Clinical trial results:
A Phase 1 Study of DCR-PH1 in Patients with Primary Hyperoxaluria Type 1 (PH1)

Summary

EudraCT number	2015-003142-51
Trial protocol	GB NL
Global end of trial date	14 October 2016

Results information

Result version number	v1 (current)
This version publication date	20 October 2017
First version publication date	20 October 2017

Trial information

Trial identification

Sponsor protocol code	DCR-PH1-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Orphan drug designation number: EU/3/15/1528, IND: 122598

Notes:

Sponsors

Sponsor organisation name	Dicerna Pharmaceuticals, Inc.
Sponsor organisation address	87 Cambridgepark Drive, Cambridge, United States, MA 02140
Public contact	Ralf Rosskamp, Chief Medical Officer, Dicerna Pharmaceuticals, Inc., 001 6176126270, rrosskamp@dicerna.com
Scientific contact	Ralf Rosskamp, Chief Medical Officer, Dicerna Pharmaceuticals, Inc., 001 6176126270, rrosskamp@dicerna.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	14 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of DCR-PH1 administered via IV infusion to patients with PH1.

Protection of trial subjects:

This study was conducted in compliance with the protocol, with Dicerna's and/or designee's SOPs and/or guidelines, the US Food and Drug Administration (FDA) regulations, with the ICH GCP guidelines and with the Declaration of Helsinki.

The study design included measures to minimize the possibility of adverse reactions to the investigational product based on previous experiences with oligonucleotide LNP formulations. Appropriate safety monitoring was performed and emergency medical care was available during the conduct and follow-up of the dosing. Patients were instructed to be premedicated with dexamethasone, diphenhydramine, and an H2 blocker (e.g. famotidine, ranitidine) 60 minutes prior to the start of DCR-PH1 infusion. Patients were carefully observed for a minimum of 8 hours following completion of the first administration of study drug (Day 1) for evidence of any TEAEs, and for collection of PK and PD assessments. Patients were monitored throughout the infusion and until 30 minutes after the end of the infusion for Infusion-Related Reactions (IRR). A dose escalation design, with staggered enrollment and treatment of patients within the dose group, was utilized to ensure patient safety.

Background therapy:

Vitamin B6 doses ranged from 400 mg to 800 mg daily; no subjects changed the dose of vitamin B6 during their participation in the study.

Evidence for comparator:

N/A

Actual start date of recruitment	13 May 2016
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: 3
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	0
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was designed to enroll patients with mild to moderate renal insufficiency with a key inclusion criterion the burden of renal desease. First subject first visit was on 13 May 2016.

Pre-assignment

Screening details:

Male or female, at least 12 years of age at the time of obtaining informed consent with diagnosis of PH1, confirmed by genotyping for homozygosity or compound heterozygosity in the AGXT (the gene that encodes AGT) gene (historically available genotype information was accepted for study eligibility).

Period 1

Period 1 title	Part A (SAD) portion (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DCR-PH1, 0.05 mg/kg

Arm description:

Cohort 1: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.05 mg/kg DCR-PH1 administered by IV infusion

Arm type	Experimental
Investigational medicinal product name	DCR-PH1
Investigational medicinal product code	DCR-PH1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DCR-PH1 was provided by the sponsor formulated as a sterile, preservative-free liquid for IV injection, in 20-mL single-use glass vials with 40 mg of drug product per vial (2 mg/mL). DCR-PH1 was administered on Day 1, as a continuous IV infusion over approximately 2 hours via a peripheral or central IV catheter following a 1-2-3 rule. During the first 30 minutes, the infusion rate was approximately 1 mL/min, followed by 2 mL/min during the second half of the first hour of infusion. The remaining amount was infused at a rate of no less than 3 mL/min during the second hour of the infusion. The lot number of the drug used was L00205.

Arm title	DCR-PH1, 0.1 mg/kg

Arm description:

Cohort 2: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.1 mg/kg DCR-PH1 administered by IV infusion

Arm type	Experimental
Investigational medicinal product name	DCR-PH1
Investigational medicinal product code	DCR-PH1
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DCR-PH1 was provided by the sponsor formulated as a sterile, preservative-free liquid for IV injection, in 20-mL single-use glass vials with 40 mg of drug product per vial (2 mg/mL). DCR-PH1 was administered on Day 1, as a continuous IV infusion over approximately 2 hours via a peripheral or central IV catheter following a 1-2-3 rule. During the first 30 minutes, the infusion rate was approximately 1 mL/min, followed by 2 mL/min during the second half of the first hour of infusion. The

remaining amount was infused at a rate of no less than 3 mL/min during the second hour of the infusion. The lot number of the drug used was L00205.

Number of subjects in period 1	DCR-PH1, 0.05 mg/kg	DCR-PH1, 0.1 mg/kg
Started	2	2
Completed	2	2

Baseline characteristics

Reporting groups	
Reporting group title	DCR-PH1, 0.05 mg/kg
Reporting group description:	
Cohort 1: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.05 mg/kg DCR-PH1 administered by IV infusion	
Reporting group title	DCR-PH1, 0.1 mg/kg
Reporting group description:	
Cohort 2: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.1 mg/kg DCR-PH1 administered by IV infusion	

Reporting group values	DCR-PH1, 0.05 mg/kg	DCR-PH1, 0.1 mg/kg	Total
Number of subjects	2	2	4
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	4
Gender categorical Units: Subjects			
Male	2	2	4

End points

End points reporting groups

Reporting group title	DCR-PH1, 0.05 mg/kg
Reporting group description:	
Cohort 1: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.05 mg/kg DCR-PH1 administered by IV infusion	
Reporting group title	DCR-PH1, 0.1 mg/kg
Reporting group description:	
Cohort 2: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.1 mg/kg DCR-PH1 administered by IV infusion	

Primary: Safety and tolerability as determined by number of subjects with adverse events

End point title	Safety and tolerability as determined by number of subjects with adverse events[1]
End point description:	
PK plasma samples collected: Before DCR-PH1 administration on Day 1, approximately at 60 min after the start of infusion, at the end of infusion; at 30, 120, 240, 360 and 480 min after end of infusion; at Days 2, 3, 8 (±1 day), 15 (±1 d), 22 (±1 d), 29 (±1 d). Blood sample collection for pharmacodynamic analysis (oxalate, glycolate) collected on Day 1, Day 15 (±1 d), Day 22 (±1 d) and end of trial - Day 29 (±1 d). Urine samples collected: Scr (BL), days 8(±1 day), 15(±1 d), 22 (±1 d)	
End point type	Primary
End point timeframe:	
Day 1 through EOS or Day 29 (±1 day).	
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: Due to the early termination of the study and small number of subjects enrolled, no statistical analysis was performed.	

End point values	DCR-PH1, 0.05 mg/kg	DCR-PH1, 0.1 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: number of subjects with adverse events	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for AEs from Day 1 through the EOS visit.

Adverse event reporting additional description:

Safety assessments included recording of all adverse events (AEs), vital sign measurements, physical examinations, laboratory test results. AE's were mild to moderate and no dose limiting toxicities were reported. All safety laboratory results were reported to be within grade 0 to grade 1.
No SAEs were reported during the conduct of the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	DCR-PH1, 0.05 mg/kg

Reporting group description:

Cohort 1: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.05 mg/kg DCR-PH1 administered by IV infusion

Reporting group title	DCR-PH1, 0.1 mg/kg

Reporting group description:

Cohort 2: Subjects enrolled in Part A (SAD portion) were to receive a single dose of 0.1 mg/kg DCR-PH1 administered by IV infusion

Serious adverse events	DCR-PH1, 0.05 mg/kg	DCR-PH1, 0.1 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (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: 5 %

Non-serious adverse events	DCR-PH1, 0.05 mg/kg	DCR-PH1, 0.1 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	2 / 2 (100.00%)	
Injury, poisoning and procedural complications			
Burns first degree			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Glossitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Fracture pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (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? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported