

**Clinical trial results:****A Phase 1 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Dose of DCR-PHXC in Patients with Primary Hyperoxaluria Type 3****Summary**

EudraCT number	2020-000344-67
Trial protocol	GB DE FR NL
Global end of trial date	07 September 2021

**Results information**

Result version number	v1 (current)
This version publication date	24 August 2022
First version publication date	24 August 2022

**Trial information****Trial identification**

Sponsor protocol code	DCR-PHXC-104
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Dicerna Pharmaceuticals, Inc.
Sponsor organisation address	75 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Andrew Henderson, Dicerna Pharmaceuticals, Inc., 001 617 612 6275, ahenderson@dicerna.com
Scientific contact	Andrew Henderson, Dicerna Pharmaceuticals, Inc., 001 617 612 6275, ahenderson@dicerna.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002493-PIP01-18
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2021
Global end of trial reached?	Yes
Global end of trial date	07 September 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of a single dose of nedosiran (DCR-PHXC) in patients with PH3

Protection of trial subjects:

The Investigator or their representative explained the nature of the study to the participant or their legally authorized representative and answered all questions regarding the study.

Participants were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the institutional review board/independent ethics committee or study center.

The medical record included a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent also signed the informed consent form (ICF).

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

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	6
EEA total number of subjects	2

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The screening period lasted up to 35 days (with an extra 7-day period for participants who were required to repeat screening 24-hour urine collections or initially unanalyzable screening laboratory assessment samples)

### Period 1

Period 1 title	Screening Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nedosiran
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nedosiran
Investigational medicinal product code	
Other name	DCR-PHXC, nedosiran sodium, DCR-L1360
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of nedosiran was given on Day 1 to those randomized to the nedosiran arm through subcutaneous injection (thigh or abdomen).

No nedosiran was administered during the Screening Period or the Follow-up Period.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	sterile saline, normal saline, saline
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.9% saline for injection was given on Day 1 to those randomized to the placebo arm through subcutaneous injection (thigh or abdomen).

No placebo was administered during the Screening Period or the Follow-up Period.

<b>Number of subjects in period 1</b>	Nedosiran	Placebo
Started	4	2
Completed	4	2

## Period 2

Period 2 title	Dosing Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

### Blinding implementation details:

All participants were centrally assigned to randomized study intervention using an interactive web response system.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nedosiran
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nedosiran
Investigational medicinal product code	
Other name	DCR-PHXC, nedosiran sodium, DCR-L1360
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

Sterile formulation of drug substance (DCR-L1360) was provided in water for injection at 170 mg/mL sodium salt (free acid equivalent [FAE] 160 mg/mL). A single dose of nedosiran was given on Day 1 to those randomized to the nedosiran arm through subcutaneous injection (thigh or abdomen) at the following dose levels:

Age ≥ 12 years: 3 mg/kg (FAE 2.8 mg/kg)

Age 6-11 years: 3.5 mg/kg (FAE 3.3 mg/kg), not to exceed 136 mg

The maximum volume of a single SC injection was 1.0 mL in participants ≥ 12 years; if the participant's weight required an injection volume > 1.0 mL, the total dose was administered as 2 or more SC injections of equal volume. The maximum injection volume in participants aged less than 12 years was 0.5 mL; if the participant's weight required an injection volume > 0.5 mL, the total dose was administered as 2 or more SC injections of equal volume.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	sterile saline, normal saline, saline
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

A single dose of 0.9% saline for injection was given on Day 1 through subcutaneous injection (thigh or abdomen), at a volume to match the active drug.

<b>Number of subjects in period 2</b>	Nedosiran	Placebo
Started	4	2
Completed	4	2

<b>Period 3</b>	
Period 3 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

<b>Arms</b>	
Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nedosiran
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nedosiran
Investigational medicinal product code	
Other name	DCR-PHXC, nedosiran sodium, DCR-L1360
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

A single dose of nedosiran was given on Day 1 to those randomized to the nedosiran arm through subcutaneous injection (thigh or abdomen).

No nedosiran was administered during the Screening Period or the Follow-up Period.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	0.9% saline
Investigational medicinal product code	
Other name	sterile saline, normal saline, saline
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

A single dose of 0.9% saline for injection was given on Day 1 to those randomized to the placebo arm through subcutaneous injection (thigh or abdomen).

No placebo was administered during the Screening Period or the Follow-up Period.

<b>Number of subjects in period 3</b>	Nedosiran	Placebo
Started	4	2
Completed	4	2

## Baseline characteristics

### Reporting groups

Reporting group title	Nedosiran
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Nedosiran	Placebo	Total
Number of subjects	4	2	6
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	4	1	5
Age continuous Units: years			
arithmetic mean	44.8	38.0	
standard deviation	± 13.60	± 36.77	-
Gender categorical Units: Subjects			
Female	2	0	2
Male	2	2	4
Baseline 24-hour urinary oxalate Units: mmol/day			
arithmetic mean	1.302	1.018	
standard deviation	± 0.6026	± 0.0753	-

## End points

### End points reporting groups

Reporting group title	Nedosiran
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Nedosiran
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Nedosiran
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety Population - Nedosiran
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received a partial or full dose of nedosiran on Day 1	
Subject analysis set title	Safety Population - Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received a partial or full dose of placebo on Day 1	
Subject analysis set title	PK Population - Nedosiran
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received a full dose of nedosiran and had at least one evaluable postdose PK assessment	
Subject analysis set title	mITT Population - Nedosiran
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All participants who were randomly assigned to nedosiran, received a partial or full dose of nedosiran, and had postdose 24-hour urinary oxalate (Uox) values on at least 2 consecutive visits	
Subject analysis set title	mITT Population - Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All participants who were randomly assigned to placebo, received a partial or full dose of placebo, and had postdose 24-hour urinary oxalate (Uox) values on at least 2 consecutive visits	

### **Primary: Incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)**

End point title	Incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) <sup>[1]</sup>
End point description: Injection site reactions were considered AESIs. Signs or symptoms at the injection site with a time to onset of 4 hours (or more) postdose were evaluated according to the CTCAE v. 5.0 criteria. All TEAEs were mild in severity.	
End point type	Primary
End point timeframe: Day 1 to End of Study	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint refers to a count of participants and/or events, for which no statistical analyses are required.

<b>End point values</b>	Safety Population - Nedosiran	Safety Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: events				
TEAEs	6	5		
SAEs	0	0		
AESIs	0	0		

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with clinically relevant clinical laboratory test results, including hematology, serum chemistry, and urinalysis

End point title	Number of participants with clinically relevant clinical laboratory test results, including hematology, serum chemistry, and urinalysis <sup>[2]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Screening to End of Study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint refers to a count of participants and/or events, for which no statistical analyses are required.

<b>End point values</b>	Safety Population - Nedosiran	Safety Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: participants	0	0		

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with clinically significant vital signs measurements

End point title	Number of participants with clinically significant vital signs measurements <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Screening to End of Study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint refers to a count of participants and/or events, for which no statistical analyses are required.

End point values	Safety Population - Nedosiran	Safety Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: participants	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with clinically significant 12-lead electrocardiogram findings

End point title	Number of participants with clinically significant 12-lead electrocardiogram findings <sup>[4]</sup>
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End point description:

One participant in the nedosiran group had a potentially clinically significant ECG finding of a high QTcF interval of 452.0 msec at Day 85. Although the Baseline ECG was normal with a QTcF of 426 msec, the Screening ECG had a high QTcF of 455 msec, suggesting no significant change after nedosiran treatment.

No other potentially clinically significant ECG findings were reported.

End point type	Primary
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End point timeframe:

Screening to End of Study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint refers to a count of participants and/or events, for which no statistical analyses are required.

End point values	Safety Population - Nedosiran	Safety Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: participants	1	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Incidence and nature of treatment-emergent clinically significant physical examination findings

End point title	Incidence and nature of treatment-emergent clinically significant physical examination findings <sup>[5]</sup>
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End point description:

One participant in the nedosiran group had a clinically significant abnormal physical examination finding of tenderness in back in right kidney region, which was reported as a TEAE.

End point type	Primary
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End point timeframe:

Day 1 to End of Study

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint refers to a count of participants and/or events, for which no statistical analyses are required.

End point values	Safety Population - Nedosiran	Safety Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: participants	1	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PK parameters of nedosiran: C(max)

End point title	Plasma PK parameters of nedosiran: C(max)
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End point description:

PK samples taken predose on Day 1, then postdose (h): 0.5, 2, 10, 24, 360 (Day 15), 696 (Day 29)

End point type	Secondary
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End point timeframe:

Day 1 (predose) to Day 29 postdose

End point values	PK Population - Nedosiran			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ng/mL				
arithmetic mean (standard deviation)	615 (± 295)			

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Plasma PK parameters of nedosiran: AUC(0-24) and AUC(0-last)**

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End point title	Plasma PK parameters of nedosiran: AUC(0-24) and AUC(0-last)
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End point description:

PK samples taken predose on Day 1, then postdose (h): 0.5, 2, 10, 24, 360 (Day 15), 696 (Day 29)

End point type	Secondary
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End point timeframe:

Day 1 (predose) to Day 29 postdose

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End point values	PK Population - Nedosiran			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: h.ng/mL				
arithmetic mean (standard deviation)				
AUC(0-24)	9560 ( $\pm$ 4440)			
AUC(0-last)	12700 ( $\pm$ 10700)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: The proportion of participants achieving a > 30% decrease from baseline in 24-hour urinary oxalate on 2 consecutive visits**

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End point title	The proportion of participants achieving a > 30% decrease from baseline in 24-hour urinary oxalate on 2 consecutive visits
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End point description:

24-hour urinary oxalate measurements taken at Study Days 29, 43, 57, and 85 (End of Study).

End point type	Secondary
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End point timeframe:

Baseline (Screening) to End of Study

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End point values	mITT Population - Nedosiran	mITT Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	2		
Units: participants	0	0		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Signing of the informed consent form (Screening) to End of Study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

Reporting group title	Nedosiran
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

<b>Serious adverse events</b>	Nedosiran	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Nedosiran	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	2 / 2 (100.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Scar pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	3	
Renal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2020	v 2.0 (Amendment 1): The 27 February 2020 version of the protocol was updated to incorporate changes to the dosing regimen for 6- to 11-year-old children and to allow for some scheduled study visits to be conducted as telemedicine visits supported by a home health nurse.
13 August 2020	v 3.0 (Amendment 2): The 27 April 2020 version of the protocol was updated to include the dosing regimen for 6-to-11-year-old children based upon modeling and simulation, to update the total blood volume collected, to perform pregnancy testing at Day 57, to perform urinary creatinine testing at Day 43, to remove the exclusion and concomitant therapy criterion related to routine or chronic use of more than 3 grams of acetaminophen/paracetamol daily, and to update the statistical analyses populations. Other administrative changes were also incorporated.
24 September 2020	v 4.0 (Amendment 3): The 13 August 2020 version of the protocol was revised to update the exclusion criterion regarding previous IMP administration, add study interruption and stopping rules, remove the drug screen exclusion criterion, add an inclusion criterion requiring participants to be affiliated with or a beneficiary of a health insurance system (if applicable per national regulations), and add text to clarify that the investigator is obligated to anticipate and address injection site pain.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported