Cover Page for Statistical Analysis Plan

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NCT number	NCT03847909
Sponsor trial ID:	DCR-PHXC-201
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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Statistical Analysis Plan

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Sponsor	Dicerna
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
Protocol Number:	DCR-PHXC-201
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Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	Print Name: [redacted]	
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[redacted]

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Dicerna protocol number DCR-PHXC-201 (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 [PH] types 1 and 2), amendment 3, protocol version 5.0 US CT, dated 13-AUG-2020. Planned analyses and reporting for other region-specific versions of the protocol are included in a separate analysis plan. Reference materials for this SAP include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), and International Council on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3] for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified in the final CSR.

This SAP is an *a priori* plan. It will be finalized and signed off prior to clinical database lock or any unblinded inferential or descriptive analysis of data pertaining to Dicerna's study DCR-PHXC-201.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the efficacy of DCR-PHXC in reducing urinary oxalate burden in patients with PH (types 1 and 2).

2.1.2. Key Secondary Objective

The key secondary objective is to identify the proportion of participants with normalized or near-normalized urinary oxalate excretion (Uox).

2.1.3. Secondary Objectives

The secondary objectives are:

1. To evaluate the effect of DCR-PHXC on stone burden in patients with PH.
2. To evaluate the effect of DCR-PHXC on plasma oxalate in patients with PH.
3. To evaluate the effect of DCR-PHXC on eGFR.
4. To assess the safety of DCR-PHXC in patients with PH.
5. To characterize the pharmacokinetics (PK) of DCR-PHXC in patients with PH.

2.1.4. Tertiary/Exploratory Objectives

The tertiary/exploratory objectives are:

1. To evaluate the effect of DCR-PHXC on stone events in patients with PH.
2. To assess the efficacy of DCR-PHXC in reducing Uox burden over 6 months period in patients with PH.
3. To assess the efficacy of DCR-PHXC in reducing Uox burden at month 6 in patients with PH.
4. To evaluate the effect of DCR-PHXC on urinary oxalate-to-creatinine ratio in patients with PH.
5. To evaluate the effect of DCR-PHXC on quality of life (QoL) assessments in patients with PH.
6. To evaluate the relationship between Uox spot urine and 24-hour urine measurement in patients with PH.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESI)
- Change from baseline in 12-lead ECG
- Physical examination findings
- Vital signs
- Clinical laboratory tests

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the area under the curve from Day 90 to Day 180 ($AUC_{24\text{-hour Uox}}$), based on percent change from baseline in 24-hour Uox (adjusted per 1.73 m^2 body surface area [BSA] in participants aged <18 years). Further details of calculations are provided in Section 6.1.9.

2.2.2.2. Key Secondary Endpoint

The key secondary endpoint is the proportion of participants with a 24-hour Uox level <0.46 mmol/24 hours (normalized), or ≥0.46 to <0.6 mmol/24 hours (near-normalized) (adjusted per 1.73 m^2 body surface area [BSA] in participants aged <18 years) on at least two consecutive visits, beginning with Day 90. Further details of calculations are provided in Section 6.1.9.

2.2.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Percentage change in the summed surface area and number of kidney stones identified via kidney ultrasound from baseline to Day 180
- Percentage change in plasma oxalate from baseline to Day 180 (for adults only)
- Rate of change in eGFR from baseline to Day 180.
- Population and individual PK parameters for DCR-PHXC

2.2.2.4. Tertiary/Exploratory Efficacy Endpoints

The tertiary/exploratory efficacy endpoints include the following:

- Number of stone events over a 6-month period
- $AUC_{24\text{-hour Uox}}$ from Day 1 to Day 180, based on percent change from baseline
- Percentage change in 24-hour Uox from baseline to Day 180
- AUC of 24-hour urinary oxalate-to-creatinine ratio ($AUC_{24\text{-hour Uox:creatinine}}$) from Day 90 to Day 180, based on percent change from baseline
- Change from baseline to Day 180 in the Short Form (36) Health Survey (SF-36) and EQ-5D-5L in adults; and in the PedsQL™ in children (including adolescents)
- Uox in spot urine and 24-hour urine

2.2.3. Pharmacokinetic Variables

Pharmacokinetic parameters to be analyzed will be described in detail in a separate Pharmacokinetic Analysis Plan (PKAP). PK TLF generation and validation will be covered in a separate analysis plan.

3. Overall Study Design and Plan

3.1. Overall Design

This is a 6 month, randomized, placebo-controlled, double-blind study of DCR-PHXC in patients with primary hyperoxaluria (PH1 and PH2).

3.2. Sample Size and Power

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

For the sample size calculations, the primary endpoint of $AUC_{24\text{-hour Uox}}$ from Day 90 to Day 180 based on percent change from baseline was used. The group sequential design with pre-specified alpha spending for interim analysis and final analysis was utilized. The randomization ratio is 2-to-1 (active-to-placebo). The primary hypothesis to be tested is a one-sided superiority hypothesis at the significance level of 0.025. The $AUC_{24\text{-hour Uox}}$ in the placebo arm is assumed to be 0, as the Uox values may oscillate up and down from baseline due to measurement variability. The $AUC_{24\text{-hour Uox}}$ 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].

The above sample size calculation was performed under the assumption that there may be an interim analysis to re-estimate sample size after two-thirds of participants complete the study. However due to late enrollment experienced in the study, an interim analysis will not be performed.

3.3. Study Population

The study population includes male and female patients, at least 6 years of age, with genotype-confirmed PH1 or PH2.

3.4. Treatments Administered

Study intervention will be administered in clinic as a subcutaneous (SC) injection into the abdomen or thigh. In adults and adolescents (aged 12 to 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 was determined from an evolving PK/pharmacodynamic (PD) modeling and simulation (M&S) model, as detailed in Section 4.3 of the protocol. The model-derived dose of 3.5 mg/kg was approved by the data safety monitoring committee (DSMC) upon review of the appropriate safety data.

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

3.5. Method of Assigning Participants to Treatment Groups

Eligible participants will be randomized in a 2-to-1 (DCR-PHXC-to-placebo) ratio using an interactive web response system (IWRS).

To balance the participants between the intervention arms based on 2 factors: age (6 to 11, 12 to 17, or ≥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. Minimization can be especially helpful for studies with small sample sizes as the minimization produces better balance than standard stratified randomization methodology. 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 two factors. Participants will be assigned to the treatment that would generate the lowest amount of imbalance with a probability of 80%, and to the treatment that would generate the highest amount of imbalance with a probability of 20%.[4,5] Please refer to the study adaptive randomization plan for further details on the minimization algorithm used for treatment assignment.

At the beginning of the study, only two age groups were enrolled (12 to 17 and ≥18). Children aged 6 to 11 years were not enrolled until modeling and simulation of PK and PD data determined an appropriate dose for that age group and the DSMC reviewed safety data from at least the first 60 days of DCR-PHXC treatment (two doses plus 30 days of follow up) in three adolescent participants (aged 12 to 17 years). Concerning participants 12 to 17 years of age, the DSMC affirmed that the overall risk-benefit balance remains positive, and that no AEs of severe intensity considered to be drug-related (per selective unblinding by DSMC), and no SAEs suspected to be drug-related (per unblinding by DSMC) have occurred in participants 12 to 17 years of age. This will not affect the minimization, as age group is already one of the prognostic factors included in the minimization algorithm.

Additionally, in case there are participants who sign the ICF and are randomized but do *not* receive the study intervention; additional patients will be enrolled in order to achieve the planned sample size. Also in the case of participants who sign the ICF, are randomized, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study prior to completion of Day 90 assessments, or who do not have any efficacy assessments after Day 90, extra participants will be enrolled to achieve the planned sample size.

When enrolling additional participants, the participants who either did not receive study intervention, withdrew prior to the Day 90 assessments, or who do not have any efficacy assessments after Day 90 will *not* be included in the imbalance calculations used to implement the minimization algorithm, since these participants do not contribute to the primary analysis. In this way, participants enrolled additionally will be assigned to treatments to minimize imbalance across all participants expected to have data for the final analysis.

3.6. Blinding and Unblinding

This is a double-blind study in which treatment assignment will be blinded for investigators and any personnel involved with study conduct, evaluation at the investigational sites, [redacted], or the sponsor.

The randomization scheme will only be disclosed to select personnel to ensure correct preparation of the study drug, correct set-up of the IWRS, correct safety monitoring by the DSMC, and expedited adverse reaction reporting. All aspects of blinding and unblinding for the study (including possible interim analysis, emergency unblinding, unblinding following database lock) is outlined in the study-specific Blinding and Unblinding Plan.

Emergency 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.

Results of on-treatment 24-hour Uox measurements will not be revealed to the investigator, sponsor or blinded study team members prior to data base lock, so as not to potentially unblind the study. Details of the ongoing quality review of 24-hour Uox measurements by the unblinded members of the study team are outlined in the Unblinded Data Review and Sample Tracking Plan.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	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

	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													
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
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 protocol 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 protocol 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 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 protocol 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 protocol 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 protocol 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 (protocol 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 (protocol section 5.3). Participants will report average daily fluid intake over the 4 to 7 days prior to each 24-hour urine collection (protocol 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 (protocol 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 (protocol 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 protocol 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 protocol 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 protocol 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 protocol 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 protocol 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 protocol 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 (protocol 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 (protocol section 8.8.1).

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

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

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

ii. PedsQL to be administered only in children (protocol 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.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations, except for PK parameter estimation, will be performed primarily using SAS (release 9.4 or higher). Pharmacokinetic parameter estimation and analysis of DCR-PHXC concentrations in serum will be described in detail in a separate analysis plan (PKAP).

Descriptive summaries for continuous (quantitative) data include the number of participants (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Descriptive summaries for categorical (qualitative) data include the frequency and percentage of participants who are in the particular category or each possible value. In general, the denominator for a percentage calculation will be based upon the total number of participants in the study population within each Group (or overall), unless otherwise specified. The denominator for by-visit displays will be the number of participants in the relevant study population with non-missing data at each visit.

Unless specified otherwise, all summaries/tabulations will be presented by each treatment (placebo and DCR-PHXC) and overall.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 decimal more than the observed data and measures of spread (e.g., SD) will be reported to 2 decimals more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Participant data will be listed.

4.2. Interim Analysis and Data Monitoring

No interim analysis will be conducted. The final analysis will use an alpha of 0.025.

A DSMC was convened to provide periodic review of the efficacy and safety data. The DSMC is comprised of three voting members independent of the study team and sponsor. At a minimum, the DSMC meets:

- prior to the first participant enrolled,
- after the first five participants have completed the Day 30 Visit,
- after three adolescent participants (aged 12 to 17 years) have been enrolled in the DCR PHXC arm and have completed the Day 60 Visit, and
- periodically thereafter (depending on enrollment).

Children aged 6 to 11 years were not enrolled until modelling and simulation of the PK and PD data determined an appropriate dose for that age group and the DSMC has reviewed safety data from at least the first 60 days of DCR-PHXC treatment (2 doses plus 30 days of follow up) in three adolescent participants (aged 12 to 17 years). For participants 12 to 17 years of age, the

DSMC affirmed that the overall risk-benefit balance remains positive. Moreover for this age group no AEs of severe intensity considered to be drug related (per selective unblinding by DSMC) and no SAEs suspected to be drug related (per unblinding by DSMC) were observed to have occurred.

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. A DSMC charter containing details of the operation of the DSMC will be developed in conjunction with the members of the DSMC before the first meeting and will be modified as required. The sponsor may request additional reviews should any other findings/issues pertaining to safety or efficacy emerge requiring DSMC review.

The unblinded analyses will be performed by the [redacted] unblinded statistician and [redacted] unblinded SAS programmers. The [redacted] unblinded statistician is an independent statistician other than the author of this plan or the person responsible for the primary analysis of this study. Treatment codes will be revealed to those parties only.

4.3. Final Analysis

An unblinded analysis of the efficacy data will occur after all study participants have completed the study. The data will be cleaned, frozen, and a blinded data review will take place. Subsequently, data will be locked, protocol deviations will be adjudicated, and study populations will be defined before breaking the study blind.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Randomized Population (RAND):** The randomized population includes all participants who were randomized.
- **Enrolled Population (ENRL):** The enrolled population includes all participants who sign the informed consent form.
- **Safety Population (SAF):** The safety population includes all participants randomly assigned to study intervention and who take at least one 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 postbaseline 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 Population (EVAL):** The evaluable population includes all participants who received 6 full doses of study intervention and completed the study.

- **Pharmacokinetic Population (PK):** The PK population includes all participants in the safety population without major dosing violations. Details will be provided in the PKAP.
- **Per-Protocol Population (PP)**: The PP population includes all participants who were randomized and had no major protocol deviations that affect efficacy endpoint assessment as adjudicated by the sponsor.

The primary and the key secondary efficacy analyses will be performed on the MITT population and repeated in further analysis populations as described in section 8.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Study Day

Study Day 1 is defined as the first dose date (i.e., date of first administration of randomized study intervention). The first dose date is used as the reference start date for analysis.

For days prior to Study Day 1:

Study Day = reference date – first dose date.

For days on or following Study Day 1, Study Day = reference date – first dose date + 1.

6.1.2. Baseline

Post baseline assessments will be those assessed after the date/time of the first dose.

For all $AUC_{24\text{-hour Uox}}$ endpoints, the baseline is an average of the two 24-hour Uox Screening results.

For the remaining endpoints, the last observation recorded prior to the first dose of study intervention will be used as the baseline observation for all calculations of change from baseline.

6.1.3. Adjustments for Covariates

Statistical models based on Uox results will include covariates for age category [6 to 11, 12 to 17, or ≥18 years] and eGFR category [<45 mL/min or ≥45 mL/min]The baseline for the endpoint being analyzed will be included as a covariate.

6.1.4. Multiple Comparisons

A hierarchical testing procedure will be used to control type I error. If the superiority is established for the primary endpoint, statistical testing and p-value estimation for the secondary endpoints will be performed in a pre-specified sequence.

The primary and secondary endpoints will be tested in the following sequence.

1. AUC from Day 90 to Day 180, based on percent change from Baseline in 24-hour Uox
2. The proportion of participants with a normalization (< 0.46 mmol/24 hours) or near-normalization (≥ 0.46 to < 0.60 mmol/24 hours) of 24-hour Uox on at least 2 consecutive visits, beginning with Day 90
3. Percent change in plasma oxalate from Baseline to Day 180 (for adults only)
4. Percent change in the number of kidney stones identified via kidney ultrasound from Baseline to Day 180
5. Percent change in the summed surface area identified via kidney ultrasound from Baseline to Day 180
6. Rate of change in eGFR from Baseline to Day 180

The hierarchical testing steps will be:

Step 1. Test for superiority of the AUC for DCR-PHXC versus control, and record the one-sided p-value, p1. If p1 <0.025, then declare the test for primary endpoint to be statistically significant and proceed to Step 2; otherwise record the nominal p-values for all the secondary endpoints.

Step 2. Test for superiority of the DCR-PHXC versus control with respect to the proportion of participants with normalized or near-normalized Uox, and record the one-sided p-value, p2. If p2 < 0.025, then declare the test for the first secondary endpoint to be statistically significant and proceed to Step 3; otherwise record the nominal p-values for the remaining secondary endpoints.

Step 3. Test for superiority of the DCR-PHXC versus control with respect to the percent change in plasma oxalate from Baseline to Day 180, and record the one-sided p-value, p5. If p5 < 0.025, then declare the test for fourth secondary endpoint to be statistically significant and proceed to Step 6; otherwise record the nominal p-values for the remaining secondary endpoints.

Step 4. Test for superiority of the DCR-PHXC versus control with respect to the percent change in the number of kidney stones identified via kidney ultrasound from Baseline to Day 180, and record the one-sided p-value, p4. If p4 < 0.025, then declare the test for third secondary endpoint to be statistically significant and proceed to Step 5; otherwise record the nominal p-values for the remaining secondary endpoints.

Step 5. Test for superiority of the DCR-PHXC versus control with respect to the percent change in the summed surface area identified via kidney ultrasound from Baseline to Day 180, and record the one-sided p-value, p3. If p3 < 0.025, then declare the test for second secondary endpoint to be statistically significant and proceed to Step 4; otherwise record the nominal p-values for the remaining secondary endpoints.

Step 6. Test for superiority of the DCR-PHXC versus control with respect to the rate of change in eGFR from Baseline to Day 180, and record the one-sided p-value, p6. If p6 < 0.025, then declare the test for the last secondary endpoint to be statistically significant.

6.1.5. Handling of Dropouts or Missing Data

6.1.5.1. Missing Efficacy Endpoint Data

While all possible efforts will be made to ensure that participants stay in the study and all data is collected as scheduled, the occurrence of missing data cannot be completely eliminated.

For the analysis of AUC related efficacy endpoints, based on the MITT or ITT populations, a multiple imputation (MI) approach under the missing-at-random (MAR) assumption will be used to handle missing endpoint data. Subsequently, the AUC related efficacy endpoints will be calculated.

That is, any participant who withdraws or is discontinued from the study or who misses a scheduled visit or assessment through Day 180 will have their missing AUC related efficacy data analyzed as imputed using MI techniques.

Multiple imputation based on a standard MAR imputation approach will be performed in SAS® software using the general approach described below. This strategy is appropriate for data sets that have an arbitrary missing data pattern.

Step 1: The Missing at Random (MAR) imputation model will impute missing values using a fully conditional specification (FCS) regression-based multiple imputation model.[7] For participants with missing data at a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and observed data (e.g., outcomes at other visits, treatment, age category [6 to 11, 12 to 17, or ≥18 years], eGFR category [<45 mL/min or ≥45 mL/min], and baseline value of the primary response variable (e.g., Uox or Uox-to-creatinine ratio) as independent variables. This process will be repeated 50 times, resulting in 50 complete analysis data sets. The seed number of 3216549 will be used for the imputation procedure described in Step 1.

SAS pseudo code is provided below:

```
PROC MI DATA=indata OUT=outdata SEED=3216549 NIMPUTE=50;
        CLASS <treatment> <age category> <eGFR category>;
        FCS REG (<day 90> <day120> <day 150> <day 180>);
        VAR <treatment> <age category> <eGFR category> <baseline> <day 90> <day120>
                <day 150> <day 180>;
RUN;
```

Step 2: The corresponding derived efficacy endpoints (e.g., $AUC_{24\text{-hour Uox}}$ from Day 90 to Day 180) will be calculated based on the imputed data for each participant and for each of the completed analysis datasets. The standard SAS code that is developed to calculate the derived efficacy endpoints (e.g. $AUC_{24\text{-hour Uox}}$ from Day 90 to Day 180) will be applied to each of the 50 imputed datasets.

Step 3: The ANCOVA analyses will be performed separately for each of the 50 completed analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect, standard error, p-value and associated 95% CI) using the SAS MIANALYZE procedure.[7,8] The treatment difference will be tested at the one-sided 2.5% level and corresponding 95% CIs will be calculated. SAS Note: As PROC GLM does not report standard error for the difference of two LSMeans, GLM cannot be used in conjunction with PROC MIANALYZE. However, the equivalent code using PROC MIXED can be used to obtain the combined results.

SAS pseudo code is provided below:

```
PROC SORT DATA=outdata1 OUT=efficacydat;
        BY <imputation number> <treatment>;
RUN;

PROC MIXED DATA=efficacydat;
        BY <imputation number>;
        CLASS <treatment> <age category> <eGFR category>;
        MODEL <efficacy variable> = <treatment> <age category> <eGFR category>
                <baseline> ;
        LSMEANS <treatment> / DIFF;
        ODS OUTPUT LSMeans=lsmeans_ds Diffs=diffs_ds;
RUN;

*COMBINES THE LS MEANS ACROSS THE MI DATASETS;
PROC SORT DATA=lsmeans_ds;
        BY <treatment> <imputation number>;
RUN:

PROC MIANALYZE DATA=lsmeans_ds;
        BY <treatment>;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;

*COMBINES THE LS MEAN DIFFERENCES ACROSS THE MI DATASETS;
PROC SORT DATA=diffs_ds;
        BY <treatment> <imputation number>;
RUN:
```

```
PROC MIANALYZE DATA=diffs_ds;
        BY <treatment>;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;
```

6.1.5.2. 24 Hr Uox Measurements Which Do Not Meet Completeness Criteria

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:
According to the protocol, there must be no more than 20% variation between the two 24-hour urinary creatinine values measured in the screening period. 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 Unblinded Clinical 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 all weight-adjusted 24-hour urinary creatinine excretion values are no more than 20% of baseline. If the percentage change in any weight-adjusted 24-hour urinary creatinine excretion values are more than 20% of baseline, then this is a violation of the completeness criteria. If weight is missing at a visit, LOCF (last observation carry forward) weight should be used in creatinine excretion values per kg calculation. 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. In the event 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.

For the analyses of AUC related endpoints, only 24 hour urine oxalate measurements that meet the completeness criteria will be used for each visit to calculate AUC. That usually would be the latest measurement in case of recollection if criteria are not met. In case there is more than one measurement that does not violate the completion criteria, the average will be taken.

Measurements that violate the completeness criteria will not be included in the AUC calculations. Rather those values will be treated as missing data and will be imputed via the MI methods described in section 6.1.5.1 prior to calculating the AUC values for analysis.

As a sensitivity analysis, when there is no measurement that meets completeness criteria for that visit, if the changes from baseline of both 24-hour urinary creatinine excretion values go in the same direction (i.e., positive or negative), then the 24-hour Uox measurement with the smallest absolute change will be used; otherwise, if they go in different direction, then the 24-hour Uox measurement with the positive change from baseline of 24-hour urinary creatinine excretion will be used. The conservative approach is to refrain from observing any effect due to an under-collection

6.1.6. Uox Measurements below the Limit of Quantitation

If a reported Uox measurement is below the limit of quantification (LLOQ), then the 24 hour Uox value will be imputed as 0. For oxalate values < 50 umol/L, the 24 hour Uox value will be imputed as 0 umol/24h.

6.1.7. Handling of Rescreened Participants

Rescreening of participants is allowed. If a patient initially screen fails and is subsequently enrolled then that participant will have two subject IDs within the EDC system (one ID for the screen failure and associated data collection, and one ID for the subsequently enrolled participant). The demographics CRF will collect the previous subject ID for rescreened participants. In these cases, the initial screening data collection will be tied to the enrolled subject ID in order to ensure compliance with CDISC standards.

6.1.8. Analysis Visit Windows

By-visit summaries will be based on electronic case report form (eCRF)-defined nominal visits.

In general, analysis of all variables for this study will use the nominal visit or time point as collected on the electronic case report form (eCRF) and/or database. Scheduled visits will be selected over unscheduled visits.

For those subjects who discontinue early from the study and the Early Termination (ET) visit satisfies the following condition:

- 20 days <= the date of ET - the date of the last visit before ET +1 <= 40 days

then the ET visit will be mapped to the next scheduled visit. Otherwise, the ET will not be mapped into any analysis visits.

Adverse events (AEs) and concomitant medications are exceptions to the above rule; all treatment-emergent AEs (TEAEs) and concomitant medications will be presented.

6.1.9. Derived Variables

Change from baseline = value at current time point – baseline value

Percentage change from baseline = $\left(\frac{value\ at\ current\ time\ point - baseline\ value}{baseline\ value}\right) * 100\%$

Treatment-emergent AE (TEAE) = any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study CRF. That is, if the start time for the AE is provided, then the AE start date and time will be compared with the first dose date and time in order to determine whether the AE is a TEAE. If the start time for the AE is not provided, then the AE start date will be compared with the first dose date. In this case if the AE start date is on or after the first dose date, then the AE is considered a TEAE.

Body Surface Area (BSA)

BSA will be calculated via the DuBois formula:

- BSA (m^2) = 0.007184 × height(cm)$^{0.725}$ × weight(kg)$^{0.425}$

BSA Adjusted Uox: for participants aged <18 years, the 24-hour Uox values will be adjusted for BSA using the following formula prior to using the values in any analyses. The adjusted values will be used for all endpoint calculations. Participants aged ≥18 years will not have any adjustments performed to their 24-hour Uox results for the primary analysis. BSA Adjusted Uox values for all participants will be used for sensitivity analysis. All BSA Adjusted Uox values will use the BSA for the participant using the height and weight taken at same visit as the 24-hour Uox value.

- BSA Adjusted Uox = 24-hour Uox value * (1.73/BSA of participant)

If the height and weight are not available from the same visit as the 24-hour Uox value, then the imputation rules described in section 6.1.10.3 Missing Height/Weight Measurements to be used for BSA Adjusted Uox Calculations will be used to impute the height and weight in order to calculate the BSA Adjusted Uox values.

eGFR Equations

Chronic Kidney Disease Epidemiology Collaboration[9] (CKD-EPI) equation – for Adult Participants (≥ 18 years)

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

S_{Cr} = standardized serum creatinine in mg/dL
k = 0.7 for females or 0.9 for males
α = -0.329 for females or -0.411 for males
min = minimum value
max = maximum value
age is in years

Schwartz 2009 creatinine-based equation[10] – for Pediatric Participants (< 18 years of age)

- eGFR = 36.5 x height/SCr

height is in centimeters

SCr = serum creatinine in µmol/L

Schwartz 2012 multivariate equation[11] – for Pediatric Participants (< 18 years of age)

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

ht = height in meters
Scr = serum creatinine in mg/dL
cysC = cystatin C in mg/L
BUN = blood urea nitrogen in mg/dL
male = 1 if the patient is a male; 0 otherwise

Matsuo eGFR Equation - For Adult Participants in Japan

- eGFR = 194 × [Cr]− 1.094 × [Age]− 0.287 (× 0.739 in females)

The above eGFR calculations will be performed by the central laboratory.

For adolescents who turn 18 during the course of the study, the equation used at baseline (eGFR 2009 Schwartz Creatinine-based equation) will be used throughout the study.

Weight Adjusted 24-hour Urinary Creatinine Excretion (WTCREA24)

24-hour urinary creatinine excretion values (SDTM.LB CREAT24) will be merged with SDTM.VS records where VSTESTCD=WEIGHT and VSSTRESN is not missing.

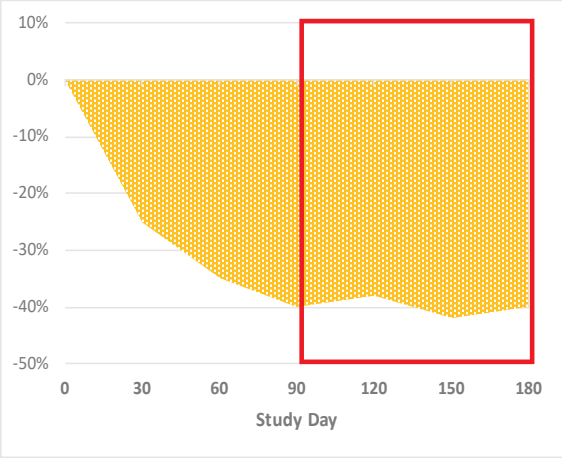
Calculate WTCREA24 = [CREAT24] / [WEIGHT]

Area Under the Curve (AUC)

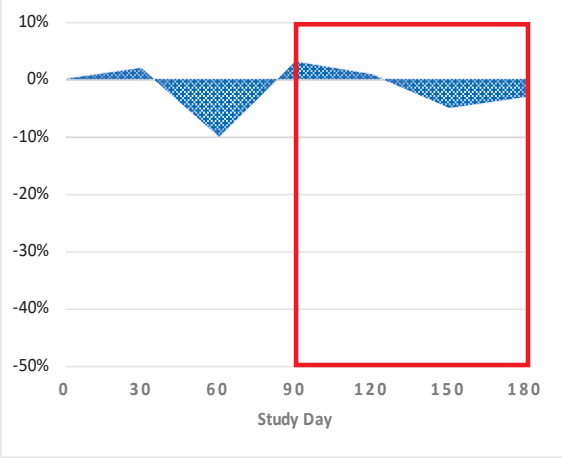
$AUC_{24\text{-hour Uox}}$ is calculated based on the percent change from baseline in Uox. The x-axis will be time in days and y-axis will be percent change from baseline in Uox. A percent decrease from baseline in Uox will be denoted as negative. A percent increase from baseline in Uox will be denoted as positive. The curve might be in its entirety, or at least in part, below the x-axis (Panel A, Figure 1). The area below the x-axis will be calculated and presented as a positive value. For an increase from baseline the percent change from baseline will be positive and that part of curve will be above the x-axis. The AUC would then be calculated as area below the axis minus area above the x-axis (Panel B, Figure 1). The AUC will be calculated using the trapezoidal rule; however, given that the percent change from baseline in Uox can change sign, we will use the approach outlined in the PharmaSUG by Jianfeng Ye[12].

The AUC will be calculated using the actual time in days between Uox collections, and not the nominal visit days. See Figure 1 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.

Figure 1 Example of AUC Graphs for Primary Endpoint



Panel A: All values below 0



Panel B: Values both above and below 0

$AUC_{24\text{-hour Uox: creatinine}}$ will be calculated as described above for Uox except that the $AUC_{24\text{-hour Uox: creatinine}}$ will be based on the percent change from baseline in the values of the Uox-to-creatinine ratio.

As illustrated in figure 1 above, the AUC for Day 90 to Day 180 is calculated based on the area underneath the 0 percent line between Day 90 and Day 180. For improvement in the subjects' condition, i.e. area below the zero percent line, we define the AUC as a positive number. For worsening of the subjects' condition, i.e. area above zero percent line, we define the AUC as a negative number. The final AUC will be the area below the zero percent line minus the area above zero percent line. The final AUC for each subject will be standardized based on 90 days.

- AUC_standardized = (AUC/actual days from Day90 visit to Day180) x 90

If data are only partially available between day 90 and day 180 (i.e. assessment dates are missing at either day 90 or day 180), the standardization will assume the actual number of days elapsed to be 90.

Quality-of-life Questionnaires

Adults - SF-36

As part of the Medical Outcomes Study (MOS), a multi-year study to explain variations in participant outcomes, RAND developed the 36-Item Short Form Health Survey (SF-36). The SF-36 is a set of generic, coherent, and easily administered quality-of-life 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[13]. Participants respond to each item on a categorical scale. Categorical answers are transformed to a range of 0 to 100. In addition to the eight health concept scales, two component summary measures are also calculated: PCS (physical component summary), and MCS (mental component summary). All items are scored so that a high score defines a more favorable health state.

For this study, the SF-36 questionnaires will be scored by the algorithm outlined in Appendix 2 based on the manual "How to Score version 2 of the SF-36 Health Survey" (Ware JE, et al. 2000). Additional detail on each of the domain and summary scores are contained therein.

Adults - EQ-5D-5L

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[14]. 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 values collected for the 5 health dimensions will be used to calculate an EQ-5D-5L index value. Index values will be calculated based on the US value set. Additional details are contained in a separate users guide document.

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.

Pediatrics - PedsQL

The PedsQL™ is a modular approach to measuring health related quality of life (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[15, 16].

Questionnaires are administered to the participant and the participant's parent. 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. The questionnaire has specific versions for the child and the child's parent based on the age of the participant (5-7 years old, 8-12 years old, 13-18 years old). Questionnaires are administered based on the age of participant at baseline. The same version of the questionnaire will be used throughout the course of the study for a given participant based on age at baseline. Additionally, the family impact module is administered to the participant's parent.

Items are reverse-scored on a 0 to 4 Likert scale and linearly transformed to a 0 to 100 scale. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. Higher scores indicate better functioning and HRQOL. Further details and scoring instructions are provided in a separate document.

6.1.10. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

All p-values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). A p-value less than 0.0001 will be shown in tables as <0.0001.

6.1.10.1. Missing or Partial Dates/Times for Adverse Events (AE) and Prior/Concomitant Medications (CM), AE Intensity, and AE Relationship

The following list describes how partially missing date information will be handled as it relates to partial or missing AE start dates. Partial AE start dates will be imputed as the following:

1. If year is not missing and is after the year of first dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first dose:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.
    c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.
3. If year is missing then impute the year as the year of the first dose date:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, then impute the day as the day of the first dose date.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first dose date then impute the start date as the first dose date.
5. For any cases involving the rules above, if the AE end date is before the AE start date, then leave the AE start date missing and assume that AE is treatment emergent for the purpose of the analysis. Further, if the AE stop date is complete and occurs prior to first dose date, leave the AE start date missing and assume that AE is <u>not</u> treatment emergent.

Dates will not be imputed if not considered potentially treatment-emergent. For example, if the AE year matches that of the first dose date but the AE month is prior to that of the first dose date the event is not considered potentially treatment-emergent and no imputed date will be assigned. No imputations will be applied to AE stop dates. No imputations will be applied to AE start or stop times.

Imputation for medication start dates will be handled similarly.

Relationship of the AE to study intervention and intensity will not be imputed for analyses.

6.1.10.2. Missing/Partial Dates for PH Diagnosis

PH diagnosis dates with partial dates will be imputed as follows: missing day values will be imputed as 15, and missing month values will be imputed as June in order to calculate the time since PH diagnosis or other related variables.

6.1.10.3. Missing Height/Weight Measurements to be Used for BSA Adjusted Uox Calculations

If the height and weight are not available from the same visit as the 24-hour Uox value, then the following imputation rules will be used to impute the height and weight in order to calculate the BSA Adjusted Uox values. Please note that the imputed height and weight values will not be summarized in any tables or provided in any listings. These imputed values will be used for the BSA Adjusted Uox calculations only.

Weight Imputations Rules for BSA Adjusted Uox Calculation

For all participants, regardless of age, missing weight values will be imputed by fitting a mixed model with weight at the dependent variable and study month as the main effect. Random coefficients will be used for the intercept and study month. In this way, the coefficients will vary by subject. The fitted line will be used to impute the missing weight value for a given value of study month. Example SAS pseudo code is shown below:

```
ODS OUTPUT SolutionF = fixed SolutionR = random
PROC MIXED DATA=weightdata;
CLASS <subject>;
MODEL <weight> = <study month> / SOLUTION;
RANDOM INTERCEPT <study month> / SUBJECT = <subject> SOLUTION;
RUN;

PROC TRANSPOSE DATA = fixed (KEEP = estimate effect) OUT = fixed1 (DROP = _name_
RENAME = (<study month> = fmonth <intercept> = fintercept));
                ID effect;
RUN;

PROC TRANSPOSE DATA = random (KEEP = <subject> estimate effect) OUT = random1
(DROP = _name_);
                BY <subject>;
                ID effect;
RUN;

DATA coefficients;
IF _n_ = 1 THEN SET fixed1;
SET random1;
<intercept> = fintercept + intercept;
                <month slope> = fmonth + <study month>;
RUN;
```

To calculate a missing weight value from a known study month, take the corresponding subject specific coefficients from the dataset above and plug them into the formula <weight> = <intercept> + <month slope> * <study month>.

Height Imputation Rules for BSA Adjusted Uox Calculation:

- For participants <18 years, missing height values will be imputed in the same way as described above for weight except that height will be the dependent variable for the model.

- For adults (≥ 18 years), height at screening will be used for BSA adjusted Uox calculation. Height will not be imputed for post-screening visits.

6.1.11. Subgroups

The same analysis for the primary endpoint (i.e. $AUC_{24\text{-hour Uox}}$ 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).

Subgroup analysis of the primary endpoint may be performed on the list of subgroups provided in Table 2, if data permitting.

Table 2: List of Subgroups

1. Age (6 to 11 years if available, 12 to 17 years, or ≥ 18 years)
2. Baseline eGFR (<45 mL/min/surface area or ≥45 mL/min/surface area)
3. PH Type (PH1 or PH2)
4. Gender (male or female)

7. Study Participants and Demographics

7.1. Disposition of Participants and Withdrawals

Disposition will include tabulations by treatment group and over-all for the number of participants enrolled, and either screen failed or randomized into each treatment group. The number and percentage of participants who: received treatment, completed treatment, completed study, reasons for treatment discontinuation/study withdrawal (overall and by reason for discontinuation/study withdrawal), and continue on to protocol DCR-PHXC-301 will be reported by treatment group and overall. The number and percentage of participants in each analysis population will also be displayed by treatment group and overall.

7.2. Protocol Violations and Deviations

Prior to database lock and unblinding, all protocol deviations will be reviewed and categorized as either 'Important' or 'Non-important':

- Important PDs are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being.
- Non-important PDs will be identified as any protocol deviation that does not meet the criteria for Important PD.

Subjects with at least 1 deviation classified in the major protocol deviation list included in the appendix to this SAP will be excluded from the PP analysis population.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, age category, gender, race, ethnicity (where available, as ethnicity may not be collected at all sites), height, weight, and BSA will be presented by treatment group and overall. Body mass index will be calculated at the site and recorded in the eCRF. Body surface area will be computed as described in Section 6.1.10.

Summary statistics will be presented by treatment group and overall for baseline eGFR category, baseline 24-hour Uox results, PH type, time since PH diagnosis, number of kidney stone events in the last 12 months, and the number and surface area of kidney stones at baseline.

These summaries will be conducted for the MITT and SAF populations.

The number and percentage of participants reporting various medical histories, grouped by medical dictionary for regulatory activities (MedDRA) system organ class (SOC) and preferred term (PT) (MedDRA; Version 23.0 or higher), will be tabulated by treatment group and overall. This analysis will be conducted for the SAF population.

Prior medications will be presented separately from concomitant medications. Medications that started prior to dosing on Day 1 will be considered prior medications whether or not they were stopped prior to Day 1 dosing. Missing dates will be handled using the methodology described in Section 6.1.11.1. Medications will be coded using world health organization drug dictionary (WHO-DD) version B3 September, 2019 or higher. The number and percentage of participants reporting prior medication use, grouped by ATC Level 2 and ATC Level 4, will be tabulated by treatment group and overall. This analysis will be conducted for the SAF population. A listing of prior medications will be provided; the analysis on concomitant medications is described in Section 9.7.

All collected demographics and other baseline characteristics will be listed by participant.

7.4. Exposure and Compliance

Study intervention will be administered in clinic once monthly as described in Section 3.4. Any deviations from the planned dose will be reported.

Summary statistics of the number of doses received, the number of participants who received study drug for each dosing visit, and the percent of scheduled doses received will be presented by treatment group.

These summaries will be conducted for the SAF population. All study drug administration information will be presented in participant data listings.

8. Efficacy Analysis

All AUC parameters referenced in the efficacy analysis refer to the standardized AUCs defined in section 6.1.9.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint of this study is the $AUC_{24\text{-hour Uox}}$ from Day 90 to Day 180, based on percent change from baseline. The primary endpoint will be compared between the active treatment group and the placebo group.

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

- H_0: $AUC_{24\text{-hour Uox, a}} = AUC_{24\text{-hour Uox, p}}$ against one-sided alternative hypothesis
- H_A: $AUC_{24\text{-hour Uox, a}} > AUC_{24\text{-hour Uox, p}}$.

where

- $AUC_{24\text{-hour Uox, a}}$ is the $AUC_{24\text{-hour Uox}}$ for the active treatment arm (DCR-PHXC),
- $AUC_{24\text{-hour Uox, p}}$ is the $AUC_{24\text{-hour Uox}}$ for the placebo arm

All hypotheses will be tested at the one-sided significance level alpha of 2.5%.

Mean $AUC_{24\text{-hour Uox}}$ from Day 90 to Day 180 will be compared between treatment groups using an ANCOVA model with treatment group as a main effect in the model; and age category [6 to 11, 12 to 17, or ≥18 years], eGFR category [<45 mL/min or ≥45 mL/min], and baseline Uox as covariates, where the BSA adjustment is applied to the 24 hour urinary oxalate values for all pediatric subjects. The adjusted means for each treatment will be presented together with their 95% confidence intervals. The adjusted mean difference will be presented along with its 95% confidence interval and p-value.

The primary efficacy analysis will be based on the MITT dataset. This analysis will be repeated for the PP population and in addition as sensitivity analyses in ITT and EVAL population (see section 8.5).

Uox concentrations which do not meet completeness criteria (see section 6.1.5.2) will be excluded from the primary efficacy analysis. Multiple imputation will be used for those excluded values as well as for all other missing values.

Descriptive statistics for actual Uox concentrations and for percent change from baseline will be presented by visit.

8.2. Key Secondary Efficacy Analysis

The key secondary endpoint of 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 one-sided Fisher's exact test at significance level alpha of 2.5% will be used for comparison between treatment groups within the hierarchical testing framework described in section 6.1.4 Multiple Comparisons.

Two separate analyses of the key secondary efficacy endpoint will be presented:

1. Primary analysis: applying the BSA Uox adjustment only to subjects < 18 years old
2. Secondary (sensitivity) analysis: applying the BSA Uox adjustment to all subjects (pediatrics and adults)

The analyses will be performed based on MITT population.

8.3. Secondary Efficacy Analysis

The secondary efficacy endpoints listed below will be summarized by treatment group. A one-sided Wilcoxon Rank Sum test will be used for the comparison between treatment groups for both change and percentage change from baseline for the following outcome variables.

- Change/Percentage change from baseline to Day 180 in the summed surface area of kidney stones
- Change/Percentage change from baseline to Day 180 in the number of kidney stones
- Change/Percentage change from baseline to Day 180 in plasma oxalate (for adults only)

The stone surface area and stone count are defined as follows:

- Stone Surface Area: sum of the measured and calculated surfaces of the stone larger than 5 mm (the longest diameter)
- Stone Count: Stones will be categorized measurable or non-measurable as follows, only measurable stones will be used in the analyses:
    - Measurable : with a minimum size of 5 mm in the longest diameter the surface area of the stones
    - Non Measurable: all other stones, including small stones (longest diameter < 5 mm); if the number is too high, they may just say "too many to count", and / or provide an approximate number

Percentage change will also be calculated for the summed surface area of kidney stones and number of kidney stones using the CT results. These will be listed for each subject for the subgroup of participants from CT sub-study as described in the Protocol Appendix B.

A linear mixed model with observed eGFR as the dependent variable and treatment, study month and the interaction between treatment and month as independent variable, will be used to estimate rate of decline in eGFR response between DCR-PHXC and placebo treatments. A random intercept and slope will be included in the mixed model to fit a different intercept and slope for each subject. In this analysis nominal month will be modeled as a continuous independent factor.

The Least Squares adjusted means will be reported for each treatment group as well as the standard errors and 95% confidence intervals for the LS means. The estimate of treatment effect will be reported as the difference in treatment means, 95% confidence interval for the difference in means, the standard error for the mean difference, and the p-value for the treatment difference.

Example SAS code is provided below for reference:

```
PROC MIXED DATA=<input data> METHOD=REML;
  CLASS <treatment> <participant ID>;
  MODEL <observed eGFR value> = <treatment> <Month> <treatment*Month> /  SOLUTION
DDFM=KWR;
RANDOM int <Month>  / SUB= <participant ID> TYPE=<covariance structure>;
ESTIMATE "Slope for Treatment='DCR-PHXC " Month 1 <treatment*Month> 1  0 ;
ESTIMATE "Slope for Treatment=Placebo" Month 1 <treatment*Month>  0 1;
ESTIMATE  “DCR-PHXC versus Placebo” <treatment*Month> 1 -1 / alpha=0.05 CL;
RUN;
```

To handle the repeated measures data an unstructured variance-covariance matrix will be considered. In the event of convergence issues, a compound symmetric variance-covariance matrix will be used.

Separate ANOVA models will be considered for the following two eGFR parameters:

- Parameter 1: including all subjects using eGFR CKD-EPI equation and Schwartz et al. 2009 creatinine-based equation.
- Parameter 2: including all subjects using eGFR CKD-EPI equation and Schwarz 2012 Cystatin C-based equation

These analyses will be performed based on the ITT population. All hypotheses will be tested at the one-sided significance level alpha of 2.5% within the hierarchical testing framework described in section 6.1.4 Multiple Comparisons.

Descriptive statistics for the summed surface area of kidney stones, number of kidney stone, plasma oxalate, eGFR, and for the percent change from baseline will be presented by visit.

8.4. Tertiary/Exploratory Efficacy Analysis

The same statistical model described above for the primary efficacy analysis will be applied to the following tertiary/exploratory efficacy endpoints.

- $AUC_{24\text{-hour Uox}}$ from Day 1 to Day 180, based on percent change from baseline (ITT population)
- Percent change in 24-hour Uox from baseline to Day 180 (ITT population)
- $AUC_{24\text{-hour Uox:creatinine}}$ from Day 90 to Day 180, based on percent change from baseline (MITT population)
- Change from baseline to Day 180 in the SF-36, EQ-5D-5L in adults, and in the PedsQL™ in children (ITT population)

The number of stone events over a 6-month period will be analyzed using an exact Poisson regression model. The model will include treatment group and baseline stone events rate (continuous). Baseline stone events rate will be the number of stone events observed over the past 12 months prior to dosing. The model will include an offset term for total follow-up time as the 'number of months exposed' equal to the total elapsed time between first dose date and last day of visit in the study, divided by 30.4375. Annualized stone event rate (number of stone events per year per person) will be derived as number of stone events in the exposure period / total number of years exposed.

Example SAS code is given below:

```
PROC GENMOD DATA=;
  CLASS TREATMENT;
  MODEL 'Number_stone_evts_6month'=Treatment Kidney_Stone_Event_Baseline
/OFFSET=Ln_Number_Of_Months_Exposed DIST=POISSON LINK=LOG DSCALE;
  EXACT Treatment Kidney_Stone_Event_Baseline / ESTIMATE;
RUN;
```

The number of stone events will be calculated as the number of discreet (non-concurrent) adverse events marked as a Kidney Stone Event on the adverse event CRF. Kidney stone events include: renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring medication. Concurrent events will be defined as events occurring within the same 4-week (28-day) window. For example, renal colic treated with medication on Monday 12 November 2019 followed by stone passage without hematuria on Friday 30 November 2019 is a single (concurrent) stone event (18 days between start and stop of single stone event). Renal colic treated with medication on Monday 12 November 2019 followed by stone passage without hematuria on Wednesday 13 December 2019 is considered two separate stone events (30 days between discreet event one and event two).

To evaluate the relationship between Uox in spot urine and 24-hour urine, the correlation between the two measurements will be examined for the ITT population.

Descriptive statistics for SF-36 and EQ-5D-5L scores in adults, PedsQL scores in children, and Uox in spot urine samples, and the percent change from baseline will be presented by visit.

8.5. Sensitivity Analyses

The following sensitivity analyses will be performed for the primary endpoint:

- Same analysis as described in Section 8.1, but performed on the ITT population.
- Same analysis as described in Section 8.1, but performed on the EVAL population.
- Non-parametric analysis of the primary endpoint ($AUC_{24\text{-hour Uox}}$) using Wilcoxon Rank Sum test for the comparison between treatment groups
- Same analysis as described in Section 8.1, but performed on BSA adjusted Uox concentration for all participants.
- Same analysis as described in Section 8.1, but rather than using the mean of the two screening 24-hour Uox values as the baseline value the lowest of the two screening 24-hour Uox values.
- Same analysis as described in Section 8.1, but using all Uox concentrations, including those which do not meet completeness criteria (see section 6.1.5.2)
- Same analysis as described in Section 8.1 but performed using an MI approach assuming that the data are missing not at random (MNAR). Control-based pattern imputation will be used together with FCS. Control-based pattern imputation explores the assumption that patients revert to control group after drop-out. Thus, it is assumed that after drop-out, the unobserved values in experimental group follow the path of observed values in control group.

  Section 6.1.5.1 describes the details of the MI approach used in the primary analysis using MAR. For this sensitivity analysis, Step 1 of section 6.1.5.1 will be replaced with the following:

  - Step 1: The MNAR imputation model will impute missing values using an FCS regression-based multiple imputation model.

    The further description of step 1 still applies, the SAS pseudo code will be amended using additional MNAR statement within PROC MI:

    MNAR model (<day 90> <day120> <day 150> <day 180> / modelobs= (<treatment> ='Placebo'));
- Same analysis as described in Section 8.1 but performed without using an MI approach

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, reported concomitant medications, changes in clinical laboratory values, changes in vital signs, electrocardiogram (ECG), echocardiogram with Doppler, and physical examination results.

All safety analyses will be performed on the SAF population. All summaries will be descriptive in nature. No statistical comparisons will be performed.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA v23.0 or higher. AEs will be classified as treatment-emergent for analysis in summary tables where applicable.

A TEAE is defined as any event that started, changed in intensity, or changed relationship to the study treatment at the time of or after the first dose date and through the study completion date.

An overview summary of AEs, including counts and percentages, the risk difference and their 95% CI will be presented for subjects with: any TEAEs, TEAEs related to study treatment; TEAEs leading to treatment discontinuation, treatment-emergent SAEs, treatment-emergent SAEs related to study treatment, TEAEs of special interest (i.e., injection site reactions; muscle pain or weakness; kidney stones: renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring intervention), and fatal TEAEs.

9.1.1. Adverse Events Summaries

The number and percentage of participants with AEs will be summarized by SOC and PT. This summary will further be tabulated by strongest relationship to study intervention (related: definitely, probably, and possibly related; unrelated: unrelated; missing). A similar summary of TEAEs will be produced by maximum intensity (mild, moderate, severe, missing). In addition, the number and percentage of participants who experienced non-serious TEAEs (all TEAEs except serious TEAEs) that occurred in more than 5% of participants in either treatment group will be presented by SOC and PT for each treatment.

To count the number of participants who experienced each TEAE, a participant experiencing the same TEAE multiple times will only be counted once for the corresponding PT. Similarly, if a participant experiences multiple TEAEs within the same SOC, the participant will be counted only once for that SOC. For summaries by maximum severity, if a participant experiences more than one TEAE with different intensities severity (e.g., the same SOC and PT), only the worst intensity/severity will be reported. If a participant has both missing and non-missing intensity for a given SOC and PT, the missing intensity is selected for reporting unless the non-missing severity is noted as Severe. Treatment-emergent AEs will be sorted alphabetically by SOC and PT and presented by decreasing order of overall frequency. Treatment-emergent AEs analyzed by strongest relationship will be selected similarly for participants experiencing more than one TEAE with different relationships. If a participant has both missing and non-missing relationship for a given SOC and PT, the missing relationship is selected for reporting unless the non-missing relationship is noted as Related.

The number of TEAEs will be presented by SOC and PT. The total number of TEAEs will also be presented in the display.

In addition, all TEAEs will be provided in a listing, which will include the participant identifier, study intervention start date/time, SOC, PT, verbatim term, intensity, seriousness, relationship, action taken, outcome, date/time of onset, study day, date/time of resolution, and event duration in days. Event duration will be calculated as: (resolution date – start date) +1.

9.1.2. Summaries for Serious Adverse Events, AEs Resulting in Early Withdrawal, and Deaths

The number and percentage of participants who experienced treatment-emergent SAEs will be presented by SOC and by PT within each SOC. Treatment-related treatment-emergent SAEs, TEAEs resulting in treatment withdrawal from the study, TEAEs will be presented similarly in separate analyses.

Moreover, the number of SAEs (as opposed to the number and percentage of participants) and TEAEs resulting in early withdrawal from the study will be presented by SOC and PT within SOC.

Listings by participant for serious adverse events, deaths, and TEAEs resulting in early withdrawal will be generated.

9.1.3. Other Significant Adverse Events

Adverse events of special interest (AESI) will be summarized and include injection site reactions, muscle pain or weakness, and kidney stone events.

An injection site reaction 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:

Individual signs or symptoms at the injection site (e.g., erythema, swelling, etc.) reported within 4 hours of study intervention administration will be recorded as AEs at injection site (not as an injection site reactions) and graded in accordance with the intensity categories detailed in Section 9.1.1.

After 4 hours post dose, signs or symptoms at the injection site will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 5.0) criteria for injection site reactions.

Because the nonclinical safety program in mice identified potential off-target effects on skeletal muscle, participants will also be monitored for signs and symptoms of muscle weakness or pain, and plasma creatine kinase measurements.

Participants with PH are predisposed to the development of multiple and recurrent urinary tract and kidney stones. Stone events, while being considered in the evaluation of efficacy, will also be considered AESIs.

Injection site reactions and treatment-emergent signs of muscle weakness or pain will be summarized by SOC and PT using the methods described in Section 9.1.1. Summaries for these events by maximum severity, as described in Section 9.1.1, will also be produced. However, summaries by maximum intensity for injection site reactions >4 hours postdose will be based on CTCAE grading criteria (Grades 1 through 5; where Grade 1 is least severe and Grade 5 is most severe) for injection site reactions. If a participant has both missing and non-missing missing CTCAE grades for a given SOC and PT, the missing CTCAE grade is selected for reporting unless the non-missing CTCAE grades is noted as Grade 4 or Grade 5. Kidney stone events will be summarized by the specific kidney stone event type that is collected on the adverse event

CRF: renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring medication. Kidney stone events will also be summarized by maximum severity.

By-participant data listings for injection site reactions, treatment-emergent signs of muscle weakness or pain, and treatment-emergent kidney stones will be provided.

9.2. Clinical Laboratory Evaluations

Descriptive summaries for safety laboratory assessments will be presented at each visit starting at baseline. Changes from baseline to each post baseline visit will also be presented for continuous outcomes.

Baseline for safety laboratory assessments will be identified as defined in Section 6.1.2 regardless of whether an evaluation was scheduled, retested, or unscheduled. Since laboratory retests can occur for individual parameters, it will be necessary to define the baseline and all subsequent visit-specific laboratory values individually for each parameter.

In the case where below the limit of quantitation (BLQ) results are observed, and the LLOQ value is known, the BLQ values will be included in the numeric summary as the reported LLOQ value. In for those lab results reported as '<x' where x is numeric value, descriptive summaries will impute x as the lab result.

The following imputation rules will be applied to safety laboratory results where LLOQ value is unknown:

- If the patient has quantifiable concentrations of that analyte from other study visits, BLQ results will be imputed as ½ of the patient's lowest concentration for that analyte
- If the patient does NOT have any quantifiable concentrations of that analyte from other study visits, BLQ results will be imputed as ½ of the lowest concentration of that analyte based on all quantifiable results within the patient's dosing group/cohort

By visit summary tables will be presented for each category of data separately. Routine clinical laboratory data will include hematology, clinical chemistry, coagulation parameters, and urinalysis. Total complement (hemolytic activity and factors) will be reported similarly but will include reporting of the first quartile and third quartile in presentations; these summaries of total complement will be based on the log-transformed values. Shift tables for baseline to maximum and minimum post baseline values, based on laboratory normal ranges (below lower limit of normal [LLN], normal, above upper limit of normal [ULN]), will be provided for hematology, coagulation, complement, cytokines and clinical chemistry parameters. This analysis of extreme value shifts (e.g., maximum and minimum post baseline values) will be based on all post baseline assessments whether scheduled or unscheduled. The set of laboratory parameters included in each table will correspond to the study protocol.

The number and percentage of potentially clinically significant (PCS) laboratory values will be tabulated by laboratory parameter: the summary will indicate the number of participants with PCS-low or PCS-high values at any time post baseline, as identified in Table 3 and Table 4. This

analysis will be based on all post baseline assessments whether scheduled or unscheduled. It is possible for participants to appear in both categories (PCS-low and PCS-high) for any parameter.

Table 3: Potentially Clinically Significant Criteria for Safety Laboratory Assessments for Participants ≥ 18 Years of Age

Parameter	Units	PCS Low	PCS High	Sex
Hemoglobin	g/L	<95	-	F
	g/L	<115	-	M
Hematocrit	%	<32	-	F
	%	<37	-	M
RBC count	10^12/L	-	>10	F
	10^12/L	-	>8	M
WBC count	10^9/L	<2.8	>16	B
Neutrophils (total)	10^9/L	<1.5	≥13.0	B
Lymphocytes	%	-	≥75	B
Monocytes	%	-	≥15	B
Eosinophils	%	-	≥10	B
Basophils	%	-	≥10	B
Platelet count	10^9/L	<75	>700	B
BUN	mmol/L	-	≥10.71	B
Serum creatinine	umol/L	-	≥176.8	B
Total bilirubin	umol/L	-	≥34.2	B
Alkaline phosphatase	U/L	-	>390	B
AST	U/L	-	>150	B
ALT	U/L	-	>165	B

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; B= both; BUN= blood urea nitrogen; F= female; HDL= high density lipoprotein; LDL= low density lipoprotein; M= male; PCS = potentially clinically significant; RBC= red blood cell; WBC= white blood cell

Table 4: Potentially Clinically Significant Criteria for Safety Laboratory Assessments for Participants < 18 Years of Age

Parameter	Units	PCS Low	PCS High	Sex
Hemoglobin (5y to 14y)	g/L	<114	>151	B
Hemoglobin (15y to 17y)	g/L	<135	>175	M
Hemoglobin (15y to 17y)	g/L	<120	>160	F
Hematocrit (5y to 14y)	%	<36	>47	B
Hematocrit (15y to 17y)	%	<40	>52	M
Hematocrit (15y to 17y)	%	<36	>46	F
RBC count (5y to 14y)	10^12/L	<4.0	>5.6	B
RBC count (15y to 17y)	10^12/L	<4.6	>5.8	M
RBC count (15y to 17y)	10^12/L	<4.1	>5.2	F
WBC count (5y to 17y)	10^9/L	<4.0	>10.7	B
Neutrophils (Abs; 2y to 6y)	10^9/L	<2.1	>8.9	B
Neutrophils (Abs; 7y to 17y)	10^9/L	<1.6	>7.4	B
Lymphocytes (2y to 6y)	%	<16	>60	B
Lymphocytes (7y to 12y)	%	<12	>49	B
Lymphocytes (13y to 17y)	%	<20	>44	B
Monocytes (2y to 6y)	%	<3	>8	B
Monocytes (7y to 17y)	%	<3	>10	B
Eosinophils (183days to 6y)	%	-	>4	B
Eosinophils (7y to 12y)	%	-	>6	B
Eosinophils (13y to 17y)	%	-	>7	B
Basophils (31days to 17y)	%	-	>2	B
Platelet count (5y to 14y)	10^9/L	<175	>420	B
Platelet count (15y to 17y)	10^9/L	<150	>350	B
Urea (0y to 9y)	mmol/L	-	>5.712	B
Urea (10y to 15y)	mmol/L	-	>6.426	B
Urea (16y to 17y)	mmol/L	-	>7.14	B

Serum creatinine (4y to 12y)	umol/L	-	>68.068	B
Serum creatinine (13y to 17y)	umol/L	-	>106.08	M
Serum creatinine (13y to 17y)	umol/L	-	>88.4	F
Total bilirubin (8days to 17y)	umol/L	-	>20.52	B
Alkaline phosphatase (1y to 12y)	U/L	-	>299	B
Alkaline phosphatase (13y to 17y)	U/L	-	>389	M
Alkaline phosphatase (13y to 17y)	U/L	-	>186	F
AST (4y to 6y)	U/L	-	>47	M
AST (4y to 6y)	U/L	-	>58	F
AST (7y to 17y)	U/L	-	>41	B
ALT (0y to 9y)	U/L	-	>30	B
ALT (10y to 17y)	U/L	-	>30	M
ALT (10y to 17y)	U/L	-	>20	F

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; B= both; BUN= blood urea nitrogen; F= female; M= male; PCS = potentially clinically significant; RBC= red blood cell; WBC= white blood cell

Results of urine pregnancy tests (females only) will be presented in a listing only. Viral serology data and anti-drug antibody tests will be handled similarly.

Data listings for all laboratory results will be generated. Where appropriate, assessments considered to be PCS will be noted; abnormal values (e.g., above the upper limit of normal or below the lower limit of normal) will be identified. A separate listing of PCS safety laboratory data will be provided.

Participant data listings will include the type of visit (e.g., scheduled test, retest, unscheduled), age, sex, laboratory test, test units, laboratory test result, and the laboratory standard normal ranges adjusted as appropriate for age and sex, if available.

9.3. Clinical Laboratory Evaluations – eGFR

The statistical analysis of eGFR in adult participants (>= 18 years old) will be based on eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR CKD-EPI). The main statistical analysis of eGFR in pediatric participants (< 18 years old) will use the Schwartz[10] et al. 2009 creatinine-based equation. For all pediatric subjects (< 18 years old) a secondary analysis will be included in the descriptive summary tables where eGFR is calculated using the Schwarz 2012 Cystatin C-based equation[11].

9.4. Clinical Laboratory Evaluations – Urinalysis

All safety laboratory results obtained from 24 hour urinalysis which do not meet the completeness criteria described in section 6.1.5.2 will be set to missing in the descriptive summary tables. These safety urinalysis tests will include:

- 24 Hour Urinary Creatinine
- 24 Hour Urinary Oxalate to Creatinine Ratio
- 24 Hour Urinary Calcium
- 24 Hour Urinary Magnesium
- 24 Hour Urinary Phosphate
- 24 Hour Urinary Citrate Excretion Rate
- 24 Hour Urinary Citrate

9.5. Vital Signs

Descriptive summaries for vital signs (systolic blood pressure, diastolic blood pressure, body temperature, pulse/heart rate, and respiration rate) will be presented for each visit starting at baseline (as defined in Section 6.1.2). Changes from baseline to each post baseline visit will also be presented.

The incidence of PCS vital sign values (Table 5 and Table 6) at any time post baseline will be summarized in a manner similar to that described for safety laboratory assessments in Section 9.2. This analysis will be based on all post baseline assessments whether scheduled or unscheduled. It is possible for participants to appear in both categories (PCS-low and PCS-high) for any parameter.

Table 5: Potentially Clinically Significant Criteria for Vital Signs for Participants ≥ 18 Years of Age

Vital sign	Criteria
Heart Rate	≥120 bpm at any time post dose and ≥15 bpm increase from baseline
	≤50 bpm at any time post dose and ≥15 bpm decrease from baseline
Systolic blood pressure	≥180 mm Hg at any time post dose and ≥20 mm Hg increase from baseline
	≤90 mm Hg at any time post dose and ≥20 mm Hg decrease from baseline
Diastolic blood pressure	≥105 mm Hg at any time post dose and ≥15 mm Hg increase from baseline
	≤50 mm Hg at any time post dose and ≥15 mm Hg decrease from baseline

Abbreviations: bpm = beats per minute; mm Hg = millimeters mercury

Table 6: Potentially Clinically Significant Criteria for Vital Signs for Participants < 18 Years of Age

Vital sign	Criteria
Heart Rate	Both (6y to 11y): ≥140 bpm and an increase from baseline ≥15 bpm Both (12y to 17y): ≥120 bpm at any time post dose and an increase from baseline ≥15 bpm
	Both (6y to 11y): ≤60 bpm at any time post dose and a decrease from baseline ≥15 bpm Both (12y to 17y): ≤50 bpm at any time post dose and a decrease from baseline ≥15 bpm
Systolic blood pressure	Both (6y to 11y): ≥125 mmHg at any time post dose and ≥15 mmHg increase from baseline Males (12y to 17y): ≥140 mmHg at any time post dose and ≥15 mmHg increase from baseline Females (12y to 17y): ≥132 mmHg at any time post dose and ≥15 mmHg increase from baseline
	Both (6y to 11y): ≤80 mmHg at any time post dose and ≥15 mmHg decrease from baseline Both (12y to 17y): ≤90 mmHg at any time post dose and ≥15 mmHg decrease from baseline
Diastolic blood pressure	Both (6y to 11y): ≥80 mmHg at any time post dose and ≥15 mmHg increase from baseline Both (12y to 17y): ≥85 mmHg at any time post dose and ≥15 mmHg increase from baseline
	Both (6y to 17y): ≤50 mmHg at any time post dose and ≥15 mmHg decrease from baseline

Abbreviations: bpm = beats per minute; mm Hg = millimeters mercury

Participant data listings of vital sign data will be provided and, where appropriate, assessments considered to be PCS will be noted. A separate listing of PCS vital sign data will be provided.

9.6. Electrocardiograms

Electrocardiograms will be conducted at each visit except for Day 2 and Day 31. On Day 1 and Day 30, the ECGs will be conducted twice (predose and 10 hours post dose).

All reporting for ECG data will be presented for central lab ECG results only. Descriptive summaries for ECG data (HR, PR interval, QRS duration, QT interval, corrected QT interval [QTcF, Fridericia correction], and RR) will be presented at each visit starting at baseline. Changes from baseline to each post baseline visit will also be presented. The predose ECGs will be compared between Days 1 and 30. Predose and post dose ECGs will be compared for Days 1 and 30 as well.

If the RR is not collected it will be derived as follows: RR = (60/HR).

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

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

Absolute postbaseline QTcF and uncorrected QT interval will be classified as follows:

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

Frequency counts and percentages will be tabulated for change from baseline and absolute post baseline QTcF values at each visit starting at baseline; participant listings will identify records where participant data falls into these regions. These summaries will also be presented for minimum and maximum post baseline values. The analysis of extreme values (e.g., maximum and minimum post baseline values) will be based on all post baseline assessments whether scheduled or unscheduled.

The number and percentage of participants with the following overall ECG results will also be tabulated at each visit. Shift tables for baseline to maximum post baseline overall ECG results, based on the three categories below will be provided. This analysis of extreme value shifts (e.g., maximum post baseline values) will be based on all post baseline assessments whether scheduled or unscheduled.

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

The incidence of PCS ECG values (Table 7 and Table 8) at any time post baseline will be summarized in a manner similar to that described for safety laboratory assessment in Section 9.2. This analysis will be based on all post baseline assessments whether scheduled or unscheduled. It is possible for participants to appear in both categories (PCS-low and PCS-high) for any parameter.

All ECG data will be presented in data listings and where appropriate, assessments considered to be PCS will be noted. A separate listing of PCS ECG data will be provided.

Table 7: Potentially Clinically Significant Criteria for Electrocardiogram Data for Participants ≥ 18 Years of Age

Parameter	Value
QRS duration	≤50 msec
	>120 msec
Heart rate	Absolute value <50 bpm and decrease from baseline ≥15bpm
	Absolute value >120 bpm and increase from baseline ≥15bpm
Frederica's QTc	>450 msec or >60 msec increase from baseline

Abbreviations: bpm = beats per minute

Table 8: Potentially Clinically Significant Criteria for Electrocardiogram Data for Participants < 18 Years of Age

Parameter	Value
QRS duration	Males (6y to 8y): <63 msec Females (6y to 8y): <59 msec Males (9y to 12y): <67 msec Females (9y to 12y): <66 msec Males (13y to 17y): <78 msec Females (13y to 17y): <72 msec
	Males (6y to 8y): >98 msec Females (6y to 8y): >95 msec Males (9y to 12y): >103 msec Females (9y to 12y): >99 msec Males (13y to 17y): >111 msec Females (13y to 17y): >106 msec
Heart rate	6y to 11y: ≥140 bpm and an increase from baseline ≥15 bpm 12y to 17y: ≥120 bpm at any time postdose and an increase from baseline ≥15 bpm
	6y to 11y: ≤60 bpm at any time postdose and a decrease from baseline ≥ 15 bpm 12y to 17y: ≤50 bpm at any time postdose and a decrease from baseline ≥15 bpm
Frederica's QTc	≥440 msec or >30 msec increase from baseline

Abbreviations: bpm = beats per minute

9.7. Echocardiogram with Doppler

Echocardiography will be performed at the Screening and final visits by a qualified sonographer/physician (and over-read by a cardiologist) using a standard, commercially available ultrasound machine. All echocardiogram data will be transmitted to a standalone imaging vendor, where qualified personnel will perform postprocessing of echocardiogram data and central over-read of all images. Only the central lab data will be reported. The report includes an overall assessment of cardiac anatomy, and quantitative evaluation of basic ventricular systolic function.

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

9.8. Physical Examination

Descriptive summaries for physical examination findings (normal, abnormal, or not performed) will be presented for each body system/category at each visit starting at baseline (as defined in Section 6.1.2). For participants who had a physical examination postbaseline, shift tables for baseline to the most abnormal result postbaseline will be presented for each body system.

The supportive data listing will include the information collected (e.g., body system, result of the observation, any investigator comment).

9.9. Concomitant Medication

Medications used at any time after the first dose date will be considered concomitant; this includes medications which initially start prior to the first dose date and continue during the posttreatment period, as well as new medications which are first recorded to have been taken after the first dose date. Missing medication start date handling will be based on the methodology described in Section 6.1.10.1. Medications will be coded using WHO-DD version B3 September 1, 2019 or higher.

Concomitant medications will be summarized according to the anatomical therapeutic chemical (ATC) level-2 class and ATC level-4 class within each treatment group and overall. To count the number of participants who took a medication, a participant taking the same medication multiple times will only be counted once for that medication. Medication use will be tabulated in decreasing order of the overall number of participants who took each medication. In addition, the total number of participants to ever take any concomitant medications will be presented.

Participant medication data will be presented in data listings.

Treatment with vitamin B6 is effective in decreasing Uox in approximately 10%-30% of patients with PH1 with certain AGXT mutations, but has not been proven effective in treating other forms of PH. Given this, some participants may be taking vitamin B6 as part of their standard of care for PH. Participants taking 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. In order to

evaluate this requirement, vitamin B6 intake will be collected on a separate CRF within the database. Participant vitamin B6 intake will be presented in a data listing.

Participant fluid intake will be presented in a data listing.

9.10. Immunogenicity Assessments

Frequency counts and percentages will be tabulated for anti-drug antibodies results (Positive/Negative) at each visit starting at baseline. Descriptive statistics for titer results and for change from baseline will be presented by visit.

The primary endpoint AUC of 24-hour Uox from Day 90 to Day 180 will be summarized separately for the Positive and Negative results.

Participant anti-drug antibody testing results will be presented in a data listing. If it happens that an adequate assay cannot be developed, then no data will be reported.

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 schedule of activities. Samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. Participant anti-dsDNA antibody testing results will be presented in a data listing.

10. Changes from Planned Analysis

Not Applicable.

11. Pharmacokinetic Analysis

Analysis of the pharmacokinetic blood samples is being performed by AxoLabs. Pharmacokinetic parameters to be analyzed will be described in detail in a separate Pharmacokinetic Analysis Plan (PKAP).

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Appendix 1: [redacted] Library of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the curve
BLQ	below the limit of quantitation
BMI	body mass index
BSA	body surface area
CI	confidence intervals
CP	conditional power
CRF	case report form
CS	clinically significant
CSR	clinical study report
CT	computed tomography
DSMC	data safety monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
eGFR	estimated glomerular filtration rate
EU	European Union
FCS	fully conditional specification
FDA	food and drug administration
HR	heart rate
HRQOL	health related quality of life
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ITT	intent-to-treat
IWRS	interactive web response system
LLOQ	lower limit of quantitation
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MNAR	missing not at random
M&S	modeling and simulation
N	number
PD	pharmacodynamic
PE	physical examination
PH	primary hyperoxaluria

Abbreviation	Definition
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PP	per-protocol
PT	preferred term
QOL	quality of life
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	standard deviation
SF-36	Short form 36 health survey
SFT or SFTP	secure file transfer or secure file transfer plan
SOC	system organ class
TEAE	treatment-emergent adverse event
Uox	urinary oxalate excretion
WHO	world health organization
WHO-DD	world health organization drug dictionary

Appendix 2: Algorithm for Calculating SF-36 Scores

This protocol uses the SF-36 version 2 form (SF36v2). Scoring this form is as follows, based on the manual "How to Score version 2 of the SF-36 Health Survey" (Ware JE, et al. 2000):

Each item on the 36-item short-form health survey (SF-36) will be answered by a patient. Some of the answers will then be re-coded so that across all questions, a higher score will indicate a better health state. Question 2 (Compared to one year ago, how would you rate your health in general now?) is not used in the calculation of domain scores. Questions 3, 4, 5, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c will scored as recorded; the other scores will be transformed as follows:

- Question 1:

Original Response	1	2	3	4	5
Re-coded Response	5	4.4	3.4	2	1

- Question 6, 9a, 9d, 9e, 9h, 11b, 11d:

Original Response	1	2	3	4	5
Re-coded Response	5	4	3	2	1

- Question 7:

Original Response	1	2	3	4	5	6
Re-coded Response	6	5.4	4.2	3.1	2.2	1

- Question 8 (If Question 7 is answered):

Original Response to #8	1	1	2	3	4	5
Original Response to #7	1	2-6	1-6	1-6	1-6	1-6
Re-coded Response	6	5	4	3	2	1

- Question 8 (If Question 7 is NOT answered):

Original Response	1	2	3	4	5
Re-coded Response	6	4.75	3.5	2.25	1

The raw score for the following 8 domains will be calculated by summing the re-coded scores for the set of questions listed in the table below if all the questions within the domain are answered. If < 50% of the questions within a domain are answered, the raw score will not be calculated.

Domain	**Questions**
Physical Functioning (PF)	3a – 3j
Role limitations due to physical health (RP)	4a – 4d
Bodily Pain (BP)	7 – 8
General Health (GH)	1, 11a – 11d
Vitality (VT)	9a, 9e, 9g, 9i
Social Functioning (SF)	6, 10
Role limitations due to emotional problems (RE)	5a – 5c
Mental Health (MH)	9b, 9c, 9d, 9f, 9h

If ≥ 50% but not all of the questions are answered, the non-missing questions are re-coded (if necessary, per above) and then summed. An average score is calculated for those non-missing scores and that average score is imputed as the score to be used for the value of the missing questions. The raw score is then calculated as the sum of all the questions in the domain. For example, for the vitality domain, if questions 9a, 9e, and 9g are answered but question 9i is missing, the algorithm will proceed as followed from left to right:

Question	**Recoded Response**	**Re-coded Response**	**Average of non-missing scores**	**Average imputed for missing responses**	**Raw Score**
9a	2	4	= (4 + 2 + 5) / 3 = 3.666…	4	= 4 + 2 + 5 + 3.666.. = 14.666…
9e	4	2		2	
9g	5	5		5	
9i	Missing	Missing		3.666…	

After the raw score is calculated, it is then converted into a normalized score (on a scale of 0 to 100) using the following transformation:

$$Normalized\ Domain\ Score = \frac{Raw\ Score - Lowest\ Possible\ Raw\ Score}{Possible\ Raw\ Score\ Range} * 100$$

The normalized domain scores will then be standardized using the following formula:

$$Standardized\ Domain\ Score = \frac{Normalized\ Score - a}{b}$$

The lowest possible raw score, possible raw score range, (a) values, and (b) values for each domain are as follows:

Domain	Lowest Possible Raw Score	Possible Raw Score Range	a	b
Physical Functioning (PF)	10	20	82.62455	24.43176
Role limitations due to physical health (RP)	4	16	82.65109	26.19282
Bodily Pain (BP)	2	10	73.86999	24.00884
General Health (GH)	5	20	70.78372	21.28902
Vitality (VT)	4	16	58.41968	20.87823
Social Functioning (SF)	2	8	85.11568	23.24464
Role limitations due to emotional problems (RE)	3	12	87.50009	22.01216
Mental Health (MH)	5	20	75.76034	18.04746

The two raw component scores will be calculated based on multiplying each standardized domain score by a constant, and then adding the 8 domains together. The constants to use for the two component scores are as follows:

Domain	Physical Component Summary (PCS)	Mental Component Summary (MCS)
Physical Functioning (PF)	0.42402	-0.22999
Role limitations due to physical health (RP)	0.35119	-0.12329
Bodily Pain (BP)	0.31754	-0.09731
General Health (GH)	0.24954	-0.01571
Vitality (VT)	0.02877	0.23534
Social Functioning (SF)	-0.00753	0.26876
Role limitations due to emotional problems (RE)	-0.19206	0.43407
Mental Health (MH)	-0.22069	0.48581

The norm-based scores for the two component summaries will then be calculated by multiplying the raw score by 10 and adding 50.

The norm-based scores for the 8 individual domains will be calculated by multiplying the standardized domains score by 10 and adding 50.

The norm-based scores will be used in the analyses.

Major Protocol Deviation List			
Deviation Category	**Deviation Description**	**Date Deviation Added**	**Exclude from Per Protocol Population**
Informed consent criteria	Subject did not sign informed consent before the initiation of study procedures (including deviations regarding protected health information / data protection forms (e.g. PHI, PIPEDA etc.)	16 Mar 2021	No
Eligibility criteria	**Subject was randomized without meeting one or more entry criteria** 1. Genetically confirmed PH 2. Uox >0.7 3. Less than 20% variation in Ucr 4. eGFR >30 5. Agree to use contraception and not pregnant 6. Prior renal/liver transplant 7. Dialysis 8. Pox>30 9. Systemic oxalosis 10. Intercurrent illness 11. Active liver disease 12. Alcohol/Drug of abuse intake 13. Serious mental illness 14. Relevant history of disorders including dermatitis and connective tissue disorder	16 Mar 2021	1. Genetically confirmed PH -Yes, those not confirmed with PH should be excluded 2. Uox <0.7 should be excluded - Yes 3. More than 20% variation in Ucr should be excluded- Yes 4. eGFR <30 should be excluded- Yes 5. Agree to use contraception and not pregnant – No 6. Prior renal/liver transplant should be excluded- Yes 7. Dialysis should be excluded - Yes 8. Participants with Pox>30 should be excluded- Yes 9. If they have Systemic oxalosis should be excluded - Yes 10. Intercurrent illness - No 11. Active liver disease - No 12. Alcohol/Drug of abuse intake – No 13. Serious mental illness- No need to exclude if not affecting urine collection 14. Relevant history of disorders including dermatitis and connective tissue disorder - No

Deviation Category	Deviation Description	Date Deviation Added	Exclude from Per Protocol Population
Eligibility criteria (continued)	15. Use of RNAi in past 6 months 16. Prior history of reaction to RNAi 17. Pyridoxine dose not stable for 4 weeks prior to enrolment 18. Clinical study participation in the past 4 months (if related to Uox need to return to baseline) 19. LFT abnormalities 20. Positive viral screen 21. Positive drug screen 22. Hypersensitivity to DCR-PHXC 23. Unwilling to comply with section 5.3 – vitamin C intake, follow standard of care, refrain from exercise, avoid oxalate rich foods	16 Mar 2021	15. Use of RNAi in past 6 months – No not unless it is Lumasiran 16. Prior history of reaction to RNAi – No, as long as no reaction is noted during the study 17. Those whose Pyridoxine dose was not stable for 4 weeks prior to enrolment should be excluded - Yes 18. Clinical study participation in the past 4 months (if related to Uox need to return to baseline) – Yes if participant did not have Uox back at baseline it should be excluded 19. LFT abnormalities - No 20. Positive viral screen - No 21. Positive drug screen - No 22. Hypersensitivity to DCR-PHXC- Yes participant should be excluded as study drug may not be effective 23. Unwilling to comply with section 5.3 – vitamin C intake, follow standard of care, refrain from exercise, avoid oxalate rich foods – Yes participants who are not compliant should be excluded
IP criteria	Patient received and dosed incorrect drug	16 Mar 2021	Yes (if subject received less than 5 or more than 7 doses)
IP criteria	Subject received IP despite failure to adhere to the storage, preparation, or handling of study drug according to the protocol and assessed as non-acceptable by quality assurance	16 Mar 2021	Yes (if more than 1 dose is affected and assessed as non-acceptable by QA).

Deviation Category	Deviation Description	Date Deviation Added	Exclude from Per Protocol Population
IP Criteria	Subject received IP despite discontinuation or withdrawal criteria	16 Mar 2021	No
Concomitant medication criteria	The subject used prohibited concomitant medications or therapies	16 Mar 2021	Yes, for medications that can affect efficacy (e.g. Lumasiran, vitamin C) No, for medications that can affect safety (e.g. acetaminophen)
Efficacy evaluation criteria	Subject is missing 2 or greater Uox assessments during the period from day 90 to day 180 Subject is missing 3 Uox assessments in a row at any given point	16 Mar 2021	Yes
Efficacy evaluation criteria	Subject has greater than 20% variance in 2 or greater Uox assessments during the period from day 90 to day 180 Subject has greater than 20% creatinine variance in 3 Uox assessments in a row	16 Mar 2021	Yes
Efficacy evaluation criteria	Subject did not collect 24 hour urine for full 24 hours and did not perform a repeat for 2 timepoints between day 90 to day 180 or 3 times in a row	16 Mar 2021	Yes
Safety monitoring	Subject is a child-bearing female who missed a pregnancy test prior to dosing and was pregnant on the subsequent pregnancy test.	16 Mar 2021	No

Deviation Category	Deviation Description	Date Deviation Added	Exclude from Per Protocol Population
Safety reporting	Subject's SAE was reported late or was not reported	16 Sep 2020	No
Other criteria	The subject or site was accidentally unblinded to the subject's treatment information during the study.	16 Sep 2020	Yes
Other criteria	Any deviations that constitute fraud, scientific misconduct or Serious Breach will be classified as major.	16 Sep 2020	Yes

Version History

Version No.	Version Date	Description of Change
1.0	16-Mar-2021	Initial version of the Major Clinical Protocol Deviation List

Signatures of Approval:

Clinical Lead: [redacted] Date [redacted]

Signature [redacted]

Medical Monitor: [redacted] Date [redacted]

Signature [redacted]

Biostatistician: [redacted] Date [redacted]

Signature [redacted]