigh or abdomen in a volume equivalent to the dose of DCR-PHXC.

1.2. STUDY SCHEMA



* An additional 7 days of screening may be added for participants who require repeated 24-hour urine collections or for repeat of initially unanalyzable screening laboratory test samples.

Abbreviations: EOS = end of study; PK = pharmacokinetics; Uox = urinary oxalate

1.3. SCHEDULE OF ACTIVITIES

	Screening	Treatment										EOS	ET
Study Day (window)	**−35 [a] to −1**	**1**	**2**	**15 (±2)**	**30 (±2)**	**31 [b]**	**45 (±2)**	**60 (±3)**	**90 (±3)**	**120 (±5)**	**150 (±5)**	**180 (±5)**	**-**
Procedure/Assessment													
Informed consent/assent [c]	X												
Inclusion and exclusion criteria [d]	X	X											
Demographic/baseline characteristics	X												
Medical history [e]	X												
PH disease history [e]	X												
Medication history [f]	X												
AGXT/*GRHPR* genotyping [g]	X												
Urine drug screen [h]	X												
Viral serology [i]	X												
FSH (postmenopausal women)	X												
Study intervention administration		X			X			X	X	X	X		
Spot urine collection [j]	X				X			X	X	X	X	X	X
24-hr urinary oxalate [k]	X				X			X	X	X	X	X	X
24-hr urinary creatinine [l]	X				X			X	X	X	X	X	X
Blood draw for vitamin B6 levels [m]		X			X			X	X	X	X	X	
Plasma PK sample [n]		X	X		X	X					X		X
Plasma oxalate sample [o]	X	X			X			X	X	X	X	X	X
Record fluid intake [p]	X	X			X			X	X	X	X	X	
12-lead ECG [q]	X	X		X	X		X	X	X	X	X	X	X
Vital signs [r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [s]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height [t]	X	X			X			X	X	X	X	X	X
Hematology and serum chemistry [u]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation studies [v]	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR [w]	X	X			X			X	X	X	X	X	X

	Screening	Treatment										EOS	ET
Study Day (window)	–35 [a] to –1	1	2	15 (±2)	30 (±2)	31 [b]	45 (±2)	60 (±3)	90 (±3)	120 (±5)	150 (±5)	180 (±5)	-
Procedure/Assessment													
Cytokines [x]		X	X		X	X							X
Complement [y]		X	X		X	X							X
Urinalysis [z]	X	X			X			X	X	X	X	X	X
Urine pregnancy test (WOCBP) [aa]	X	X			X			X	X	X	X	X	X
Record stone events (as applicable) [bb]		X	X	X	X	X	X	X	X	X	X	X	X
Kidney ultrasound [cc]	X											X	X
Echocardiogram [dd]	X											X	X
ADA & anti-dsDNA sample [ee]	X						X					X	X
Pediatric burden assessment [ff]		X		X	X		X	X	X	X	X	X	X
SF-36 [gg]	X											X	X
EQ-5D-5L [hh]	X											X	X
PedsQL [ii]	X											X	X
Record SAEs [jj]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs [kk]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [f]		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; AE = adverse event; *AGXT* = the gene that codes for alanine–glyoxylate aminotransferase; anti-dsDNA = anti-double-stranded deoxyribonucleic acid antibody; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination; FSH = follicle stimulating hormone; *GRHPR* = the gene that codes for glyoxylate and hydroxypyruvate reductase; PedsQL = Pediatric Quality of Life Inventory; PH = primary hyperoxaluria; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short Form 36 Health Survey; WOCBP = women of childbearing potential

Table footnotes:

a. Potential participants allowed a second attempt at achieving < 20% variation in 24-hour urinary creatinine excretion, as described in Section **8.1.1.1**, will be given an extra 7 days within which to complete the second pair of collections. An additional 7 days will also be granted for retest of initially unanalyzable screening laboratory samples.

b. Day 31 visit to be conducted the day after the Day 30 visit, regardless of when the Day 30 visit occurs within the ± 2-day window.

c. Informed consent (and assent if applicable) may be given outside of the 35-day screening period, i.e., provision of consent does not start the clock for the screening period. In no case should more than 2 weeks elapse between the provision of consent and initiation of the first screening procedure/assessment. Initiation of the first screening procedure will start the 35-day window.

d. Participant eligibility (with the exception of clinical laboratory testing) will be re-confirmed prior to administration of study intervention on Day 1.

e. Record 5 years of general medical history. PH history to include 12-month history of stone events, as described in Section **8.1.6.1**.

f. To include vitamin B6 (pyridoxine).

g. Participants without documented genotyping must provide a DNA sample for testing.

h. Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines. Drug screening is not required for individuals aged 12 or younger. Investigator discretion in excluding participants with a positive test is allowed.

i. HIV 1 and 2 antibodies, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody. If tested in the past 3 months, medical record documentation of this testing may be used. Viral serology is not required in participants < 18 years of age.

j. A sample of urine from the void immediately prior to the initiation of each 24-hour urine collection will be collected and stored apart from the 24-hour urine collection. Should the two 24-hour screening collections occur on consecutive days, no spot urine sample will be collected on the second day.

k. Two screening samples should ideally be collected on 2 consecutive days, but with no more than 8 days between collections. Collection of on-treatment samples must be performed within the 7 days prior to the scheduled study visit. It is desired that ehe elapsed time between monthly collections should be at least 3 weeks and not more than 5 weeks. Participants should avoid taking vitamin C supplements (including multivitamins) for 24 hours prior to and during the collection of 24-hour urine samples. See Section **8.1.1.1**.

l. Urinary creatinine excretion will be determined from 24-hour urine samples in order to assess the quality of the 24-hour collection. Any post-screening sample that violates the urine quality review criteria should be repeated within 10 days of the scheduled study visit whenever possible. See Section **8.1.1.1.1** for details.

m. Samples for vitamin B6 levels will only be collected in participants aged ≥ 18 years who are taking vitamin B6 supplements.

n. Plasma sampling times for PK analysis of DCR-PHXC and its metabolites (see Section **8.5.1**):

- Aged ≥ 18 years:
  - Days 1 and 30: predose and at 5, 15, and 30 minutes and 1, 2, 4, 6, 10, and 12 hours postdose
  - Days 2 and 31: 24 hours postdose
  - Day 150: predose and at 2, 6, and 12 hours postdose
- Aged 6–17 years:
  - Days 1 and 30: predose and at 30 minutes and 2 and 10 hours postdose
  - Days 2 and 31: 24 hours postdose
  - Day 150: predose and at 2 and 10 hours postdose

A single plasma sample should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Windows for the collection of PK samples are as follows:

- Predose to be collected within 30 minutes before administration of study intervention
- 5, 15, and 30 minutes and 1 hour postdose, ± 3-minute window is allowed
- 2, 4, 6, 10, and 12 hours postdose, ± 30-minute window is allowed
- 24 hours postdose, ± 1-hour window is allowed

o. In adults, blood samples for plasma oxalate analysis to be collected prior to dosing (Section **8.1.5**). Participants aged 6 to 17 years will have plasma oxalate sampling only at Screening.

p. Participants should maintain consistent fluid intake (i.e., hyperhydration) over the course of the study (Section **5.3**). Participants will report average daily fluid intake over the 4 to 7 days prior to each 24-hour urine collection (Section **8.2.7**).

q. On Days 1 and 30, ECG to be performed predose and at 10 hours (± 30-minutes) postdose. A single ECG to be performed at other visits, as indicated (Section 8.2.5). If multiple assessments are due at the same time point, PK sampling should be performed preferably at the nominal time point, with the preferred order of assessments ECG, vitals, PK, and then other assessments.

r. Vital signs on Day 1 and Day 30 to be assessed predose and at 10 hours (± 30-minutes) postdose (Section 8.2.3). If multiple assessments are due at the same time point, PK sampling should be performed preferably at the nominal time point, with the preferred order of assessments ECG, vitals, PK, and then other assessments.

s. A full physical exam will be performed at Screening and Day 180 (or ET). A brief physical examination may be performed at other scheduled visits (Day 1 through Day 150) or unscheduled visits at the Investigator's discretion. See Sections **8.2.1** and **8.2.2**.

t. In participants ≥ 18 years of age, height to be recorded only at screening. In participants < 18 years of age, height will be recorded at specified visits for calculation of eGFR and BSA adjustment of Uox excretion. Weight to be recorded in all participants at specified visits. In participants aged 6-to-11 years, the weight on Day 1 will be used to calculate the mg/kg dose of study intervention.

u. Blood samples for hematology and serum chemistry to be collected predose on dosing days. To include cystatin C in participants < 18 years of age for calculation of eGFR. See Section **10.2** for the list of parameters.

v. Blood samples for coagulation studies to be collected predose. Coagulation panel will include activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR). Additional coagulation studies should be performed as clinically indicated.

w. eGFR to be calculated as described in Section **8.2.4.1**.

x. Blood samples for cytokines to be collected in participants aged ≥ 18 years within 30 minutes before administration of study intervention and 2, 10, and 24 hours postdose. A ± 30-minute window is allowed for samples collected at 2 and 10 hours postdose. A ± 1-hour window is allowed for sample collected at 24 hours postdose. A single sample will be collected in participants prematurely discontinuing study intervention. See Section **10.2** for parameters. Cytokine testing is not required in participants < 18 years of age.

y. Blood samples for complement panel to be collected in participants aged ≥ 18 years within 30 minutes before administration of study intervention and 2, 10, and 24 hours postdose. A ± 30-minute window is allowed for samples collected at 2 and 10 hours postdose. A ± 1-hour window is allowed for sample collected at 24 hours postdose. A single sample will be collected in participants prematurely discontinuing study intervention. See Section **10.2** for parameters. Complement testing is not required in participants < 18 years of age.

z. Urinalysis with microscopy at Screening and as clinically indicated. Dipstick urinalysis may be performed at other scheduled visits. Collect sample for urinalysis before dosing. See Section **10.2** for parameters.

aa. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Administration of study intervention will be discontinued in any participant with a positive pregnancy test. A final pregnancy test will be conducted 2-3 weeks following the last dose of study intervention in any WOCBP who prematurely discontinues the study.

bb. Participants will report instances of renal stones requiring medical intervention, stone passage, and/or renal colic requiring medication (Section **8.1.6.1**).

cc. In the event of rescreening, if a participant had been screened for this study within the last 3 months and had kidney ultrasound data sent to the central over-readers, repeat of the kidney ultrasound will not be required during the rescreen.

dd. In the event of rescreening, if a participant had been screened for this study within the last 3 months and had echocardiogram data sent to the central over-readers, repeat of the echocardiogram will not be required during the rescreen.

ee. Blood samples for analysis of anti-drug antibodies will be analyzed once a validated methodology is available (Section **8.8.1**).

ff. Participants < 18 years of age to be queried as to the ongoing burden of the study (Section **2.3.2**).

gg. Short Form 36 Health Survey to be administered only in adults (Section **8.1.7.1**).

hh. EQ-5D-5L to be administered only in adults (Section **8.1.7.2**).

ii. PedsQL to be administered only in children (Section **8.1.7.3**).

jj. Serious adverse events to be collected from time of ICF signature through 30 days after the last study visit.

kk. Adverse events to be collected from the time of ICF signature through the End of Study/Early Termination Visit. Participants will be questioned as to the occurrence of muscle pain or weakness.

2. INTRODUCTION

2.1. STUDY RATIONALE

Primary hyperoxaluria encompasses 3 genetically distinct, autosomal-recessive, inborn errors of glyoxylate metabolism characterized by the over-production of oxalate, a highly insoluble metabolic end-product that is eliminated mainly by the kidney. Patients with PH are predisposed to the development of multiple and recurrent urinary tract (urolithiasis) and kidney (nephrolithiasis) stones. Calculi formation is accompanied by nephrocalcinosis in some patients with PH. This deposition of calcium oxalate in the renal parenchyma produces tubular toxicity and renal damage that is compounded by the effects of renal calculi-related obstruction and frequent superimposed infections (Cochat & Rumsby, 2013). Most patients are diagnosed in childhood or early adulthood.

There is a significant unmet need for treatment in all subtypes of PH. At present, no therapies are approved by regulatory authorities for the treatment of patients with PH. A number of supportive therapies are used in an attempt to mitigate some of the effects of the disease.

DCR-PHXC is designed to substantially reduce the activity of a key oxalate-producing enzyme. The potential medical value of decreasing liver oxalate production in patients with PH has been demonstrated by the marked improvement in disease outcome in patients with PH1 in whom liver oxalate production has been reduced by liver transplantation.

This study is being conducted to assess the effect of DCR-PHXC on urinary oxalate (Uox) burden in patients with either PH1 or PH2, the most severe forms of PH.

2.2. BACKGROUND

2.2.1. Overview of Primary Hyperoxaluria

PH encompasses 4 related rare diseases, 3 of which are attributed to mutations in specific genes (PH1, PH2, and PH3) and a fourth for which there is currently no identified genetic cause (no-mutation-detected primary hyperoxaluria, known as NMD-PH).

PH is a devastating disease that presents across the age continuum with a broad range of medically important abnormalities (Cochat & Rumsby, 2013). All 3 genetic forms of PH exhibit some extent of overlap in the clinical manifestations, where overproduction of oxalate is a prominent observation (Hoppe, 2012; Hoppe et al., 2009). Renal oxalate deposition in patients with PH1 and some patients with PH2 and PH3 leads to nephrocalcinosis, tubular dysfunction, and progression to end-stage renal disease (ESRD). Systemic oxalosis occurs in patients with PH1 and some patients with PH2 due to the over-production of oxalate by the liver and the impairment of the body's ability to eliminate oxalate; producing a broad range of serious life-threatening complications. The consequences of systemic deposition of calcium oxalate crystals in patients with systemic oxalosis include fracturing bone disease, nonhealing painful cutaneous ulcers, treatment-refractory anemia, retinal calcium oxalate deposition, and cardiomyopathy and arrhythmias due to deposition in the cardiac conduction system (Hoppe et al., 2009).

A review of 330 patients with PH1 demonstrated that the outlook for these patients without treatment is poor, with ESRD present in 50% of patients by the age of 15 years and in 80% by the third decade (Latta & Brodehl, 1990). Although early initiation of aggressive conservative treatment (high fluid intake, inhibitor of calcium oxalate crystallization, and pyridoxine in responsive cases) can help slow or delay progression to ESRD, there is still substantial morbidity across the age continuum.

PH2 was first described in 1968 based on the absence of glycolate and the presence of L-glyceric acid in the urine from 4 cases with hyperoxaluria (Williams & Smith, 1968). PH2 is much rarer than PH1 and is characterized by recurrent nephrolithiasis with nephrocalcinosis and ESRD in some patients.

2.2.2. Nonclinical Overview

DCR-PHXC consists of the drug substance (DCR-L1360) in WFI. DCR-L1360 is a synthetic double-stranded (hybridized duplex) RNA oligonucleotide conjugated to GalNAc aminosugar residues. After SC administration, the GalNAc sugars conjugated to the RNA oligonucleotide bind to asialoglycoprotein receptors (ASGR) to deliver DCR-L1360 to hepatocytes. DCR-L1360 reduces the level of mRNA encoding the dominant form of the LDH enzyme, specifically, the *LDHA* isoenzyme. The selective reduction of hepatic LDH reduces the production of oxalate by the liver.

Administration of DCR-L1360 to mice expressing human *LDHA* mRNA resulted in significant reduction of *LDHA* mRNA. A single SC dose of 1 to 6 mg/kg was associated with dose-dependent knockdown that was evident at 1-week postdose and persisted for 4 weeks postdose. Significant reduction in *LDHA* mRNA, LDH protein expression, and LDH activity in the liver was observed for at least 4 weeks after administration of 2 doses of DCR-L1360 in monkeys; however, these dose levels were well in excess of the pharmacologically relevant dose level.

DCR-L1360 was not associated with any adverse effects on cardiovascular, respiratory, or neurological function in cynomolgus monkeys when administered as a single SC injection at doses up to 300 mg/kg. In addition, in the pivotal repeat-dose toxicity studies (up to 6 months in mice and up to 9 months in monkeys), DCR-L1360 was well tolerated at dose levels up to 300 mg/kg in both mice and monkeys.

The results from these studies demonstrate that a reduction of hepatic *Ldha* mRNA lowered or eliminated excess oxalate production in the livers of PH model mice and protected the kidney from calcium oxalate crystal deposition and the resultant damage.

See the DCR-PHXC Investigator's Brochure (IB) for more details on the nonclinical studies.

2.2.3. Clinical Overview

At present, no therapies are approved by regulatory authorities for the treatment of patients with PH. A number of supportive therapies are used in an attempt to mitigate some of the effects of the disease. Current medical management before renal failure develops is underpinned by hyperhydration with fluid intake recommendations of at least 3 liters per day per square meter of body-surface area (5 L/day for a 70-kg adult) (Cochat et al., 2012). These regimens can be problematic in infants and toddlers, necessitating placement of a gastrostomy tube to ensure adequate night-time fluid administration. Affected patients are at considerable risk of serious complications during periods of increased fluid loss (fever, diarrhea/vomiting, and urinary tract infections) or when oral hydration is compromised (following surgical procedures). Oral

potassium citrate administration is used to inhibit crystallization and alkalinize the urine. Treatment with vitamin B6 is effective in decreasing Uox in approximately 10% to 30% of patients with PH1 with certain *AGXT* mutations but has not been proven effective in treating other forms of PH (Salido et al., 2012; Hoppe et al., 2009; Hoyer-Kuhn et al., 2014).

For patients with more advanced disease, dialysis may be used in an attempt to remove endogenously over-produced oxalate. In contrast to the more typical 3-times-weekly hemodialysis regimens used in other types of renal failure, patients with PH may require hemodialysis 6 or 7 days per week. Given the limitations of dialysis and the inability to substantially impact oxalate over-production in most patients with PH1, most centers now consider liver transplantation approaches earlier in the disease course to minimize the risk of irreversible tissue damage. Other treatments include renal transplantation or, in patients with PH1, combined liver and kidney transplantation (Nolkemper et al., 2000; Rogers et al., 2001). As with organ transplantation in other diseases, these procedures are associated with significant medical risk and a requirement for long-term treatment with immunosuppressive drugs that are also associated with significant side effects.

2.2.3.1. Clinical Studies of DCR-PHXC

DCR-PHXC is being evaluated in 5 ongoing studies in healthy volunteers and patients with PH1 or PH2.

As of September 2019, in Study DCR-PHXC-101, after single-dose administration of DCR-PHXC, normalization of Uox (defined as Uox excretion < 0.46 mmol/24 hours) was achieved in 10 of 18 participants with PH1 or PH2, with an additional 4 participants achieving near-normalization (defined as Uox excretion 0.46 to < 0.60 mmol/24 hours).

No significant safety findings have emerged from this or other ongoing studies. DCR-PHXC has an acceptable safety profile in both healthy volunteers and participants with PH1 and PH2.

Please see the DCR-PHXC Investigator's Brochure for additional details of this ongoing study.

2.3. Risk/Benefit and Burden Assessment

2.3.1. Known Potential Risks

Risks associated with DCR-PHXC may be characterized into 2 broad categories: risks associated with the small interference RNA (siRNA) molecule and risks associated with an off-target knockdown of LDHA.

2.3.1.1. Risks Related to the siRNA Molecule

DCR-PHXC is conjugated to GalNAc sugars that target the molecule to the liver. Due to the lack of excipients in the drug product, the potential risks associated with DCR-PHXC are limited to the risks associated with the siRNA oligonucleotide portion of the drug product (DCR-L1360). To date, DCR-L1360 has been associated with little to no toxicity in the nonclinical studies. Results of nonclinical toxicity studies of DCR-L1360 conducted to date are presented in Section **2.2.2**. As with all oligonucleotides, there is a potential for immunogenicity.

Clinical observations associated with other siRNAs have included occasional reports of stimulation of pattern recognition receptors (e.g., Toll-like receptors) leading to cytokine release,

inflammation, and injection site reactions, and low elevations of liver function tests (LFT). Published clinical observations from older nucleic acid therapy platforms, such as single-stranded antisense programs based on fully phosphorothioate-modified oligonucleotides, have included coagulopathies, thrombocytopenia, complement activation, and mild to moderate hepatotoxicity. Until further clinical safety information for DCR-PHXC is available, general precautions relevant to siRNA molecules should be considered. Participants will be monitored for injection site reactions, liver abnormalities, markers of inflammation (cytokine release) and direct (anti-drug antibodies; ADA) or indirect (anti-double-stranded deoxyribonucleic acid antibodies; anti-dsDNA) markers of antibody formation against DCR-L1360.

2.3.1.2. Risks Related to LDHA Knockdown and Potential Off-target Effects

LDHA deficiency (Glycogen storage disease XI) is a near complete loss of LDHA function caused by mutations in the *LDHA* gene and has been described in approximately 22 subjects. People with this condition experience fatigue, muscle pain, and cramps during exercise (exercise intolerance). In some extreme cases, high-intensity exercise or other strenuous activity may lead to rhabdomyolysis. Liver-associated changes have not been reported (Kanno et al.,1995; Lee et al., 2011; Maekawa et al., 1989; Miyajima et al., 1993, Sudo et al., 1994).

DCR-L1360 has been designed to minimize the potential for effects outside of the liver tissue and, thus, an effect outside of the liver tissue is unlikely at the proposed clinical doses. DCR-L1360 was designed with 4 GalNAc sugar residues that direct delivery of the siRNA preferentially to hepatocytes, due to their high expression of ASGR. Although ASGR expression has been detected on extra-hepatic cells, the expression of ASGR on hepatocytes far exceeds expression in other tissues (D'Souza & Devarajan, 2015). Together, tissue distribution and turnover of the ASGR make GalNAc conjugation ideal for targeted delivery of materials to the hepatocytes. Tissue distribution studies in mice confirm that, after SC administration, DCR-L1360 is distributed primarily to the liver. In pharmacology studies in mice, knockdown of *Ldha* mRNA by DCR-m355, the murine surrogate, was specific to the liver and was not observed in muscle; these results suggest that DCR-L1360 will be similarly specific. Furthermore, no adverse skeletal muscle effects were observed in monkeys at DCR-L1360 dose levels up to 300 times the minimally active dose. Although the 5-week toxicity study in mice identified potential off-target effects on skeletal muscle (degeneration of skeletal muscle, esophageal muscle, and tongue in one 300-mg/kg mouse, and increased creatine kinase (CK) in one 100-mg/kg mouse), no effects on skeletal muscle were observed in the 6-month chronic study. Nonetheless, in addition to measurement of plasma CK, participants should be monitored for signs and symptoms of muscle weakness or pain.

DCR-L1360 shows high sequence specificity. In silico analysis suggests that it has minimal potential for off-target effects via siRNA hybridization to the human genome. Among the off-target sites identified in non-target mRNAs, only 2 genes contained a seed region sequence complementarity thought to be important in affecting ribonucleic acid interference (RNAi) activity; both had relatively short partial homologies, which suggests the potential for only weak, if any, impact of DCR-L1360 treatment on these genes. SATB1 protein does not appear to be expressed in the liver or skeletal muscle. DCP1A protein is expressed broadly, including in liver, but is not expressed in the skeletal muscle. Neither gene has been reported to be associated with human disease. As both genes are fully conserved among primates, any off-target effects related

to complementarity to these genes would be detected by the toxicity studies in monkeys, but none have been observed.

2.3.2. Pediatric Burden Assessment

With respect to the overall burden of the study, patients with PH have regular visits at their treating physician, which includes routine measurements of hematology and chemistry, vital signs, kidney ultrasound, ECG, echocardiography, and analysis of 24-hour urine (Cochat et al., 2012). Therefore, the burdens of the current protocol procedures are considered minimal in comparison to the standard treatment for PH (see **Table 1** for details).

At each study visit, pediatric participants and their parent or guardian will be asked a few study-specific questions to ensure that the burden of continued study participation is not too extensive. This pediatric burden assessment is in line with the requirements put forth in the European Commission's *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors* (18 September 2017).

Table 1 Risk/Burden Assessment

Procedure	Risk/Burden	Assessment
Blood sampling, including cannulation	Risks include acute pain, bleeding, vessel injury, and, in rare instances, arterial vessel blockage, potentially leading to infection.	The risk/burden is minimal and not over and above the risk/burden associated with blood sampling as part of the standard treatment for PH. Due to the increased frequency of blood sampling in the trial for the purposes of ensuring patient safety, it is possible that the likelihood of patients experiencing minor effects from blood sampling is higher during the study.
12-lead ECG	N/A	Conducted in supine position after 10 minutes at rest. No risks identified.
Blood pressure measurement	N/A	Measurements performed at a single time point with an appropriately sized blood pressure cuff. No risks identified.
Subcutaneous injection	The study drug is administered via SC injection. Subcutaneous injection is associated with pain, and may cause vasovagal reactions, allergic reactions, infections, or bleeding.	The risk/burden associated with the SC injection of the study drug is minimal. This injection is outside the standard treatment for PH and therefore is assessed as a minimal risk/burden to patients.
Kidney ultrasound	N/A	Kidney ultrasound is part of the standard treatment for PH patients. Kidney ultrasound does not involve any invasive procedures. No risks identified.
Echocardiogram	N/A	Echocardiography is part of the standard treatment for PH patients. Echocardiography does not involve any invasive procedures. No risks identified.
24-hour urine collection	Due to the frequency of collection in the current protocol, minor burden is involved.	24-hour urine collection is part of the standard treatment for PH patients. Urine collection in this study does not involve catheterization or invasive procedures of any kind. No risks identified.

Abbreviations: ECG: electrocardiogram; N/A: not applicable; PH: primary hyperoxaluria

2.3.3. Known Potential Benefits

The biological relationship between urinary oxalate supersaturation and the subsequent calcifications in kidney and extra-renal organs has been well established (Hoppe et al, 2009; Hoppe, 2012; Cochat & Rumsby, 2013). The degree of hyperoxaluria has been shown to predict the development and severity of nephrocalcinosis, and is described as an independent risk factor for ESRD in patients with PH (Zhao et al., 2016).

As increased urinary oxalate is an independent risk factor for the development of calcium oxalate crystallization, a reduction in oxalate excretion should lower the risk of calcium-oxalate supersaturation and the subsequent negative consequences on the renal system and beyond. Several researchers have demonstrated that pre-emptive liver transplantation normalizes oxalate excretion and stabilizes or improves kidney function in long-term follow-up if no systemic oxalosis is present (Kemper et al 1998; Galanti & Contreras, 2010; Perera et al., 2011).

Results from nonclinical studies of DCR-PHXC demonstrated that a reduction of hepatic *Ldha* mRNA lowered or eliminated excess oxalate production in the livers of PH-model mice and protected the kidney from calcium oxalate crystal deposition and the resultant damage. Based on results achieved in the murine models of PH, administration of DCR-PHXC to patients with PH, who do not have systemic oxalosis, is expected to result in a measurable reduction in urinary oxalate.

Results from the ongoing study DCR-PHXC-101 are summarized in Section **2.2.3.1** and demonstrate that single-dose administration of DCR-PHXC can reduce the urinary oxalate burden in patients with PH1 and PH2 and potentially decrease the risk for the development of calcium oxalate crystallization.

2.3.4. Risk Management

Measures to minimize the risks to participants have been incorporated into the following study design elements:

- An independent Data Safety Monitoring Committee (DSMC) will review all safety and efficacy data in an unblinded fashion, using group labels, on an ongoing basis.
- Clinical Laboratory Monitoring: At time of study entry, study participants are required to have safety laboratory values within acceptable ranges. Serial measurements of safety laboratory parameters (complete blood count [CBC], platelet count, creatinine, cytokines, complement, LFTs, and coagulation parameters) are planned, with regular medical review by the Medical Monitor, as outlined in the medical management plan, in addition to interim review as defined in the DSMC charter.
- Monitoring of signs and symptoms of muscle pain and/or weakness, along with measurement of plasma creatine kinase.

- Total blood volume collected: The following blood volumes will be collected during the trial:
    - Adult participants: A total of 315 mL, with a maximum of 172 mL in a 30-day period
    - Aged 6-17 participants: A total of 136.4 mL, with a maximum of 43.8 mL in a 28-day period. In order to minimize blood loss, blood samples for screening tests should be collected not less than 28 days prior to samples drawn on Day 1. If met with blood draw difficulty, the Investigator team will make not more than 3 attempts at venipuncture.

With regard to pediatric participants, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: *Clinical Investigation of Medicinal Products in the Pediatric Population* (E11, 20 July 2000) and the European Commission *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors* (18 September 2017) have been considered during the design of the trial, and blood volume minimized where possible. Practical considerations include the use of laboratories experienced in handling small volumes of blood for PK, PD, and laboratory safety analyses.

Wherever possible, routine clinical safety, PD, and PK blood samples will be collected at the same time point. If there is difficulty in obtaining a full blood collection, clinical chemistry and hematology tests detailed in **Table 3** will be prioritized. Furthermore, indwelling catheters will be used where deemed appropriate by the Investigator team to minimize the potential distress of venipuncture.

2.3.5. Overall Risk-Benefit Analysis

At present, no therapies are approved by regulatory authorities for the treatment of patients with PH. A number of supportive therapies are used in an attempt to mitigate some of the effects of the disease, but affected patients are at considerable risk of serious complications like renal stones, nephrocalcinosis, renal failure, and systemic tissue damage due to oxalate deposition. Combined liver-and-kidney transplantation is the only causative therapy but is associated with short- and long-term complications as well. DCR-PHXC treatment has the potential benefit to reduce or eliminate the excess oxalate production in the liver and thus avoid the need for a combined liver and kidney transplantation in patients not already on renal replacement therapy. The potential risks with DCR-PHXC include low elevations of liver function tests, muscle damage, and stimulation of pattern-recognition receptors (e.g., Toll-like receptors) leading to cytokine release, inflammation, and injection site reactions. These risks can be monitored and should be reversible after drug discontinuation. The preliminary results from the ongoing study, DCR-PHXC-101, demonstrate the potential for DCR-PHXC to bring patients into a near-normal or normal range of their 24-hour Uox values. Continuous risk-benefit assessments will be conducted by the Sponsor, the Medical Monitor of the contract research organization (CRO), and the DSMC on an ongoing basis.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden in patients with PH	AUC from Day 90 to Day 180, based on percent change from Baseline in 24-hour Uox
Key Secondary	
To identify the proportion of participants with normalized or near-normalized Uox	The proportion of participants with a 24-hour Uox level < 0.46 mmol/24 hours or ≥ 0.46 to < 0.60 mmol/24 hours (adjusted per 1.73 m^2 BSA in participants aged < 18 years) on at least 2 consecutive visits, beginning with Day 90
Secondary	
1. To evaluate the effect of DCR-PHXC on stone burden in patients with PH	1. Percent change in the summed surface area and number of kidney stones identified via kidney ultrasound from Baseline to Day 180
2. To evaluate the effect of DCR-PHXC on plasma oxalate in patients with PH	2. Percent change in plasma oxalate from Baseline to Day 180 (for adults only)
3. To evaluate the effect of DCR-PHXC on eGFR	3. Rate of change in eGFR from Baseline to Day 180
4. To assess the safety of DCR-PHXC in patients with PH	4. AE and SAE; change from Baseline in 12-lead ECG, physical examination findings, vital signs, and clinical laboratory tests
5. To characterize the PK of DCR-PHXC in patients with PH	5. Population and individual PK parameters for DCR-PHXC
Tertiary/Exploratory	
1. To evaluate the effect of DCR-PHXC on stone events in patients with PH	1. Number of stone events over a 6-month period
2. To assess the efficacy of DCR-PHXC in reducing Uox burden over 6 months in patients with PH	2. AUC of 24-hour Uox from Day 1 to Day 180, based on percent change from Baseline
3. To assess the efficacy of DCR-PHXC in reducing Uox at month 6 in patients with PH	3. Percent change in 24-hour Uox from Baseline to Day 180
4. To evaluate the effect of DCR-PHXC on urinary oxalate-to-creatinine ratio in patients with PH	4. AUC of 24-hour urinary oxalate-to-creatinine ratio from Day 90 to Day 180, based on percent change from Baseline
5. To evaluate the effect of DCR-PHXC on QoL Assessments in patients with PH	5. Change from Baseline to Day 180 in the SF-36 and EQ-5D-5L in adults; and in the PedsQL™ in children
6. To evaluate the relationship between Uox spot urine and 24-hour urine measurement in patients with PH	6. Uox in spot urine and 24-hour urine

Abbreviations: AE: adverse events; AUC: area under the curve; BSA: body surface area; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; PedsQL: Pediatric Quality of Life Inventory; PH: primary hyperoxaluria (types 1 and 2); PK: pharmacokinetic; QoL: quality of life; SAE: serious adverse events; SF-36: Short Form 36 Health Survey; Uox: urinary oxalate

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is Phase 2 multicenter trial of DCR-PHXC in patients with primary hyperoxaluria (PH1 and PH2). The primary hypothesis to be tested is that DCR-PHXC is superior to placebo in lowering Uox burden over a 6-month test period.

This is a randomized, placebo-controlled, double-blind, parallel-group trial, in which participants will be randomized in a 2 to 1 ratio (DCR-PHXC to placebo). An adaptive randomization via minimization method will be used to allocate patients to treatment groups with respect to age and eGFR. See Section **9.3** for details of the minimization scheme.

Following the up-to-35-day screening period, participants will return to the clinic for interim visits through Day 180. Note: an extra 7 days will be allowed for participants who are required to repeat screening 24-hour urine collections or for repeat of initially unanalyzable screening laboratory assessment samples. The total time on study for each participant is approximately 7 months. Participants completing this study may be eligible for enrollment into a long-term open-label extension study (see Section **6.7**).

It is expected that the entire trial will have an 18-month duration.

Blinding will be maintained using an unblinded pharmacist or designee and tinting or shrouding of the administration syringe to obscure the slight color difference between DCR-PHXC and placebo.

It is expected that approximately 40 participants will be screened, such that 36 participants will be evaluable.

An interim analysis of the data may be conducted when two-thirds of participants have completed study assessments through the Day 180 visit. See Section **9.6** for details of the interim analysis.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

The randomized, double-blind, placebo-controlled, parallel-group trial is the optimal design for evaluation of efficacy and safety of an investigational drug. The 6-month duration of the treatment period is considered sufficient to demonstrate a sustained superiority of DCR-PHXC as compared with placebo in lowering Uox in patients with PH.

The primary endpoint of this Phase 2 study will be 24-hour urinary oxalate excretion, measured as the AUC of percent change from baseline over the last 3 months of treatment. This endpoint is proposed in order to assess a reduction in oxalate burden over time rather than at a single time point at the end of study (EOS). The Sponsor believes the biological relationship between urinary oxalate supersaturation and the subsequent calcifications in kidney and extra-renal organs has been well established. The degree of hyperoxaluria predicts the development and severity of nephrocalcinosis and is an independent risk factor for ESRD in patients with PH (Zhao et al., 2016). In order to demonstrate a substantial change from baseline in 24-hour Uox in patients with highly elevated Uox levels, a population of patients with at least one baseline Uox value ≥ 1.6 mmol/24 hours will be enrolled and analyzed in a subgroup analysis.

4.3. JUSTIFICATION FOR DOSE

The safety margins for this study were calculated based on the no observed adverse effect levels (NOAELs) determined in the chronic toxicity studies in mice and monkeys and the supporting pharmacology data in non-GLP exploratory studies (see the IB for additional details).

4.3.1. PK/PD Model for Dose Selection in Adults and Adolescents

In the Phase 1 study (Study No. DCR-PHXC-101), single doses of DCR-PHXC have been administered to patients with PH1 or PH2 at either 1.5, 3.0, or 6.0 mg/kg and to healthy volunteers in the dose range of 0.3 to 12 mg/kg.

A preliminary PK/PD M&S analysis explored the relationship between model-predicted DCR-L1360 plasma concentrations and 24-hour Uox concentrations in patients with PH. The PK model was developed using the PK data from both healthy volunteers (N=15) and patients with PH (N=10). The PK-PD model only involved the PD data from patients with PH. The model fits were evaluated using several diagnostic plots and further qualification was done using prediction corrected visual predictive check (pcVPC). The model adequately described the observed data, with an even distribution of observations above and below the 10^{th} and 90^{th} prediction intervals. From the data available, the predictive performance of the model was considered acceptable. Various simulations were conducted to optimize both the dose and dosing regimen to predict the proportion of participants with a 24-hour Uox < 0.6 mmol/24 hours (near-normal range) and < 0.46 mmol/24 hours (normal range).

From these simulations, a dose of 170 mg administered monthly was selected for adults and for adolescents weighing at least 50 kg. For adults and adolescents weighing less than 50 kg, a lower dose of 136 mg was selected.

4.3.2. PK/PD Model for Dose Selection in Children Younger than 12 Years of Age

The preliminary PK-PD model that was developed using the adult and adolescent data from the DCR-PHXC-101 study was updated to include data from studies DCR-PHXC-102, DCR-PHXC-103, all available adult data from Study DCR-PHXC-301, and at least 3 adolescents from the DCR-PHXC-201 and DCR-PHXC-301 studies. The model fits were evaluated using several diagnostic plots and further qualification was done using pcVPC. The model adequately described the observed data, with an even distribution of observations above and below the 10^{th} and 90^{th} prediction intervals. From the data available, the predictive performance of the model was considered acceptable.

The dose selection for the 6- to 11-year-old participants was based on PK and PK-PD simulations. The dose was selected such that the 6- to11-year-old participants will have a similar exposure to DCR-PHXC as participants receiving the 170 mg dose and to provide for a comparable proportion of participants with normal or near-normal levels of 24-hour Uox. Based on these simulations, a dose regimen of 3.5 mg/kg once monthly was selected. Note: the total dose administered in 6- to 11-year-old participants will not exceed 136 mg.

4.3.3. Placebo Comparator

Normal saline for injection is of a similar osmolality to DCR-PHXC and is approved for SC injection.

4.4. END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section **1.3**.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Age

1. At least 6 years of age, at the time of signing the informed consent/assent

Type of Participant and Disease Characteristics

2. Documented diagnosis of PH1 or PH2, confirmed by genotyping (historically available genotype information is acceptable for study eligibility)
3. 24-hour Uox excretion ≥ 0.7 mmol (adjusted per 1.73 m^2 BSA in participants < 18 years of age) in both collections performed in the screening period. At least 12 participants must have at least one 24-hour Uox excretion ≥ 1.6 mmol (adjusted per 1.73 m^2 BSA in participants aged < 18 years).
4. Less than 20% variation between the two 24-hour urinary creatinine excretion values obtained in the screening period. Individuals who do not achieve < 20% variation between the 2 screening values may undergo a second round of urine collection. An extra 7 calendar days may be added to the screening window for participants to complete a second round of urine collection. Should potential participants again fail to achieve the within-20% variation, they will be excluded from participation.
5. Estimated GFR at screening ≥ 30 mL/min normalized to 1.73 m^2 BSA, calculated using the CKD-EPI equation in participants aged ≥ 18 years (Levey & Stevens, 2010) or the multivariate equation by Schwartz in participants aged 6 to 17 years (Schwartz et al., 2012)

Sex

6. Male or female

   Male participants:

   A male participant with a female partner of childbearing potential must agree to use contraception, as detailed in Section **10.4.2**, during the treatment period and for at least 12 weeks after the last dose of study intervention and refrain from donating sperm during this period.

Female participants:

A female participant is eligible to participate if she is not pregnant (see Section **10.4.1**), not breastfeeding, and at least 1 of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in Section **10.4.1**

OR

A WOCBP who agrees to follow the contraceptive guidance in Section **10.4.2** during the treatment period and for at least 12 weeks after the last dose of study intervention.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent/Assent

7. Participant (and/or participant's parent or legal guardian if participant is a minor [defined as patient < 18 years of age, or younger than the age of majority, according to local regulations]) is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   a. Adolescents (12 to < 18 years of age, or older than 12 years but younger than the age of majority, according to local regulations) must be able to provide written assent for participation.
   b. For children younger than 12 years of age, assent will be based on local regulations.

5.2. EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

Medical Conditions

1. Prior renal or hepatic transplantation, or planned transplantation within the study period
2. Currently receiving dialysis, or anticipating requirement for dialysis during the study period
3. Plasma oxalate > 30 μmol/L
4. Documented evidence of clinical manifestations of systemic oxalosis (including pre-existing retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations)
5. Presence of any condition or comorbidities that would interfere with study compliance or data interpretation or potentially impact patient safety including, but not restricted to:
   a. severe intercurrent illness
   b. known causes of active liver disease/injury or transaminase elevation (e.g., alcoholic liver disease, nonalcoholic fatty liver disease/steatohepatitis)

c. physician concerns about intake of drugs of abuse or excessive alcohol intake, or history of excessive alcohol intake in the 2 years prior to enrollment (defined as ≥ 21 units of alcohol per week in men and ≥ 14 units of alcohol per week in women; where a "unit" of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1-ounce shot of hard liquor)

d. history of serious mental illness that includes, but is not limited to, schizophrenia, bipolar disorder, or severe depression requiring hospitalization or pharmacological intervention

e. clinically relevant history or presence of cardiovascular, respiratory, gastrointestinal, hematological, lymphatic, neurological, musculoskeletal, genitourinary, immunological diseases, including dermatological (e.g., rash, severe eczema or dermatitis), or connective tissue diseases or disorders

Prior/Concomitant Therapy

6. Use of an RNA interference (RNAi) drug within the last 6 months
7. History of one or more of the following reactions to an oligonucleotide-based therapy:
   a. severe thrombocytopenia (platelet count ≤ 100,000/μL)
   b. hepatotoxicity, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) and total bilirubin > 2 × ULN or international normalized ratio (INR) >1.5
   c. severe flu-like symptoms leading to discontinuation of therapy
   d. localized skin reaction from the injection (graded severe) leading to discontinuation of therapy
   e. coagulopathy/clinically significant prolongation of clotting time
8. Participants receiving pyridoxine must have been at a stable dose for at least 4 weeks prior to Day 1 and must be willing to remain on the same stable dose throughout the study.

Prior/Concurrent Clinical Study Experience

9. Participation in any clinical study in which they received an investigational medicinal product (IMP) within 4 months before Screening
   a. for IMPs with the potential to reduce urine and/or plasma oxalate concentrations, these concentrations must have returned to historical baseline levels prior to Screening

Diagnostic assessments

10. Liver function test abnormalities: ALT and/or AST >1.5 × ULN for age and gender
11. Positive screening for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or anti-human immunodeficiency virus (HIV) 1 and 2 antibodies. If participant has been tested in the past 3 months, medical record documentation of this testing can be used for screening. Viral serology testing not required in participants < 18 years of age.

12. Positive urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines). Investigator discretion is allowed. Urine drug screening is not required in participants ≤ 12 years of age.

Other Exclusions

13. Known hypersensitivity to DCR-PHXC, or any of its ingredients
14. Inability or unwillingness to comply with the specified study procedures, including collection of 24-hour urine samples, and the lifestyle considerations detailed in Section **5.3**

5.3. LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- refrain taking vitamin C supplements, including multivitamins, for 24 hours prior to and during the 24-hour urine specimen collections
- avoid oxalate-rich foods
- abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests
- continue to follow standard of care for PH, including, but not limited to hyperhydration regimens, oral potassium citrate administration, and treatment with vitamin B6 (if applicable).

5.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Rescreened participants will be assigned a new participant number for re-screening. Potential participants may undergo rescreening only with approval of the Sponsor.

5.5. STRATEGIES FOR RECRUITMENT AND RETENTION

Given the rare-disease nature of PH, potential participants may be under the care of the Investigator. Others may be referred to the clinical site by their treating physicians, or through other patient networks.

Participants will be reimbursed for expenses associated with study visits, such as parking, transportation, and meals. For car travel, mileage will be reimbursed at the current regional government rate. Participants must submit supporting documentation for the reimbursement(s) requested.

6. STUDY INTERVENTION

6.1. STUDY INTERVENTION(S) ADMINISTRATION

6.1.1. Study Intervention Description

DCR-PHXC is a synthetic RNAi drug that consists of a double-stranded oligonucleotide conjugated to GalNAc ligands. DCR-PHXC is a sterile formulation of the drug substance (DCR-L1360) in WFI, intended for SC administration.

DCR-PHXC is not commercially available in any country.

The placebo comparator is 0.9% normal saline for injection.

6.1.2. Dosing and Administration

Study intervention will be administered in clinic as a SC injection into the abdomen or thigh using a 25- to 27-gauge needle, 3/8 to 5/8 inches long.

In adults and in adolescents (aged 12-17 years) weighing ≥ 50 kg, study intervention will be administered once monthly at a dose of 170 mg DCR-PHXC (or the equivalent volume of placebo). In adults and adolescents weighing < 50 kg, study intervention will be administered once monthly at a dose of 136 mg DCR-PHXC (or the equivalent volume of placebo). Participants who begin the study weighing less than 50 kg will have their dose increased to the 170 mg dose should they reach the 50 kg threshold. Participants receiving the 170 mg dose will not have their dose decreased to the 136 mg dose should they fall below the 50 kg threshold.

The dose for participants aged 6 to 11 years will be 3.5 mg/kg monthly, not to exceed 136 mg. The total dose for 6- to 11-year-old participants will be based upon body weight recorded on study Day 1 and will be constant throughout the study, regardless of any weight gain or loss or change in age (i.e. an 11-year-old turns 12 during the study). The volume of a single injection should not exceed 0.5 mL. Should the calculated dose require a volume greater than 0.5 mL, the dose should be administered in 2 equally divided injections.

An unblinded pharmacist or designee will prepare the dose of DCR-PHXC or placebo as detailed in Section **6.2.4**.

To prevent any blinded site staff or study participants from visually observing color differences between DCR-PHXC and placebo, syringes will be tinted or shrouded to mask the color difference.

6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1. Acquisition and Accountability

DCR-PHXC will be provided to the site pharmacy by the Sponsor. Study intervention accountability records will be maintained by an unblinded pharmacist or designee to maintain the study blind, and an unblinded study monitor will be employed to review accountability records.

The placebo control will be supplied by the site pharmacy.

6.2.2. Formulation, Appearance, Packaging, and Labeling

DCR-PHXC is a colorless to pale yellow, preservative-free, sterile solution of DCR-L1360 at a concentration of 170 mg/mL in WFI. The product is filled into clear Type-I 2-mL glass vials sealed with Flurotec-coated chlorobutyl rubber stoppers with aluminum flip-off overseals. Each vial is intended for single use and contains an extractable volume of not less than 0.5 mL of DCR-PHXC. Each vial is labeled with a booklet label or a single panel label that contains country-specific related information, in compliance with regulatory and safety requirements.

The placebo comparator is 0.9% sterile normal saline for injection provided by the study site.

6.2.3. Product Storage and Stability

DCR-PHXC is to be stored at 2°C to 8°C (inclusive). DCR-PHXC is to be stored in an appropriately secured location in a refrigerator, and storage must comply with institutional procedures in effect at the study site for handling investigational products. Access must be limited to authorized clinic personnel. A temperature log will be maintained.

The placebo comparator should be stored in accordance with the product labeling.

6.2.4. Preparation

Study intervention will be prepared by the unblinded pharmacist or designee.

A second medically qualified person must check the dose preparation prior to administration to be sure the correct dose has been prepared.

The product should be allowed to warm to room temperature for approximately 1 hour but no more than 4 hours before administration.

6.3. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a double-blind study in which treatment assignment will be blinded for the Investigators and any personnel (other than the unblinded pharmacist or designee) involved with the study conduct or evaluation at the investigational sites, the CRO, and the Sponsor.

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

The randomization scheme will only be disclosed to selected personnel to ensure correct preparation of the study drug, correct set-up of the IWRS, safety monitoring by the DSMC, and expedited adverse reaction reporting. All aspects of blinding and unblinding for the study is outlined in the study-specific Blinding and Unblinding Plan.

Unblinding, i.e., breaking the code for an individual patient during the study, is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper handling of the participant. The decision to break the code must be made by the Investigator. The study monitor and Sponsor must be informed about the code break as soon as possible. Detailed unblinding procedures are provided in a separate IWRS manual.

As DCR-PHXC is colorless to pale-yellow, an unblinded pharmacist or designee will prepare the syringes for delivery to the Investigator. To prevent any blinded site staff or study participants

from visually observing color differences between DCR-PHXC and placebo, syringes will be tinted or shrouded to mask the color difference.

Results of on-treatment 24-hour Uox measurements will not be returned to the Investigator prior to closure of the study, so as not to potentially unblind the study.

6.4. STUDY INTERVENTION COMPLIANCE

Study intervention will be administered by a member of the study staff.

6.5. CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Concomitant therapies to be recorded in the case report form (CRF) at every visit include concomitant prescription medications, over-the-counter medications, and supplements.

Participants taking pyridoxine (vitamin B6) must have been at a stable dose for at least 4 weeks prior to Day 1 and must remain on the same stable dose throughout the study.

Participants should avoid taking vitamin C supplements, including multivitamins, for 24 hours prior to and during the collection of 24-hour urine samples.

6.5.1. Rescue Medicine

Not applicable.

6.6. DOSE MODIFICATION

No dose modifications are allowed, other than those described in Section **6.1.2**.

6.7. INTERVENTION AFTER THE END OF THE STUDY

In order to provide continued patient access to DCR-PHXC and to expand the safety database for the product, a roll-over long-term extension study is planned (DCR-PHXC-301). Participants may be screened for entry into the roll-over study when all DCR-PHXC-201 study assessments have been completed; including confirmation that the Day 180/EOS 24-hour urine collection satisfies the urine-collection completeness criteria. Participants not eligible for, or electing not to roll over into, Study DCR-PHXC-301 will be followed until Uox returns to ≥ 80% of baseline. Hematology, clinical chemistry, urinalysis, and pregnancy testing (as detailed in **Table 3**), and 24-hour urine collections will be repeated monthly. Should this follow-up take more than 6 months, participants will be re-consented for additional follow-up.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. DISCONTINUATION OF STUDY INTERVENTION

Study intervention for an individual participant may be permanently discontinued at any time at the discretion of the Investigator.

Study intervention for an individual participant must be temporarily interrupted and may be permanently discontinued for the following, as determined by the DSMC:

- any severe AE possibly, probably, or definitely related to study intervention

Study intervention for an individual participant will be permanently discontinued for any of the following:

- any SAE possibly, probably or definitely related to study intervention
- any of the changes in hepatic function detailed in Section **7.1.1**
- pregnancy, as detailed in Section **10.4**

Re-challenge with study intervention is not allowed.

Discontinuation from study intervention does not mean discontinuation from the study. Remaining visits and study procedures should be completed as indicated by the SoA. Additionally, participants in whom study intervention is prematurely discontinued will be followed until Uox returns to ≥ 80% of baseline. Hematology, clinical chemistry, urinalysis, and pregnancy testing (as detailed in **Table 3**) and 24-hour urine collections will be repeated monthly. Should this follow-up take more than 6 months, participants will be re-consented for additional follow-up.

7.1.1. Drug-Induced Liver Injury Monitoring

Safety laboratory test results will be monitored by a central laboratory in real time with potential drug-induced liver injury (DILI) alerts sent to the Investigator.

For participants with normal liver biochemistries at baseline:

- **Close Monitoring**: An increase of serum ALT or AST to > 3 x ULN should be followed by repeat testing of ALT, AST, alkaline phosphatase, and total bilirubin within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry should also be made about symptoms, strenuous exercise, or previous seizures. Repeat testing 2 or 3 times weekly is recommended. All participants showing possible DILI should be followed until abnormalities return to normal or to the baseline state. If a participant lives remote from the study site, local testing may be performed, and the test results reported to the Investigator (along with the reference ranges for the local laboratory).
- **Study Intervention Discontinuation**: Study intervention will be discontinued when a participant meets one of the conditions outlined below (from 2009 FDA Guidance for Industry-Drug Induced Liver Injury: Premarketing Clinical Evaluation), or if the Investigator believes that it is in best interest of the participant. Safety laboratory

parameters will be monitored by a central laboratory in real time, with potential drug-induced liver injury (DILI) alerts sent to the Investigator.

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (total bilirubin >2 × ULN or INR >1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Close monitoring should be continued. Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the SoA. Participants should be followed until Uox returns to ≥ 80% of baseline.

Patients should be monitored at each study visit and instructed to call the Investigator for new or worsening symptoms of clinical hepatitis. Both symptoms and calls should be captured in dedicated CRFs.

For participants with elevated transaminases at baseline: The following Alternative DILI Monitoring Algorithm should be used.

- **Close Monitoring**: If participants develop elevations of AST or ALT > 2 times the screening value or total bilirubin > 1.5 times the screening value while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2 to 3 times per week with or without study intervention discontinuation (see below).
- **Study Intervention Discontinuation**: Study intervention will be discontinued for abnormal liver function when a participant meets the following condition. Close monitoring should be continued. If a participant's home is remote from the study site, local testing may be performed, and the test results reported to the Investigator (along with the reference ranges for the local laboratory).
  - ALT or AST >5 × the screening value in participants with the screening value < 2 × ULN

  Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the SoA. Participants should be followed until Uox returns to ≥ 80% of baseline.

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention noncompliance

- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Participants who sign the ICF and are randomized but do not receive the study intervention may be replaced. In order to ensure that there is an adequate number of participants in the modified intent-to-treat population (see Section **9.4**) additional participants may be enrolled and randomized if there are participants who sign the ICF and are randomized and receive the study intervention, and subsequently withdraw or are withdrawn or discontinued from the study prior to completion of the Day 90 assessments, or who do not have any efficacy assessments after Day 90.

Participants who are withdrawn from the study will be followed until Uox returns to ≥ 80% of baseline. Hematology, clinical chemistry, urinalysis, and pregnancy testing (as detailed in **Table 3**), and 24-hour urine collections will be repeated monthly. Should this follow-up take more than 6 months, participants will be re-consented for additional follow-up.

7.3. LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 business day and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter [or local equivalent] to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. EFFICACY ASSESSMENTS

8.1.1. 24-Hour Urinary Oxalate

Oxalate is a dicarboxylic acid that is a normal end-product of metabolism. Most oxalate in the body is produced in the liver. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. In individuals with PH, mutations in the *AGXT* or *GRHPR* gene result in the overproduction of oxalate by the liver, which causes increased oxalate excretion by the kidneys.

The measurement of oxalate in the urine will be via 24-hour urine collection. During the screening period, participants will perform two 24-hour urine collections at home. The oxalate level in both collections must be ≥ 0.7 mmol (adjusted per 1.73 m^2 BSA in those younger than 18 years) for a participant to be eligible for study entry. Note that 12 of the participants enrolled must have at least one 24-hour Uox excretion value ≥ 1.6 mmol. There must be less than a 20% variation between the 2 urinary creatinine excretion values obtained in the screening collections for a participant to be eligible for study entry (see Section **8.1.1.1.1**). Potential participants will be allowed a second attempt at achieving a less than a 20% variation should the first pair of measurements differ by more than 20%.

8.1.1.1. Collection of 24-hour Urine Samples

Collection of the two 24-hour urine samples during Screening should occur on consecutive days; in no case should more than 8 days elapse between collections. For example, if a participant initiates collection of the first 24-hour sample beginning on a Saturday morning, the second collection must begin no later than the following Sunday morning.

Ongoing assessment of Uox will continue at select visits throughout the study, as defined in the SoA. Collection of on-treatment samples must be performed within the 7 days prior to the scheduled study visit. The elapsed time between monthly collections should be at least 3 weeks and not more than 5 weeks.

Any participant who prematurely discontinues study intervention should perform a last 24-hour collection as directed by the Medical Monitor.

Participants should be instructed to avoid consuming vitamin C, including multivitamins, in the 24 hours preceding urine collection and throughout the 24-hour collection period. The urine void immediately preceding initiation of the 24-hour collection will be collected and stored separately from the 24-hour collection for spot urine analysis (see Section **8.1.4**), and the 24-hour collection will commence with the next void. At all visits for which 24-hour urine collections will be performed, the research staff will review collection instructions with the participants to ensure complete and timely collections. Home health aides are available to participants who desire assistance in completing at-home urine collection. Participants accepting home health aide assistance will provide additional consent for this service.

Complete instructions for the 24-hour urine collection will be provided in the Urine Collections Instructions.

8.1.1.1.1. Completeness Criteria for 24-hour Urine Samples

To maintain the integrity of all analyses related to 24-hour Uox measurement, urine completeness criteria have been established to ensure adequate, valid collection of all 24-hour Uox samples.

- **Screening Period 24-hour Urine Collection Completeness:**

  There must be less than 20% variation between the two 24-hour urinary creatinine values measured in the screening period (Section **8.1.2**).

  Should the initial pair of screening values not meet this criterion, participants will be given the opportunity to perform a second pair of collections. The screening period may be extended by 7 days (for a total of 42 days in screening) to allow time to repeat the additional 24-hour urine collections.

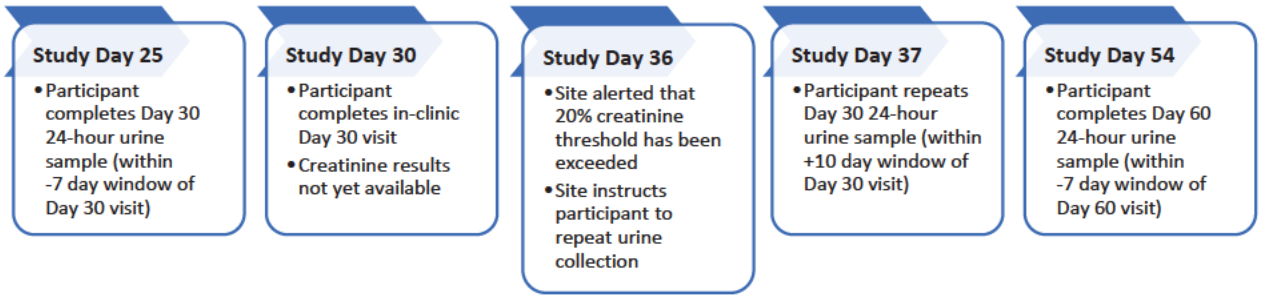
  Additionally, the site will review the 24-Hour Urine Collection Schedule worksheets completed by the participant. Any collection with a duration of less than 22 hours or greater than 26 hours will be considered invalid and must be repeated.

- **Treatment Period 24-hour Urine Collection Completeness:**

  As detailed in the Study Monitoring Plan, certain members of the unblinded study team will conduct an ongoing review of treatment-period 24-hour urinary creatinine excretion values, to ensure that all 24-hour urinary creatinine excretion values are within 20% of baseline. Baseline is defined as the mean of the 2 screening values. Additionally, the site will review the 24-Hour Urine Collection Schedule worksheets completed by the participant. Any collection with a duration of less than 22 hours or greater than 26 hours will be considered invalid.

  Should a treatment-period value not meet these criteria, participants will be required to complete another 24-hour urine collection. Recollection should occur within 10 calendar days from the time of the visit for which the collection was intended whenever possible (see **Figure 1**). In the event that the repeated 24-hour urine collection violates the completeness criteria, the 24-hour urine collection for that visit will not be repeated a second time. Statistical considerations for 24-hour urine measurements that violate the completeness criteria are outlined in the Statistical Analysis Plan (SAP).

Figure 1: Timeline Example for Repeat of Treatment-period 24-Hour Urine Collection



8.1.2. 24-Hour Urinary Creatinine Excretion

The completeness of 24-hour urine collections can be assessed by calculating the variability of 24-hour urinary creatinine excretion. Clifford-Mobley et al. suggest that a 20% variability in urinary creatinine excretion exceeds biologic variation and should be considered the upper bound for acceptability of samples (Clifford-Mobley et al., 2016).

The measurement of urinary creatinine excretion will be via 24-hour urine collection, as described in Section 8.1.1.1.

8.1.3. Other Parameters Determined from 24-Hour Urine Collections

In addition to Uox and urinary creatinine excretion, urinary citrate, calcium, phosphate, and magnesium will be measured via 24-hour urine collection. The calculation of the urinary oxalate-to-creatinine ratio will also be determined from the 24-hour urine samples.

8.1.4. Urinary Oxalate from Spot Urine

In order to evaluate the relationship between Uox levels in spot urine and 24-hour urine samples, participants will collect a spot urine sample each time a 24-hour collection is performed. A sample of urine from the void immediately prior to the initiation of each 24-hour urine collection will be collected and stored apart from the 24-hour urine collection. Should the two 24-hour screening collections occur on consecutive days, no spot urine sample will be collected on the second day.

Complete instructions for the spot urine collection will be provided in the Urine Collections Instructions.

8.1.5. Plasma Oxalate

Plasma oxalate concentration is a reflection of the body pool size. The plasma oxalate pool size is increased in individuals with PH and impaired renal function. When the pool increases, oxalate may precipitate in tissues and cause toxicity.

In order to limit blood loss in children, plasma oxalate testing will not be conducted in participants aged 6 to 17 years, other than at Screening.

Complete instructions for collection and handling of samples will be provided in the Central Laboratory Manual.

8.1.6. Kidney Assessments

Patients with PH are predisposed to the development of multiple and recurrent urinary tract (urolithiasis) and kidney (nephrolithiasis) stones. This deposition of calcium oxalate in the renal parenchyma produces tubular toxicity and renal damage that is compounded by the effects of renal calculi-related obstruction and frequent superimposed infections (Cochat & Rumsby, 2013).

8.1.6.1. Kidney Stone Events and Stone Burden

Participants will provide a 12-month history of stone events at Screening and will report any stone events during the study.

For the purpose of this study, "stone events" are all events that meet one or more of the following criteria:

- **renal stone requiring medical intervention** (e.g., outpatient procedures such as lithotripsy, or hospitalization and/or inpatient surgical intervention for confirmed stone-related pain and/or complications);
- **stone passage with or without hematuria**;
- **renal colic requiring medication.**

Concurrent events will be defined as events occurring within the same 4-week (28-day) window.

Note: Although the number of stone events is an efficacy endpoint, stone events will be considered AEs of special interest (Section **10.3.3**), as participants may enter the study with pre-existing stones.

For the purpose of the study, "stone burden" is a term used primarily as a metric for quantifying and qualifying changes from baseline in the overall number and 2-dimensional surface area of renal stones, as observed via kidney ultrasound over the course of the study.

Taken together, the terms stone event and stone burden will be used to derive meaningful quantification and qualification of overall impact of clinical sequelae of renal stones during the course of the trial.

8.1.6.2. Kidney Ultrasound

Kidney ultrasound will be performed at time points specified in the SoA. The kidneys should be examined in the longitudinal (sagittal) and transverse scan planes, ideally with images acquired in both the supine and prone positions. In adult participants, a curved array transducer with center frequencies of 3 to 6 MHz should be used. A linear array transducer with higher center frequencies should be used in participants younger than 18 years of age. Participants should have a full bladder during image acquisition.

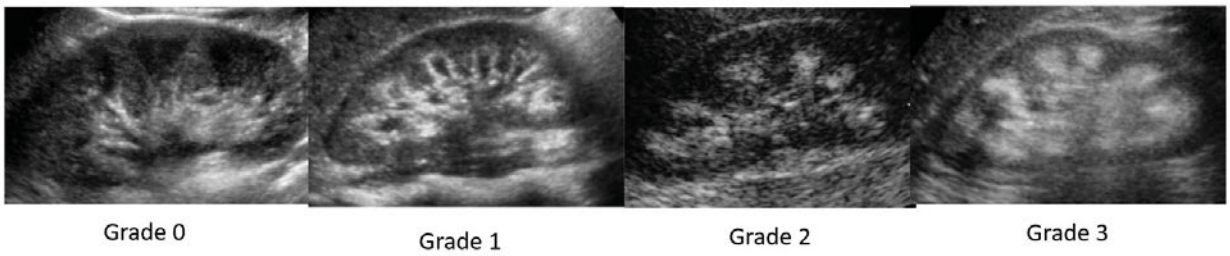
All kidney ultrasound data will be transmitted to a standalone imaging vendor, where qualified personnel will perform central overread of all images. The number and size of stones will be determined by the central readers. The details of any findings should be placed in the participant's source record and recorded in the electronic case report form (eCRF). Site personnel will be trained in the processes relating to ultrasound performance and data transmission.

The end-to-end process of centralized kidney ultrasound overread is detailed in a separate DCR-PHXC-201 Centralized Imaging Overread plan.

Centralized overread will include standardized nephrocalcinosis grading in accordance with the staging criteria outlined in **Figure 2**.

Figure 2: Standardized Nephrocalcinosis Grading

- Grade 0: No echogenicity
- Grade 1: Mild echogenicity around medullary pyramid borders
- Grade 2: Moderate echogenicity around and inside pyramids
- Grade 3: Severe echogenicity of entire pyramids



From Boyce et al., 2013

8.1.7. Quality of Life Assessments

Health-related quality of life (HRQOL) surveys will be administered in adult and pediatric participants at Screening and EOS as indicated in the SoA. For consistency, the same member of the study staff should administer the surveys to a participant at both Screening and EOS. When possible, HRQOL surveys should be completed prior to other study-specific assessments and procedures.

8.1.7.1. Short Form 36 Health Survey – Adults Only

As part of the Medical Outcomes Study (MOS), a multi-year study to explain variations in patient outcomes, RAND® developed the 36-Item Short Form Health Survey (SF-36). The SF-36 is a set of generic, coherent, and easily administered QoL measures that taps 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. The 36 items are identical to the MOS SF-36 described in Ware and Sherbourne (1992). Participants respond to each item on a categorical scale. Categorical answers are transformed to a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. All items are scored so that a high score defines a more favorable health state.

8.1.7.2. EQ-5D-5L – Adults Only

The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the previously 3-level EQ-5D (Herdman et al., 2011). The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Participants are asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the participant's health state. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score.

The EQ VAS records the participant's self-rated health on a 20-cm vertical VAS, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. Participants are asked to place an "X" on the line that represents their health on that day. The VAS can be used as a quantitative measure of health outcome that reflect the participant's judgement.

8.1.7.3. Pediatric Quality of Life Inventory – Children Only

The Pediatric Quality of Life Inventory (PedsQL™) is a modular approach to measuring HRQOL in healthy children and adolescents and in those with acute and chronic health conditions. The multidimensional PedsQL Generic Core Scales were designed to measure the 3 core dimensions of health, as delineated by the World Health Organization (WHO) in 1948 (physical, emotional, and social functioning), as well as role (school) functioning (Varni et al., 1998; Varni et al., 2001).

The 23-item PedsQL is comprised of 5 items in the Emotional, Social and School Functioning dimensions (Psychosocial Health) and 8 items in the Physical Functioning (Physical Health) dimension. Items are reverse-scored on a 0 to 4 Likert scale and linearly transformed to a 0 to 100 scale, so that higher scores indicate better functioning and HRQOL. Scale Scores are the sum of the items in each dimension, divided by the number of items answered.

Age-appropriate self-reporting questionnaires are available for children aged 5 to 7, 8 to 12, and 13 to 18. Parental proxy reports are available for children aged 5 to 7, 8 to 12, and 13 to 18. Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL after introductory instructions from the administrator. If the administrator determines that a child or teen is unable to self-administer the PedsQL (e.g., due to illness, fatigue, or reading difficulties), the PedsQL should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL should be administered by reading the instructions and each item to the young child word for word.

If a child has difficulty understanding the age-appropriate PedsQL, the preceding age group version may be administered to the child (e.g., administering the Young Child [5-7] Self-Report version with the 3 faces response choices to an 8-year-old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent/guardian.

In addition to the PedsQL Generic Core Scales, parents of pediatric participants will complete the PedsQL Family Impact Module (Varni et al., 2004). The PedsQL Family Impact Module was designed to measure the impact of pediatric chronic health conditions on parents and the family. The 36-item Module measures parent self-reported physical, emotional, social, and cognitive

functioning, communication, and worry. The Module also measures parent-reported family daily activities and family relationships.

8.2. SAFETY AND OTHER ASSESSMENTS

8.2.1. Weight, Height, and Body Surface Area

Body weight and height should be measured without shoes.

Body weight will be recorded in kilograms (kg). Weight should be measured on the same calibrated scale at each scheduled visit. In participants aged 6-to-11 years, the weight on Day 1 will be used to calculate the mg/kg dose of study intervention.

Height will be recorded in centimeters (cm). Height is measured only at screening for adults. Height in participants ≤ 18 years of age should be measured on the same stadiometer at each scheduled visit.

For the BSA-adjustment of 24-hour Uox in participants < 18 years of age, BSA will be calculated using the height and weight measured at the visit for which the 24-hour urine is collected. Should BSA adjustments be calculated in participants ≥ 18 years of age, the height recorded at screening will be used for all visits. Body surface area will be calculated using the following formula (DuBois & DuBois, 1916):

$$BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$$; with weight in kilograms and height in centimeters.

8.2.2. Physical Examination

A full physical examination will include a complete review of body systems: eyes, ears, nose, and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological. A full physical exam will be conducted at Screening and EOS/ET.

A brief physical examination will include, at a minimum, chest/respiratory, heart/cardiovascular, dermatological/skin, and gastrointestinal/liver. A brief physical examination may be performed at scheduled visits (Day 1 through Day 150) or unscheduled visits at the Investigator's discretion.

Study intervention injection sites should be inspected at each visit.

8.2.3. Vital Signs

Vital signs include blood pressure, pulse/heart rate, oral body temperature, and respiratory rate.

Parameters will be measured in the supine position, using an automated instrument or manually, after the participant has rested comfortably for 10 minutes. In the pediatric population, an age-appropriate cuff size should be used for blood pressure measurements.

Temperature will be obtained in degrees Celsius (°C), pulse rate will be counted for a full minute and recorded in beats per minute, and respirations will be counted for a full minute and recorded in breaths per minute. Note that when a 12-lead ECG is performed at the same time as vital signs, heart rate should be taken from the ECG.

Age-appropriate normal values will be considered when evaluating pediatric participants.

8.2.4. Clinical Safety Laboratory Assessments

See Section **10.2** for the list of clinical laboratory tests to be performed.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Age-appropriate normal values will be considered when evaluating pediatric participants.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

8.2.4.1. Estimated Glomerular Filtration Rate (eGFR)

For study inclusion, eGFR (mL/min/1.73 m^2) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (≥ 18 years; **Figure 3**) or the multivariate 2012 Schwartz equation (6-17 years; **Figure 4b**).

Because cystatin C was not collected in pediatric participants who were screened using the Schwartz et al. 2009 equation (**Figure 4**a), the statistical analysis of eGFR in pediatric participants will use the Schwartz et al. 2009 equation. As a sensitivity analysis, the rate of change in eGFR will be analyzed using the Schwartz et al. 2012 equation in participants for whom cystatin C values are available.

For adolescents who turn 18 during the course of the study, the equation used at baseline will be used throughout the study.

Figure 3: CKD-EPI eGFR Equation - for Adult Participants

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if Black)}$$

where

S_{Cr} (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = –0.329 (females) or –0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

age = years

From Levey & Stevens, 2010

Figure 4: Schwartz eGFR Equations - for Pediatric Participants (< 18 Years of Age)

(a) Creatinine-based equation:

eGFR = 36.5 x height ÷ SCr

where

SCr (serum creatinine) = µmol/L

height = cm

From Schwartz et al., 2009

(b) Multivariate equation:

$eGFR = 39.8 \times [ht/Scr]^{0.456}[1.8/cysC]^{0.418}[30/BUN]^{0.079}1.076^{male}[ht/1.4]^{0.179}$

where

ht (height) = meters

Scr (serum creatinine) = mg/dL

cysC (cystatin C) = mg/L

BUN (blood urea nitrogen) = mg/dL

From Schwartz et al., 2012

8.2.5. 12-Lead ECG

Standard 12-lead ECGs will be performed with the participant in the supine position, after the participant has rested comfortably for 10 minutes. The parameters assessed will be rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTcF, Fridericia correction). The Investigator or designee is responsible for reviewing the ECG(s) to assess whether the results are within normal limits and to determine the clinical significance of the results. These assessments will be recorded on the eCRF.

Standardized ECG acquisition equipment will be provided to all clinical trial sites at the start of the trial, to ensure parity across all sites. All ECG data will be transmitted to a standalone imaging vendor, where qualified personnel will perform central overread of all ECG readouts. Site personnel will be trained in the processes relating to ECG acquisition and transmission. The end-to-end process of centralized ECG acquisition and overread is detailed in a separate DCR-PHXC-201 Centralized Imaging Overread plan.

8.2.6. Echocardiogram with Doppler

Echocardiography will be performed by a qualified sonographer/physician (and overread by a cardiologist), using a standard, commercially available ultrasound machine. The echocardiography technician should perform standard 2-dimensional (2-D) transthoracic echocardiography with Doppler, as described by the American Society of Echocardiography (ASE) recommendations (Picard et al., 2011). The full ASE protocol need not be followed but

should include a gross assessment of the overall cardiac anatomy and quantitative evaluation of basic ventricular systolic function. The final echocardiogram report should note the details of the protocol that were followed. The overreading cardiologist should note any findings in the department's standard reporting format. Findings from the echocardiogram should be included in the participant's source record and documented in the eCRF. Any findings that, in the opinion of the Investigator, may disqualify the participant should be discussed with the Medical Monitor.

Additionally, all echocardiogram data will be transmitted to a standalone imaging vendor, where qualified personnel will perform postprocessing of echocardiogram data and central overread of all images. Site personnel will be trained in the processes relating to echocardiogram performance and data transmission.

The end-to-end process of centralized echocardiogram overread and postprocessing is detailed in a separate DCR-PHXC-201 Centralized Imaging Overread plan.

8.2.7. Reporting Fluid Intake

Hyperhydration regimens are a central feature in the conservative management of urinary oxalate levels in patients with PH. As such, participants are asked to maintain a consistent fluid intake throughout the study (Section **5.3**). Participants will be asked to report their average daily fluid intake during the 4- to 7-day period before each of the 24-hour urine collections, including the 2 collections conducted during screening.

8.3. Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

The definitions of AEs, SAEs, and adverse events of special interest (AESI) are located in Section **10.3**.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section **7.1**).

8.3.1. Time Period and Frequency for Event Assessment

All SAEs will be collected from the signing of the ICF until 30 days after the last day of study participation.

All AEs will be collected from the signing of the ICF until the EOS at the time points specified in the SoA (Section **1.3**).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably

related to the study intervention or study participation, the Investigator must notify the Sponsor promptly.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section **10.3.4**.

Adverse events may be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) as either unsolicited reports or in response to general questioning, such as "Have you noticed anything different since you began the study?" Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Participants will be questioned as to the occurrence of muscle pain or weakness. The occurrence of an AE or SAE may also be detected upon review by a study monitor.

8.3.3. Follow up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESI (as defined in Section **10.3.3**), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section **7.3**). Further information on follow-up procedures is given in Section **10.3.4**.

8.3.4. Serious Adverse Event Reporting

All SAEs will be recorded and reported to the sponsor or designee immediately; under no circumstance should this exceed 24 hours, as indicated in Section **10.3.5**. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that obligations and ethical responsibilities towards the safety of participants and the safety of the study intervention under clinical investigation are met.

The Sponsor has a responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and will be forwarded to Investigators as necessary.

8.3.5. Reporting of Pregnancy

Details will be collected of all pregnancies in female participants occurring after the start of study intervention and until 12 weeks after the last dose of study intervention.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section **10.4**.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4. TREATMENT OF OVERDOSE

For this study, any dose of study intervention greater than the protocol-specified dose will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 28 days).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. PHARMACOKINETICS

8.5.1. Plasma Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of DCR-PHXC and its metabolites, as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the Central Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded. Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Pharmacokinetic parameters to be determined may include clearance (CL) and volume of distribution (V) estimates, along with secondary parameters of area under the concentration curve (AUC), maximum observed concentration (Cmax), minimum observed concentration (Cmin), time to maximum concentration (Tmax), and terminal elimination half-life (t1/2). The population PK parameters will be reported separately from the study.

8.6. PHARMACODYNAMICS

Pharmacodynamic parameters other than urinary and plasma oxalate, and urinary oxalate-to-creatinine ratio (Sections **8.1.1**, **8.1.5** and **8.1.3**, respectively) are not evaluated in this study.

8.7. GENETICS

Genetics are not evaluated in this study. However, participants without documented PH genotyping must provide a deoxyribonucleic acid (DNA) sample for testing at screening.

8.8. BIOMARKERS

See Sections **8.1.1** and **8.1.5** for descriptions of urinary and plasma oxalate assessments. Other biomarkers are not evaluated in this study.

8.8.1. Immunogenicity Assessments

Plasma samples for the detection and characterization of antibodies to DCR-PHXC will be collected from all participants according to the SoA. Plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

The detection and characterization of antibodies to DCR-PHXC will be performed using a validated assay method by or under the supervision of the Sponsor, once a validated assay method is available.

Endogenous anti-nuclear antibodies are believed to recognize oligonucleotides 40- to 50-base pairs in length. Anti-double-stranded DNA antibodies will be measured as long as there is no validated assay for direct antibodies to DCR-PHXC. Serum samples for detection of anti-dsDNA will be collected from all participants, as indicated in the SoA. Samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to DCR-PHXC.

8.9. PHARMACOECONOMICS

Pharmacoeconomic analysis will be performed on collected data. These data will be summarized separately from the Clinical Study Report.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

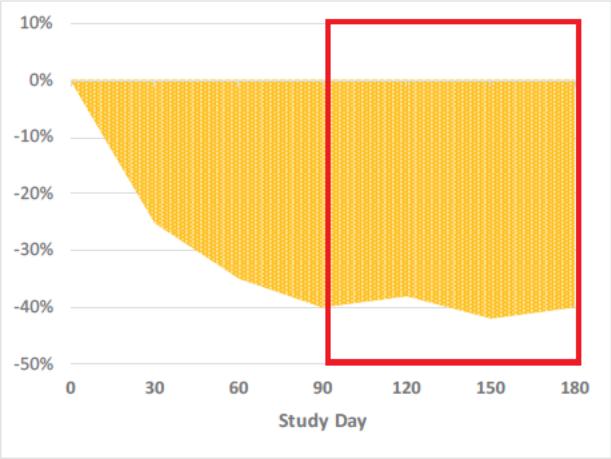
This is a superiority study. For the primary endpoint, the null hypothesis to be tested is

H_0: $AUC_a = AUC_p$ against 1-sided alternative hypothesis H_A: $AUC_a > AUC_p$ where

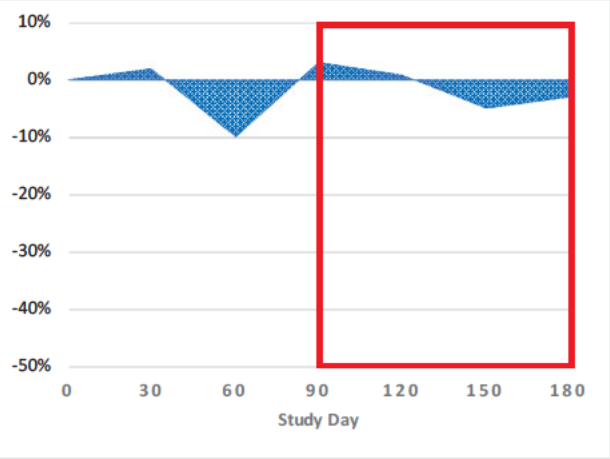
- AUC_a is the area under the curve for the active arm (DCR-PHXC)
- AUC_p is the area under the curve for the placebo arm

AUC is calculated based on the percent change from baseline in Uox. The x-axis will be time in days and y-axis will be percent change from baseline in Uox. The percent decrease from baseline in Uox will be denoted as negative. Therefore, the curve might be in its entirety or at least in part below 0 (x-axis, **Figure 5** Panel A). The area below the x-axis will be summed up and presented as a positive value. For an increase from baseline, the percent change from baseline will be positive and that part of the curve will be above the x-axis. The AUC would then be calculated as area below the axis minus area above the x-axis (**Figure 5** Panel B). AUC will be calculated using the actual time in days between Uox collections, and not the nominal visit days. If there are no Uox measurements after Day 90 visit, the AUC will be considered missing. See **Figure 5** for examples of the AUC, where the portion of the data to be used in calculation of the primary endpoint is contained within the orange box. If data are available from only a part of the time period between 90 and 180 days, the AUC will be standardized to 90 days. Details of calculations will be provided in the SAP.

Figure 5 Example of AUC Graphs for Primary Endpoint



Panel A: All values below 0



Panel B: Values both above and below 0

All hypotheses will be tested at the significance level of 0.025.

9.2. SAMPLE SIZE DETERMINATION

Approximately 40 participants will be screened to achieve an estimated total of 36 evaluable participants.

For the sample size calculations, the primary endpoint of the AUC of 24-hour Uox from Day 90 to Day 180 based on percent change from Baseline is used. The group sequential design with prespecified alpha spending for interim analysis and final analysis is utilized. The randomization ratio is 2:1 (active:placebo). The primary hypothesis tested is a 1-sided superiority hypothesis at the significance level of 0.025. The AUC Uox in the placebo arm is assumed to be 0, as the Uox values may oscillate up and down from baseline due to the measurement variability. The AUC Uox in the active arm is assumed to be 3600 based on 40% decrease over the 90 days. The effect size is assumed to be 1.2. Under these assumptions, the sample size of 36 patients (24 in the active arm and 12 in the placebo arm) will yield a power of approximately 94%. All calculations were performed using [redacted]. There may be one interim analysis to re-estimate sample size after two-thirds of participants complete the study.

9.3. RANDOMIZATION METHOD

To balance the participants between the intervention arms based on 2 factors: age (6-11, 12-17, > 18 years) and eGFR (eGFR < 45 mL/min, eGFR ≥ 45 mL/min), an adaptive randomization via minimization method will be used to allocate patients to treatment groups. Minimization aims to ensure that the intervention arms are balanced with respect to the predefined factors, as well as for the number of patients in each arm. Imbalance scores are calculated for the possible patient allocations to treatment groups, which represent the imbalance that would be generated in each of the treatment arms, while taking into account these 2 factors. The participant will be assigned to the treatment that results in the *lowest* amount of imbalance with an 80% probability, and the treatment which results in the *highest* amount of imbalance with a 20% probability (Taves, 1974; Pocock & Simon, 1975).

9.4. POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined:

- **Enrolled:** The enrolled population includes all participants who sign the ICF.
- **Safety Population:** The safety population includes all participants randomly assigned to study intervention and who take at least 1 partial or full dose of study intervention. Participants will be analyzed according to the intervention they actually received.
- **Intent-To-Treat Population (ITT):** The ITT population includes all participants who were randomized and have at least one post-baseline efficacy assessment. Participants will be analyzed according to the intervention they were randomized to.
- **Modified Intent-To-Treat Population (MITT):** The MITT population includes all participants in the ITT population who have at least one efficacy assessment after the Day 90 dosing visit.
- **Evaluable:** The evaluable population includes all participants who received 6 full doses of study intervention and completed the study.
- **Pharmacokinetic Population:** The PK Population includes all participants in the Safety Population without major dosing violations. Details will be provided in the Pharmacokinetics Analysis Plan (PKAP).

- **Per Protocol (PP)**: The PP Population includes all participants who received 6 full doses of study intervention, had no major protocol deviations, and completed the study.

9.5. STATISTICAL ANALYSES

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The primary population for efficacy analyses is MITT. Primary analysis methods are listed in Sections **9.5.1** through **9.5.3**. In addition, sensitivity analyses will be performed that will be described in detail in the SAP.

9.5.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The AUC of 24-hour Uox from Day 90 to Day 180, based on percent change from baseline, will be compared between the active treatment group and placebo group. A multiple imputation approach will be used to handle missing Uox data and then calculate the AUC.ANCOVA model with the Uox baseline value, age category, and eGFR category as the covariate will be used. The primary efficacy analysis will be based on MITT population. The normality will be investigated by examining Q-Q plots and histograms. In case the data are not normal, they will be log-transformed.
Key Secondary	The proportion of participants whose Uox values normalized or near-normalized on at least 2 consecutive visits starting at Day 90 will be summarized by treatment group. A 1-sided Fisher's exact test at significance level alpha of .025 will be used for comparison between treatment groups. The analysis will be performed based on MITT population.
Secondary	For percent change from baseline to Day 180 in the summed surface area and number of kidney stones, and plasma oxalate, the Wilcoxon Rank Sum test will be used. Rate of change in eGFR will be summarized by treatment group. The mixed model with the Uox baseline value and the endpoint's baseline value (eGFR) as covariates will be used.
Exploratory	The number of stone events will be analyzed using an exact Poisson regression model. The model will include treatment group and baseline stone events rate (continuous). More details will be provided in the SAP.

9.5.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Descriptive statistics will be presented.

The number and percentage of patients with AEs, SAEs and AEs leading to withdrawal from the study will be presented by system organ class (SOC) and preferred term within each SOC.

Descriptive statistics for clinical safety laboratory data (laboratory data) will be presented overall and by treatment group at each visit starting at baseline. Change from baseline to post-baseline visit will also be presented. Laboratory parameter shifts from baseline to abnormal post-baseline values will be presented. No statistical comparisons will be performed.

- For the evaluation of eGFR over time in pediatric participants (6 to 17 years of age), the Schwartz et al. 2009 equation will be used for the primary analysis. As a sensitivity analysis, eGFR will be calculated using the multivariate Schwartz et al. 2012 equation.

Descriptive statistics for vital signs will be presented overall and by treatment sequence for systolic blood pressure, diastolic blood pressure, body temperature, pulse/heart rate, and respiration rate, at each visit starting at baseline. Change from baseline to post-baseline visit will also be presented. No statistical comparisons will be performed.

ECG parameters will be summarized by treatment group and visit. The pre-dose ECGs will be compared across visits. Pre- and postdose 12-lead ECGs will be compared within the dosing visits.

Frequency counts will be presented per treatment for both change and absolute values, with changes categorized as per the bullets below. Individual listings presenting patients with flags will be created for both change and absolute values. The summary will be tabulated by treatment.

Change from baseline for QTcF and uncorrected QT will be classified per treatment as follows:

- ≤ 30 msec or > 30 msec
- ≤ 60 msec or > 60 msec

Absolute post-baseline QTcF and uncorrected QT interval will be classified per treatment as follows:

- ≤ 450 msec or > 450 msec
- ≤ 480 msec or > 480 msec
- ≤ 500 msec or > 500 msec

Additionally, the number and percentage of participants with the following overall ECG result will be presented:

- Normal
- Abnormal, clinically significant

Descriptive statistics will be produced for echocardiogram results. Shift tables will be presented in reference to normal ranges.

The results of the physical examinations will be summarized for the participants who had an examination post-baseline. Each site/system will be summarized with respect to being normal or abnormal, or not performed. Shift tables will be presented.

9.5.3. Other Analyses

Pharmacokinetic and all exploratory analyses will be described in the SAP finalized before database lock. The population PK analysis will be presented separately from the main Clinical Study Report.

9.6. INTERIM ANALYSES

An interim analysis may be conducted upon completion of two-thirds of the participants for the purpose of re-evaluation of sample size. The interim unblinded analysis will be performed by an independent statistician other than the person responsible for the primary analysis of this study and treatment codes will be revealed to that party only. The re-evaluation of sample size will use the conditional power approach based on the test statistics from the interim analysis. A minimal fraction of alpha (.0001) will be spent at the interim analysis, as the trial will not be stopped early for efficacy or futility based on the results from the interim analysis. The final analysis will use alpha of 0.0249 for the primary endpoint, in order to preserve an overall type I error at the 1-sided 0.025 level.

Conditional power will be calculated based on the observed treatment effect and standard error at the interim analysis. Conditional power will be partitioned into three zones – favorable, promising, and unfavorable.

- In the favorable zone, the interim analysis results are sufficiently favorable, and the conditional power is sufficiently high, so that the study can continue with the original sample size and an increase is not needed.
- In the promising zone, the conditional power is moderately high and can be elevated by an increase of sample size to recover the targeted power 1-β at least 80%.
- In the unfavorable zone, the conditional power is fairly low, and cannot achieve the targeted level with an increase in sample size. In this instance, the study would continue with the original planned sample size.

The SAP will describe the planned interim analyses in greater detail.

9.6.1. Data Safety Monitoring Committee (DSMC)

The DSMC will consist of 3 voting members who are independent of the study team and Sponsor. At a minimum, the DSMC will meet prior to the first participant being enrolled, when the first 5 participants have been enrolled and have completed the Day 30 visit, when the first 3 adolescent participants (aged 12-17 years) have been enrolled and have completed the Day 60 visit, and periodically thereafter, depending on enrollment.

The DSMC reviewed safety data from 4 adolescent participants with at least 60 days of exposure in this study, as well as data from 3 adolescents with 60, 93, and 148 days of exposure in the open-label multi-dose study DCR-PHXC-301. Following completion of M&S of PK and PD data from these 7 adolescent participants, determination of the dose for 6- to 11 year-old children, and the aforementioned safety review, the DSMC affirmed that the overall risk-benefit balance remained positive and approved the enrollment of 6- to 11-year-old children.

The DSMC will review unblinded safety and efficacy data and will make determinations on whether to continue the study following each periodic review of the data. At the DSMC's discretion, they will be provided with participant-level unblinded data.

Complete details regarding the constitution and responsibilities of the DSMC will be specified in the committee charter.

9.7. SUBGROUP ANALYSIS

The same analysis for primary endpoint (i.e., AUC of 24-hour Uox from Day 90 to Day 180, based on percent change from baseline) will be performed on the subgroup of participants with at least one baseline 24-hour Uox ≥ 1.6 mmol (adjusted per 1.73 m^2 BSA in participants aged < 18 years).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (parent or legal guardian for participants younger than 18 years or the local age of majority) will be required to sign a statement of informed consent that meets the

requirements of the IRB/IEC, 21 CFR 50, local regulations, ICH guidelines, and Health Insurance Portability and Accountability Act (HIPAA) requirements where applicable.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within (30) days from the previous ICF signature date.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

After de-identification, all individual data collected during the trial will be shared with Investigators whose proposed use of the data has been approved by an independent review committee. See Section **10.1.9** for more details on the publishing of study information.

Study results will be posted to the US National Institutes of Health's website www.ClinicalTrials.gov.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on eCRF, unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies, and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and

monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (i.e., Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 5 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Closure

The Sponsor reserves the right to terminate the study, or terminate an investigational site's participation in the study, at any time. Should Sponsor or designee, and/or the Investigator discover conditions during the course of the study that indicate that it should be discontinued, an appropriate procedure for termination will be instituted. Reasons for study or site termination include the following:

1. Investigator noncompliance with the protocol, Good Clinical Practice (GCP), or regulatory requirements
2. Unsatisfactory enrollment with respect to quantity or quality
3. Incomplete data collection; inaccurate or knowingly false data submission
4. The Principal Investigator is no longer capable of performing the tasks of the principal investigator, and no replacement can be found.
5. The DSMC determines that termination of the study is in the best interest of the research participants.
6. The Sponsor, Investigator, or IRB/IEC determines that continuation of the study will not serve any scientific purpose.

7. Circumstances beyond the control of the Sponsor or Investigator make it unreasonable to require the study's continuation.
8. A request to discontinue the study by a regulatory or health authority

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. CLINICAL LABORATORY TESTS

Table 2 summarizes the efficacy endpoints that will be determined from 24-hour and spot urine collections.

Table 2: Efficacy Measures Determined from Urine

Laboratory Assessments	Parameters
24-Hour urine	urinary oxalate excretion urinary creatinine excretion urinary oxalate-to-creatinine ratio urinary citrate urinary calcium urinary phosphate urinary magnesium
Spot urine	urinary oxalate excretion urinary creatinine urinary oxalate-to-creatinine ratio

The tests detailed in **Table 3** will be performed by the central laboratory, with the exception of urine pregnancy testing, which may be performed locally. Testing associated with close monitoring of liver function (as described in Section **7.1.1**) may be performed at a local laboratory should the participant reside at a distance remote from the study site.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section **5** of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 3: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Red blood cell count: hemoglobin hematocrit platelet count mean platelet volume (MPV) reticulocytes mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC)	White blood cell count: lymphocytes, absolute and % monocytes, absolute and % eosinophils, absolute and % basophils, absolute and % neutrophils, absolute and %
Clinical Chemistry	alanine aminotransferase (ALT) aspartate aminotransferase (AST) glutamate dehydrogenase (GLDH) gamma-glutamyl transferase (GGT) alkaline phosphatase (ALP) bilirubin (total and direct) lactate dehydrogenase (LDH) total protein albumin	creatine kinase sodium chloride potassium creatinine blood urea nitrogen (BUN) cystatin C in participants < 18 years of age plasma oxalate (only in adults after Screening)
Complement	total complement hemolytic activity (CH50), C3, C4, C3a, C4a, C5a, and Bb (Note: testing not required in participants aged < 18 years)	
Coagulation Parameters	activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR)	
Cytokines *	epidermal growth factor (EGF), IFN-α, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF) (Note: testing not required in participants aged < 18 years)	
Vitamin B6	collected only in participants aged ≥ 18 years who are taking vitamin B6 supplements	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)	
Pregnancy testing	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (WOCBP)	
Antibodies	• Antidrug antibodies (samples will be tested when an assay is available) • Anti-double-stranded DNA antibodies	
Other Screening Tests	• Follicle-stimulating hormone (as needed in postmenopausal women of non-childbearing potential only) • Urine drug screen: to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines (not required in participants ≤ 12 years of age) • Serology (HIV 1 and 2 antibodies, HBsAg, and hepatitis C virus antibody) - If tested in the past 3 months, medical record documentation of this testing may be used. Testing not required in participants < 18 years of age.	

Investigators must document their review of each laboratory safety report.

* Note that cytokine reports will not require Investigator review due to the extended turn-around time for results.

10.3. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1. Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Adverse Event of Special Interest

An AESI is a noteworthy event for the particular product or class of products that a Sponsor may wish to monitor carefully (CIOMS VI, 2005).

Events Meeting the AESI Definition:

Injection site reaction (ISR):

An ISR is a disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. Potential ISRs will be graded as follows:

Signs or symptoms at the injection site (e.g., erythema, swelling) with a time to onset of 4 or more hours from the time of study intervention administration will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 criteria for ISR, detailed below. If any of the CTCAE criteria for ISR are met, the event will be recorded as an ISR and graded in accordance with **Table 4**. If the criteria are not met, individual signs or symptoms will be recorded as AEs and graded in accordance with the intensity categories detailed in Section **10.3.4**.

Table 4: Grading of Injection Site Reactions, CTCAE v 5.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Individual signs or symptoms at the injection site with a time to onset of less than 4 hours from the time of study intervention administration will be recorded as AEs (not as an ISR) and graded in accordance with the intensity categories detailed in Section **10.3.4**.

Muscle pain or weakness

Because the nonclinical safety program in mice identified potential off-target effects on skeletal muscle, participants should be monitored for signs and symptoms of muscle weakness or pain, in addition to measurement of plasma CK.

Kidney Stone Events

Patients with PH are predisposed to the development of multiple and recurrent urinary tract and kidney stones. As participants may enter the study with pre-existing stones, stone events (as defined in Section 8.1.6.1), while being considered in the evaluation of efficacy, will be considered AESI.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information for marketed products in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the SAE coordinator.**

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions will be used in assessing causality:

- **Not Related**: Event for which sufficient evidence exists to conclude that the etiology is unrelated to study intervention.
- **Possibly Related**: There is some temporal relationship between the event and the administration of the study intervention, and the event is unlikely to be explained by the participant's medical condition or other therapies.
- **Probably Related**: The temporal relationship between the event and administration of the study intervention is suggestive and the event is unlikely explained by the participant's medical condition or other therapies.
- **Definitely Related**: The event follows reasonable temporal sequence from administration of the study intervention, follows a known or suspected response pattern to the study intervention, is confirmed by improvement upon stopping the study intervention, and reappears upon repeated exposure, if that occurs.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated, or as requested by the Sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found on Page **3**

10.4. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal with one of the following:
   - Documented hysterectomy

- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from Day 1 through 12 weeks after the last dose of study intervention:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year, as described in **Table 5**, when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

Male participants must refrain from donating sperm for the duration of the study and for 12 weeks after the last dose of study intervention.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly throughout the study and for 12 weeks following the last dose of study intervention, as described in Table 5.

Table 5: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • Oral
  • Intravaginal
  • Transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation
  • Oral
  • Injectable

Highly Effective Methods That Are User Independent [a]

• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  • Intrauterine device (IUD)
  • Intrauterine hormone-releasing system (IUS)
  • Bilateral tubal occlusion

• Vasectomized partner A vasectomized partner is a highly effective contraception method, provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical-use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

10.4.3. Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test. Positive urine tests should be confirmed with a serum test.

- Additional pregnancy testing should be performed at monthly intervals during the treatment period and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed 2-3 weeks after administration of the last dose of study intervention in any WOCBP who prematurely discontinues the study.
- Pregnancy testing with a sensitivity of at least 10 mIU/mL will be performed.

10.4.4. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section **10.3.5**. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5. ABBREVIATIONS, ACRONYMS, INITIALISMS

Term	Description
ADA	antidrug antibody(ies)
AE	adverse event
AESI	AE of special interest
AGXT	the gene that encodes alanine:glyoxylate-aminotransferase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-dsDNA	anti-double-stranded-DNA antibody(ies)
aPTT	activated partial thromboplastin time
ASE	American Society of Echocardiography
ASGR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the curve
BSA	body surface area
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase (creatine phosphokinase)
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DCR-L1360	drug substance for this IMP
DCR-PHXC	drug product for this IMP
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
e.g.	for example (*exempli gratia*)
EGF	epidermal growth factor
eGFR	estimated GFR
EOS	end of study
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram(s)
GalNAc	*N*-acetyl-D-galactosamine
GCP	Good Clinical Practice

Term	Description
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GRHPR	glyoxylate reductase/hydroxypyruvate reductase
hr	hour(s)
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related QoL
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.e.	that is (*id est*)
IEC	Independent Ethics Committee
IFN-α	interferon alpha
IFN-γ	interferon gamma
IL-1 α	interleukin 1 alpha
IL-1β	interleukin 1 beta
IL-2	interleukin 2
IL-4	interleukin 4
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent to treat
IUD	intra-uterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web-response system
kg	kilogram(s)
LDH	lactate dehydrogenase
LDHA	lactate dehydrogenase type A
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP-1	monocyte chemoattractant protein 1
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Term	Description
mg	milligram(s)
min	minute(s)
MITT	modified ITT
mL	milliliter(s)
MOS	Medical Outcomes Study
MPV	mean platelet volume
mRNA	messenger ribonucleic acid
M&S	modeling and simulation
NOAEL	no-observed-adverse-effect level
NMD-PH	no mutation detected PH
pcVPC	prediction-corrected visual predictive check
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PH	primary hyperoxaluria(s)
PH1	primary hyperoxaluria type 1
PH2	primary hyperoxaluria type 2
PH3	primary hyperoxaluria type 3
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
QoL	quality of life
RNA	ribonucleic acid
RNAi	RNA interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form 36 Health Survey
siRNA	small interfering RNA
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
t1/2	terminal elimination half-life
Tmax	time to maximum observed concentration
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
Uox	urinary oxalate excretion
V	volume of distribution
VAS	visual analog scale
VEGF	vascular endothelial growth factor
WFI	water for injection
WOCBP	woman(en) of childbearing potential

10.6. INVESTIGATOR SIGNATURE PAGE

A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (subcutaneous use) in Patients with Primary Hyperoxaluria

Protocol Number: DCR-PHXC-201

Version: 5.0 US

Date: 13-Aug-2020

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and local regulations (as applicable).

Signature: **Date:**

Name:

Institution: **Site Number:**

10.7. PROTOCOL AMENDMENT HISTORY

Amendment 3 (version 5.0 US), 13-Aug-2020

The 12 March 2020 version of the protocol was updated to include the dose of DCR-PHXC to be administered in children aged 6-to-11 years. An appendix detailing measures to be undertaken during the COVID-19 pandemic was added. A tabular summary of changes is detailed in the table that follows.

Description of Change	Brief Rationale	Affected Sections
Added the dose to be administered in 6- to 11-year-old participants **Updated language related to reflect that the DSMC has affirmed the overall risk benefit balance for children aged 6- to 11-years based on updated M&S data and agreed to the enrollment of these patients**	Dose newly determined via modeling and simulation	1.1.1 Overall Design 1.1.6 Description of Study Intervention 1.3 Schedule of Activities 4.3.2 PK/PD Model for Dose Selection in Children Younger than 12 Years of Age 6.1.2 Dosing and Administration 9.6.1 Data Safety Monitoring Committee
Expanded the window for repeat of 24-hour urine samples that violate completeness criteria	To provide additional flexibility for participants and sites	1.3 Schedule of Activities 8.1.1.1 Collection of 24-hour Urine Samples 8.1.1.1.1 Completeness Criteria for 24-hour Urine Sample
Updated text requiring that at least 12 of the first 24 participants have at least one 24-hour Uox screening value > 1.6 mmol	To clarify that the 12 “high baseline” participants need not be among the first 24 participants enrolled	1.1.4 Study Population 5.1 Inclusion Criteria 8.1.1 24-Hour Urinary Oxalate
Updated the Schwartz 2009 eGFR equation	To reflect that serum creatinine, rather than plasma creatinine will be utilized in calculation of eGFR	8.2.4.1 Estimated Glomerular Filtration Rate (eGFR)
Increased the maximum total blood volume to be withdrawn from pediatric participants by 3 mL	Change in laboratory testing vendor	2.3.4 Risk Management

Description of Change	Brief Rationale	Affected Sections
Removed text restricting chronic use of acetaminophen/paracetamol	As chronic nonclinical toxicity studies have shown no adverse effects in the liver, this restriction is no longer required. Stopping rules for possible drug-induced liver injury remain in place for the safety of participants.	5.2 Exclusion Criteria 6.5 Concomitant Therapy
Added Appendix A to describe changes to the study conduct that can be employed during the COVID-19 pandemic	To limit participant exposure to the SARS-CoV-2 virus	Appendix A (newly added)
Updated Sponsor contacts and titles	Changes in Sponsor personnel	Sponsor Signature Page Medical Monitor and Pharmacovigilance Contact Information

Amendment 2 (version 4.0 US), 12-Mar-2020

The 30 April 2019 version of the protocol was updated to incorporate revisions requested by regulators and IECs/IRBs and other operational changes. Principal changes include updates in the equations used to calculate eGFR, a change in the dose of DCR-PHXC to be administered in adults weighing less than 50 kg, changed laboratory testing requirements to limit blood loss in children, added additional immunogenicity testing, updated instructions for monitoring of liver injury, clarified the performance of an interim analysis, and specified that metabolites of DCR-PHXC will be included in pharmacokinetic analyses. A summary of changes is detailed in the table that follows.

Description of Change	Brief Rationale	Affected Sections
Updated equations for calculation of eGFR 1. Changed the Schwartz 2009 equation to the Schwartz 2012 equation 2. Required that the eGFR equation used at baseline be used throughout the study for adolescents who turn 18 during the study 3. Added collection of cystatin C in pediatric participants **4.** Added measurement of height at each visit at which eGFR is calculated in pediatric participants	1. The multivariate 2012 eGFR equation is considered to be more accurate than the univariate 2009 equation 2. To ensure that change over time is made with reference to the same baseline equation 3. Cystatin C is required for calculation of eGFR in new equation 4. Height is required for calculation of eGFR in new equation	1.1.4 Study Population 1.3 Schedule of Activities 5.1 Inclusion Criteria 8.2.1 Weight, Height and Body Surface Area 8.2.4.1 Estimated Glomerular Filtration Rate (eGFR) 9.5.2 Safety Analyses 10.2 Clinical Laboratory Tests 11 References
Changed the dose for adults weighing < 50 kg from 170 mg to 136 mg	Increased participant safety. The 136 mg dose was previously only specified for adolescents weighing < 50 kg.	1.1.6 Description of Study Intervention 4.3.1 PK/PD Model for Dose Selection in Adults and Adolescents 6.1.2 Dosing and Administration
Updated the statistical calculation of 24-hour Uox AUC	To remove time-weighted standardization and use multiple imputation instead.	1.1.1 Overall Design 1.1.3 Objectives and Endpoints 3 Objectives and Endpoints 4.2 Scientific Rationale for Study Design 9.5.1 Efficacy Analyses 10.5 Abbreviations
Added duration-of-collection-time criteria for assessment of 24-hour urine collection completeness	To ensure quality of urine collections	8.1.1.1.1 Completeness Criteria for 24-hour Urine Sample

Description of Change	Brief Rationale	Affected Sections
Updated results of ongoing DCR-PHXC studies	To provide more up-to-date information	2.2.3 Clinical Overview
Revised language around reporting of pregnancy and pregnancy testing in WOCBP 1. Added pregnancy testing in women of childbearing potential to the screening visit in the Schedule of Activities 2. Clarified that urine pregnancy testing may be performed locally **3.** Corrected timing of reporting of participant pregnancy from 2 weeks to 12 weeks after last dose of study intervention	1. Correction of omission 2. Additional clarification 3. Correction of error	1.3 Schedule of Activities 8.3.5 Reporting of Pregnancy 10.2 Clinical Laboratory Tests
Added anti-dsDNA antibody testing	Increased participant safety. To clarify the potential for immunogenicity, as endogenous anti-nuclear antibodies are believed to recognize oligonucleotides 40- to 50-base pairs in length.	1.3 Schedule of Activities 2.3.1.1 Risks Related to the siRNA Molecule 8.8.1 Immunogenicity Assessments 10.2 Clinical Laboratory Tests 10.6 Abbreviation, Acronyms, Initialisms
Deleted cytokine and complement testing, viral serology screening, and testing of vitamin B6 blood levels in participants less than 18 years of age	To minimize blood loss volumes in children	1.3 Schedule of Activities 2.3.4 Risk Management 5.2 Exclusion Criteria 10.2 Clinical Laboratory Tests
Updated instructions for the monitoring of participants with suspected drug-induced liver injury	Increased participant safety.	7.1.1 Drug-Induced Liver Injury Monitoring

Description of Change	Brief Rationale	Affected Sections
Added language to require that age-appropriate normal values will be used when evaluating pediatric participants	Increased participant safety.	8.2.3 Vital Signs 8.2.4 Clinical Laboratory Assessments
Clarified time windows for assessments: 1. Added window for collection of samples for cytokine and complement testing **2.** Clarified window for performance of ECG and vital signs measurements	1. To align with collection of blood samples for PK analysis 2. Additional clarity	1.3 Schedule of Activities
Updated specifications for physical examinations 1. Removed calculation of body mass index **2.** Updated timing of when height should be measured and recorded	1. Body mass index was not used for any study assessments 2. To ensure that height was recorded when needed for calculation of eGFR	1.3 Schedule of Activities 8.2.1 Weight, Height and Body Surface Area
Updated language around drug screen testing to indicate that investigator discretion is allowed	Participants may be treated with prescribed analgesics for pain management	1.3 Schedule of Activities 5.2 Exclusion Criteria
Added urinary phosphate and urinary magnesium to the list of parameters to be determined from 24-hour urine samples	Correction of previous omission.	8.1.3 Other Parameters Determined from 24-Hour Urine Collections 10.2 Clinical Laboratory Tests
Removed estradiol testing for confirmation of post-menopausal status	Testing not required	10.2 Clinical Laboratory Tests

Description of Change	Brief Rationale	Affected Sections
Added that participants are not eligible to roll over to Study DCR-PHXC-301 until all assessments in the current study are completed, including 24-hour Uox	To ensure that the final 24-hour urine sample meets completeness criteria	6.7 Intervention After the End of the Study
Added language to the definition of injection site reactions	To clarify that events with a time to onset of less than 4 hours are not considered ISRs	10.3.3 Definition of Adverse Event of Special Interest
Deleted the criterion relating to progression of disease in the list of events not considered AEs	To eliminate confusion surrounding how to classify PH-related signs and symptoms	10.3.1 Definition of Adverse Event(s)
Noted that kidney ultrasound and echocardiogram re-testing is not required for rescreening if results of a prior screening had been sent to central over-readers within the past 3 months.	To decrease burden on the participant, as substantial change would not be expected in a 3-month period.	1.3 Schedule of Activities
Specified that site personnel will be trained in procedures surrounding performance of kidney ultrasound, ECG, and echocardiogram	To ensure consistency across all sites.	8.1.6.2. Kidney Ultrasound 8.2.5 12-Lead ECG 8.2.6 Echocardiogram
Clarified that the DSMC may review "unblinded" rather than "partially unblinded" safety and efficacy data	Increased participant safety	2.3.4 Risk Mitigation 9.6.1 Data Safety Monitoring Committee

Description of Change	Brief Rationale	Affected Sections
Updated language relating to performance of interim analysis	To clarify that an interim analysis "may" be performed, rather than "will" be. To describe the zones for which a sample size adjustment would be made. Updated alpha spending related to the interim analysis	1.1.1 Overall Design 4.1 Overall Design 9.6 Interim Analysis
Added language to state that a participant will be assigned to the treatment that results in the lowest amount of imbalance with an 80% probability, and the treatment which results in the highest amount of imbalance with a 20% probability	To clarify randomization procedures with respect to imbalance	9.3 Randomization Method
Added language to indicate that additional participants may be enrolled if participants discontinue prior to Day 90	To ensure that there is an adequate number of participants for analysis of the primary endpoint	7.2. Participant Discontinuation/Withdrawal from the Study
Added that calculation of PK parameters will also be performed for metabolites of DCR-PHXC	For more complete characterization of pharmacokinetics	1.3 Schedule of Activities 8.5.1 Plasma Pharmacokinetics
Corrected inconsistencies between the 2 tables of Objectives and Endpoints	Correction	1.1.3 Objectives and Endpoints 3 Objectives and Endpoints
Updated Sponsor information	To update the corporate address, add the Sponsor Medical monitor email address and update the Title for the Executive Director of Regulatory Affairs	Cover page Sponsor Signature page Medical Monitor and Pharmacovigilance Contact Information

Amendment 1 (version 3.0 US), 30-Apr-2019

The 16 November 2018 version of the protocol was updated to include feedback from regulatory authorities, including the United States Food and Drug Administration (FDA). Version 3.0 represents the initial filing of Study DCR-PHXC-201 to the FDA.

Administrative Update (version 2.0), 16-Nov-2018

The 24 October 2018 version of the protocol was updated to include the dose selected for adolescent participants aged 12 to 17. Additional detail was added to standardize the definition of kidney stone-related events and to describe how stone burden will be determined. Other administrative updates were also included. The 24 October 2018 version was not submitted to any Investigator, Ethics Committee, or Regulatory Authority for review, approval, or initiation.

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APPENDIX A: COVID-19 EMERGENCY RESPONSE MEASURES

A.1. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus ("SARS-CoV-2") that was first detected in Wuhan City, Hubei Province, China, and that has now been detected in many locations internationally, including cases in the United States. The disease caused by the SARS-CoV-2 virus has been named "Coronavirus Disease 2019," or, simply, "COVID-19."

In response to the COVID-19 pandemic, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) issued guidance to provide general considerations to assist Sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to clinical trial integrity (FDA, 2020).

In these guidances, FDA and EMA acknowledge that the pandemic may result in challenges that could lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. The Agencies recognize that "changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the IND or IDE, but are required to be reported afterwards" (FDA, 2020) and "Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks" (EMA, 2020).

Based upon this information, Dicerna proposes that the recommendations detailed below be made with respect to Study DCR-PHXC-201, for as long as the COVID-19 health emergency continues. Once the local site determines that participants are no longer at elevated risk, the site may return to following the currently approved version of the protocol.

A.2. SUMMARY OF RECOMMENDATIONS PROPOSED FOR STUDY DCR-PHXC-201

A.2.1. Adjustments to Study Visits

1) **Duration of the Screening Period**
   a) The screening period will be extended from 35 to 60 days to allow flexibility to obtain all completed assessments.
   b) All screening assessments must be performed at the clinical site.
2) **Study Visits for Days 1, 30, and 60**
   a) Because participants entering the Study are naïve to DCR-PHXC, administration of blinded study intervention at the first 3 visits (Days 1, 30, and 60) must occur at the clinical site, along with all protocol-specified safety assessments.

b) Should the site encounter difficulty with the duration or frequency of blood sampling for PK at Days 1 or 30:

i) the schedule in adults may be abbreviated to include only the predose and 4-hour samples; with the samples scheduled at 5, 15, and 30 minutes and 1, 2, 6, 10, and 12 hours postdose being omitted;

ii) the schedule in children aged 6 to 17 may be abbreviated to include only predose and 4 hours postdose; with the samples scheduled at 30 minutes and at 2 and 10 hours postdose being omitted.

3) Study Visits for Days 2 and 31

a) At-clinic site visits are not required for Visits at Days 2 and 31. A combination of telemedicine and home nursing care will allow participants to undergo "virtual" visits.

b) The Investigator (or designee) is expected to call the participant on these visit days to assess the participant's overall health status and to record any AE or SAEs.

c) The 24-hour postdose blood sample for PK analysis should be collected as scheduled (participants ≥ 18 years of age).

4) Study Visits for Days 15, 45, 90, 120, and 150

a) At-clinic site visits are not required for Visits at Day 15, 45, 90, 120, and 150. A combination of telemedicine and home nursing care will allow participants to undergo "virtual" visits.

b) Dicerna is working with the Illingworth Nursing Group to extend their responsibilities for collection and processing of safety labs and vital signs, as well as for administration of double-blind study intervention.

c) On Days 90, 120, and 150, the home nurse will call the Investigator the day before the scheduled home visit to obtain permission to administer study intervention to the participant. The nurse will follow-up with the Investigator again on the day after the home visit.

d) The Investigator (or designee) is expected to call the participant on these visit days to assess the participant's overall health status and to record any AE or SAEs.

e) The specific responsibilities of the home nurses and the execution of the virtual visits will be outlined in an at-home nursing visit guidance.

5) Study Visits for Day 180

a) The Day 180 Visit (with End-of-Study assessments) must occur at the clinical site due to the required imaging procedures.

A.3. 24-HOUR URINE COLLECTIONS

As urinary oxalate (Uox), determined from 24-hour urine collections, is the primary endpoint of the study, participants are encouraged to continue collecting 24-hour urines as planned.

The window for repeat collection of 24-hour urine samples that violate completeness criteria will be extended from 10 days to 14 days due to issues with courier availability and shipping issues across borders.

A.4. SAFETY LABORATORY TESTING

Hematology and serum chemistry are the essential laboratory tests for the evaluation of safety.

1) For both at-home and in-clinic visits, should delays or difficulties arise with the use of the central laboratory, a local laboratory may be utilized to monitor participant safety.
    a. Should the use of a local laboratory be required, the collection of samples for the testing of coagulation parameters, cytokines, and complement may be omitted.

A.5. PROTOCOL DEVIATIONS

Dicerna recognizes that there may be minor protocol deviations for visits and assessments that fall outside of the protocol-specified windows. These should be continued to be documented as minor deviations.

A.6. INFORMED CONSENT

All participants who will undergo virtual site visits must provide their consent to the change in their participation. If provision of in-person written consent is not possible, consent may be provided to the Investigator (or designee) orally, over the telephone. This consent must be documented by the Investigator.

A.7. SPONSOR RISK ASSESSMENT

Primary Hyperoxaluria Types 1 and 2 are both serious and life-threatening diseases which ultimately may lead to kidney or combined kidney-liver transplantation. There are no approved therapies available and current supportive therapy consists of hyperhydration and alkalization of urine.

In Study DCR-PHXC-101, a single dose of 3 mg/kg DCR-PHXC (also called nedosiran), was shown to substantially lower Uox (mean 67%, range 42-80%) in participants with PH1 or PH2. As the magnitude of Uox levels has been shown to correlate with the risk of developing renal complications (Zhao et al., 2016), a lowering of Uox might potentially be of clinical benefit for patients with PH1 or PH2.

Participants in Study DCR-PHXC-201 are randomized 2 to 1 to DCR-PHXC or placebo. Participants in the DCR-PHXC arm might have a potential for direct benefit by remaining in the study, based on the possibility that DCR-PHXC may lower Uox concentrations. Participants in the placebo arm will derive no direct benefit in this study, but they will have the opportunity to roll-over into an open-label study with DCR-PHXC at the end of the study (Day 180).

Measures taken by the Sponsor in response to the COVID-19 emergency mainly consist of switching certain site visits to at-home visits conducted by an authorized local nurse. The Principal Investigator will call participants to assess their general health status and to conduct SAE/AE reporting with the participant. This measure is implemented as certain clinical sites are

no longer able to conduct site visits and/or some participants are no longer able to visit a site due to local travel restriction.

Participants remaining in the clinical study could potentially receive clinical benefits either during the study or after the study is completed by enrolling into an open-label study. Switching from site visits to a combination of at-home nurse visits and telehealth assessments by the Investigator or designee only minimally increases the risk associated with study participation for study participants but does decrease their risk of acquiring COVID-19 infection by not needing to travel to study sites if they are open. Therefore, the overall risk/benefit for a study participant in study DCR-PHXC-201 with these additional COVID-19 emergency measures remains unchanged.

A.8. REFERENCES

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A.9. UPDATED SCHEDULE OF ACTIVITIES

A copy of the Schedule of Activities that highlights the visits that can be performed virtually and the changes in the PK sampling schedule is attached as **Table A1**.

Table A1 Schedule of Activities – COVID-19 Adjustments

	Screening	Treatment										EOS	ET
Study Day (window)	–60 [a] to –1	1	2	15 (±2)	30 (±2)	31 [b]	45 (±2)	60 (±3)	90 (±3)	120 (±5)	150 (±5)	180 (±5)	-
Procedure/Assessment													
Informed consent/assent [c]	X												
Inclusion and exclusion criteria [d]	X	X											
Demographic/baseline characteristics	X												
Medical history [e]	X												
PH disease history [e]	X												
Medication history [f]	X												
AGXT/*GRHPR* genotyping [g]	X												
Urine drug screen [h]	X												
Viral serology [i]	X												
FSH (postmenopausal women)	X												
Study intervention administration		X			X			X	X	X	X		
Spot urine collection [j]	X				X			X	X	X	X	X	X
24-hr urinary oxalate [k]	X				X			X	X	X	X	X	X
24-hr urinary creatinine [l]	X				X			X	X	X	X	X	X
Blood draw for vitamin B6 levels [m]		X			X			X	X	X	X	X	
Plasma PK sample [n]		X	X		X	X					X		X
Plasma oxalate sample [o]	X	X			X			X	X	X	X	X	X
Record fluid intake [p]	X	X			X			X	X	X	X	X	
12-lead ECG [q]	X	X		X	X		X	X	X	X	X	X	X
Vital signs [r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [s]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height [t]	X	X			X			X	X	X	X	X	X
Hematology and serum chemistry [u]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation studies [v]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment										EOS	ET
Study Day (window)	–60 [a] to –1	1	2	15 (±2)	30 (±2)	31 [b]	45 (±2)	60 (±3)	90 (±3)	120 (±5)	150 (±5)	180 (±5)	-
Procedure/Assessment													
eGFR [w]	X	X			X			X	X	X	X	X	X
Cytokines [x]		X	X		X	X							X
Complement [y]		X	X		X	X							X
Urinalysis [z]	X	X			X			X	X	X	X	X	X
Urine pregnancy test (WOCBP) [aa]	X	X			X			X	X	X	X	X	X
Record stone events (as applicable) [bb]		X	X	X	X	X	X	X	X	X	X	X	X
Kidney ultrasound [cc]	X											X	X
Echocardiogram [dd]	X											X	X
ADA & anti-dsDNA sample [ee]	X						X					X	X
Pediatric burden assessment [ff]		X		X	X		X	X	X	X	X	X	X
SF-36 [gg]	X											X	X
EQ-5D-5L [hh]	X											X	X
PedsQL [ii]	X											X	X
Record SAEs [jj]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs [kk]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [f]		X	X	X	X	X	X	X	X	X	X	X	X

NOTE: Shaded visits may be conducted "virtually" via home nurse and telemedicine during the COVID-19 public health emergency.

Abbreviations: AE = adverse event; *AGXT* = the gene that codes for alanine–glyoxylate aminotransferase; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination; FSH = follicle stimulating hormone; *GRHPR* = the gene that codes for glyoxylate and hydroxypyruvate reductase; PedsQL = Pediatric Quality of Life Inventory; PH = primary hyperoxaluria; PK = pharmacokinetic; SAE = serious adverse event; SF-36 = Short Form 36 Health Survey; WOCBP = women of childbearing potential

Table footnotes:

a. Potential participants allowed a second attempt at achieving < 20% variation in weight-adjusted 24-hour urinary creatinine excretion, as described in Section **8.1.1.1.1**, will be given an extra 7 days within which to complete the second pair of collections. An additional 7 days will also be granted for retest of initially unanalyzable screening laboratory samples.

b. Day 31 visit to be conducted the day after the Day 30 visit, regardless of when the Day 30 visit occurs within the ± 2-day window.

c. Informed consent (and assent if applicable) may be given outside of the 60-day screening period, i.e., provision of consent does not start the clock for the screening period. In no case should more than 2 weeks elapse between the provision of consent and initiation of the first screening procedure/assessment. Initiation of the first screening procedure will start the 60-day window.

d. Participant eligibility (with the exception of clinical laboratory testing) will be re-confirmed prior to administration of study intervention on Day 1.

e. Record 5 years of general medical history. PH history to include 12-month history of stone events, as described in Section **8.1.6.1**.

f. To include vitamin B6 (pyridoxine).

g. Participants without documented genotyping must provide a DNA sample for testing.

h. Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines. Drug screening is not required for individuals aged 12 or younger. Investigator discretion in excluding participants with a positive test is allowed.

i. HIV 1and 2 antibodies, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody. If tested in the past 3 months, medical record documentation of this testing may be used. Viral serology is not required in participants < 18 years of age.

j. A sample of urine from the void immediately prior to the initiation of each 24-hour urine collection will be collected and stored apart from the 24-hour urine collection. Should the two 24-hour screening collections occur on consecutive days, no spot urine sample will be collected on the second day.

k. Two screening samples should ideally be collected on 2 consecutive days, but with no more than 8 days between collections. Collection of on-treatment samples must be performed within the 7 days prior to the scheduled study visit. It is desired that the elapsed time between monthly collections should be at least 3 weeks and not more than 5 weeks. Participants should avoid taking vitamin C supplements (including multivitamins) for 24 hours prior to and during the collection of 24-hour urine samples. See Section **8.1.1.1**.

l. Urinary creatinine excretion will be determined from 24-hour urine samples in order to assess the quality of the 24-hour collection. Any postdose sample that violates the urine quality review criteria should be repeated within 14 days of the scheduled study visit whenever possible. See Section **8.1.1.1.1** for details.

m. Samples for vitamin B6 levels will only be collected in participants aged ≥ 18 years who are taking vitamin B6 supplements.

n. Plasma sampling times for PK analysis (see Section 8.5.1):

- Aged ≥ 18 years:
  - Days 1 and 30: predose and at 4 hours postdose 5, 15, and 30 minutes and 1, 2, 6, 10, and 12 hours postdose (shaded timepoints may be omitted if necessary)
  - Days 2 and 31: 24 hours postdose (may be collected by home nurse)
  - Day 150: predose and at 4 hours postdose 2, 6, and 12 postdose (shaded timepoints may be omitted if necessary)
- Aged 6–17 years:
  - Days 1 and 30: predose and at 4 hours postdose 30 minutes and 2 and 10 hours postdose (shaded timepoints may be omitted if necessary)
  - Days 2 and 31: 24 hours postdose (may be collected by home nurse)
  - Day 150: predose and at 4 hours postdose 2 and 10 hours postdose (shaded timepoints may be omitted if necessary)

A single plasma sample should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Windows for the collection of PK samples are as follows:

- Predose to be collected within 30 minutes before administration of study intervention
- 5, 15, and 30 minutes and 1 hour postdose, ± 3-minute window is allowed
- 2, 4, 6, 10, and 12 hours postdose, ± 30-minute window is allowed
- 24 hours postdose, ± 1-hour window is allowed

o. In adults, blood samples for plasma oxalate analysis to be collected prior to dosing (Section **8.1.5**). Participants aged 6 to 17 years will have plasma oxalate sampling only at Screening.

p. Participants should maintain consistent fluid intake (i.e., hyperhydration) over the course of the study (Section **5.3**). Participants will report average daily fluid intake over the 4 to 7 days prior to each 24-hour urine collection (Section **8.2.7**).

q. On Days 1 and 30, ECG to be performed predose and at 10 hours (± 30 minutes) postdose. A single ECG to be performed at other visits, as indicated (Section 8.2.5). If multiple assessments are due at the same time point. In such cases, PK sampling should be performed preferably at the nominal time point, with the preferred order of assessments ECG, vitals, PK, and then other assessments.

r. Vital signs on Day 1 and Day 30 to be assessed predose and at 10 hours (± 30 minutes) postdose (Section 8.2.3). If multiple assessments are due at the same time point. In such cases, PK sampling should be performed preferably at the nominal time point, with the preferred order of assessments ECG, vitals, PK, and then other assessments.

s. A full physical exam will be performed at Screening and Day 180 (or ET). A brief physical examination may be performed at other scheduled visits (Day 1 through Day 150) or unscheduled visits at the Investigator's discretion. See Sections **8.2.1** and **8.2.2**.

t. In participants ≥ 18 years of age, height to be recorded only at screening. In participants < 18 years of age, height will be recorded at specified visits for calculation of eGFR and BSA adjustment of Uox excretion. Weight to be recorded in all participants at specified visits. In participants aged 6-to-11 years, the weight on Day 1 will be used to calculate the mg/kg dose of study intervention.

u. Blood samples for hematology and serum chemistry to be collected predose on dosing days. To include cystatin C in participants < 18 years of age for calculation of eGFR. See Section **10.2** for the list of parameters.

v. Blood samples for coagulation studies to be collected predose. Coagulation panel will include activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR). Additional coagulation studies should be performed as clinically indicated. If met with difficulty, sample collection for coagulation studies may be omitted.

w. eGFR to be calculated as described in Section **8.2.4.1**.

x. For the first and second doses of study intervention, blood samples for cytokines to be collected in participants aged ≥ 18 years within 30 minutes before administration of study intervention and 2, 10, and 24 hours postdose. A ± 30-minute window is allowed for samples collected at 2 and 10 hours postdose. A ± 1-hour window is allowed for sample collected at 24 hours postdose. A single sample will be collected in participants prematurely discontinuing study intervention. See Section **10.2** for parameters. Cytokine testing is not required in participants < 18 years of age. If met with difficulty, sample collection for cytokine testing may be omitted.

y. For the first and second doses of study intervention, blood samples for complement panel to be collected in participants aged ≥ 18 years within 30 minutes before administration of study intervention and 2, 10, and 24 hours postdose. A ± 30-minute window is allowed for samples collected at 2 and 10 hours postdose. A ± 1-hour window is allowed for sample collected at 24 hours postdose. A single sample will be collected in participants prematurely discontinuing study intervention. See Section **10.2** for parameters. Complement testing is not required in participants < 18 years of age. If met with difficulty, sample collection for complement testing may be omitted.

z. Urinalysis with microscopy at Screening and as clinically indicated. Dipstick urinalysis may be performed at other scheduled visits. Collect sample for urinalysis before dosing. See Section **10.2** for parameters.

aa. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Administration of study intervention will be discontinued in any participant with a positive pregnancy test. A final pregnancy test will be conducted 2-3 weeks following the last dose of study intervention in any WOCBP who prematurely discontinues the study.

bb. Participants will report instances of renal stones requiring medical intervention, stone passage, and/or renal colic requiring medication (Section **8.1.6.1**).

cc. In the event of rescreening, if a participant had been screened for this study within the last 3 months and had kidney ultrasound data sent to the central over-readers, repeat of the kidney ultrasound will not be required during the rescreen.

dd. In the event of rescreening, if a participant had been screened for this study within the last 3 months and had echocardiogram data sent to the central over-readers, repeat of the echocardiogram will not be required during the rescreen.

ee. Blood samples for analysis of anti-drug antibodies will be analyzed once a validated methodology is available (Section **8.8.1**).

ff. Participants < 18 years of age to be queried as to the ongoing burden of the study (Section **2.3.2**).

gg. Short Form 36 Health Survey to be administered only in adults (Section **8.1.7.1**).

hh. EQ-5D-5L to be administered only in adults (Section **8.1.7.2**).

ii. PedsQL to be administered only in children (Section **8.1.7.3**).

jj. Serious adverse events to be collected from time of ICF signature through 30 days after the last study visit.

kk. Adverse events to be collected from time of ICF signature through the End of Study/Early Termination Visit.