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

Published: 07-02-2019
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Primary:To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden in patients with PH (types 1 and 2)Key Secondary:To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden over time in patients with PHSecondary:1. To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49278

Source
ToetsingOnline

Brief title
DCR-PHXC-201 (PHYOX 2)

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Renal disorders (excl nephropathies)

Synonym
Hyperoxaluria, Primary Hyperoxaluria

Research involving
Human

Sponsors and support

Primary sponsor: Dicerna Pharmaceuticals Inc
Source(s) of monetary or material Support: Dicerna Pharmaceuticals Inc

Intervention

Keyword: Carbohydrate Metabolism, Inborn Errors, Kidney Diseases, Primary Hyperoxaluria

Outcome measures

Primary outcome

Primary End point:

The proportion of participants with a reduction from baseline in 24-hour Uox of

at least 70%, based on a AUC and/or reaching normalization or

near-normalization of 24-hour Uox on at least 2 consecutive visits, starting

from Day 90. Normalization of Uox is defined as < 0.46 mmol/24 hours;

near-normalization is defined as * 0.46 to < 0.60 mmol/24 hours (values

adjusted per 1.73 m2 BSA in participants aged < 18 years).

Secondary outcome

Key Secondary Endpoint:

AUC from Day 90 to Day 180, based on percent change from Baseline in 24-hour Uox

Secondary Endpoints:

1. Percent change in the summed surface area and number of kidney stones

identified via kidney ultrasound from Baseline to Day 180

2. Percent change in plasma oxalate from Baseline to Day 180 (for adults only)

3. Rate of change in eGFR from Baseline to Day 180

4. AE and SAE; change from Baseline in 12-lead ECG, physical examination findings, vital signs, and clinical laboratory tests

5. Population and individual PK parameters for DCR-PHXC

Exploratory Endpoints

1. Number of stone events over a 6-month period

2. TWS AUC of 24-hour Uox from Day 1 to Day 180, based on percent change from Baseline

3. Percent change in 24-hour Uox from Baseline to Day 180

4. TWS AUC of 24-hour urinary oxalate-to-creatinine ratio from Day 90 to Day 180, based on percent change from Baseline

5. Change from Baseline to Day 180 in the SF-36 and EQ-5D--5L in adults; and in the PedsQL* in children

6. Uox in spot urine and 24-hour urine

Study description

Background summary

DCR-PHXC consists of the drug substance (DCR-L1360), a synthetic double-stranded (hybridized duplex) ribonucleic acid (RNA) oligonucleotide conjugated to N-acetyl-D-galactosamine (GalNAc) amino-sugar residues, as a sterile solution in water for injection (WFI). DCR-PHXC is designed to selectively reduce LDHA messenger ribonucleic acid (mRNA) and lactate dehydrogenase (LDH) activity in the liver, and subsequently decrease liver oxalate production. DCR-PHXC is being developed as a treatment for PH, an ultra-rare autosomal recessive disease characterized by excessive production of oxalate in the liver.
The proposed study is designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of DCR-PHXC versus placebo in patients with PH1 and

PH2.

Study objective

Primary:
To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden in patients with PH (types 1 and 2)

Key Secondary:
To assess the efficacy of DCR-PHXC in reducing urinary oxalate burden over time in patients with PH

Secondary:
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 PK of DCR-PHXC in patients with PH

Tertiary/Exploratory:
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 in patients with PH over 6 months
3. To assess the efficacy of DCR-PHXC in reducing Uox in patients with PH at month 6
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 QoL Assessments in patients with PH
6. To evaluate the relationship between Uox spot urine and 24-hour urine measurement in patients with PH

Study design

This is a 6-month, randomized, placebo-controlled, double-blind study of DCR-PHXC in patients with primary hyperoxaluria (PH1 and PH2). Potential participants are screened over an up-to-6-week period prior to randomization to DCR-PHXC or placebo.Approximately 40 participants will be screened to achieve 36 evaluable participants.

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

The total time on study for each participant is approximately 7 months.

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

A DSMC will be convened to provide periodic review of the efficacy and safety data. The DSMC will consist of 3 voting members who are independent of the study team and Sponsor.

Intervention

DCR-PHXC is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to a GalNAc ligand. DCR-PHXC is a pale yellow, sterile solution of the siRNA (DCR-L1360) at a concentration of 170 mg/mL in water for injection (WFI).
DCR-PHXC is administered monthly as a SC injection into the abdomen or thigh. The dose of DCR-PHXC in adults and in adolescents (12-17 years old) weighing at least 50 kg will be 170 mg. For adolescents weighing less than 50 kg, the dose will be 136 mg. In children aged 6 to 11 years of age, the dose of DCR-PHXC will be determined from ongoing review of pharmacokinetic (PK) and pharmacodynamic (PD) data via a Modelling and Simulation (M&S) approach. The placebo comparator is a sterile, preservative-free normal saline 0.9% solution for subcutaneous (SC) injection, which is of similar osmolality to the DCR-PHXC formulation. Placebo will be administered as a SC injection in the thigh or abdomen in a volume equivalent to the dose of DCR-PHXC.

Study burden and risks

In studies with other drugs of the same class as the study drug, there have been events such as a release of immune substances called a cytokine release, a response of the body to injuries, resulting in inflammation, mild reddening, soreness, itching, or swelling at the place where the study treatment was injected (called injection site reactions), and elevated liver enzymes may be indicative of abnormalities of the liver.

Other symptoms that patients may develop are fatigue, nausea, vomiting, abdominal pain or tenderness around the liver, fever, or rash. Patients may also have general muscle pain or weakness from the study drug.

Observations from older drugs of the same class as the study drug have been changes in blood clotting, a reduction in blood platelets (called thrombocytopenia), and mild or moderate abnormalities of the liver. The study drug used in this research may have risks that are not well-known or understood. Therefore, there may be other risks that are not yet known.

Please refer to Protocol Section 2.3.3.Known Potential Benefits and 2.3.5. Overall Risk-Benefit Analysis for the possible benefits of the participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Key inclusion criteria:
- 24-hour Uox excretion * *0.7 mmol (adjusted per 1.73 m2 body surface area [BSA] in participants < 18 years of age) in both collections performed in the screening period. Of the first 24 participants enrolled, at least 12 (50%) must have at least one 24 hour Uox excretion * 1.6 mmol (adjusted per 1.73 m2 BSA in

participants aged < 18 years).
- Less than 20% variation between the two 24-hour urinary creatinine excretion values [mmol/24 hr/kg] derived from the two 24-hour urine collections in the screening period.
- Estimated GFR at screening * 30 mL/min normalized to 1.73 m2 BSA, calculated using the CKD-EPI formula in participants aged * 18 years or the 2012 multivariate equation by Schwartz in participants aged 6 to 17 years.

Exclusion criteria

Key exclusion criteria:
- Prior renal or hepatic transplantation; or planned transplantation within the study period
- Currently receiving dialysis or anticipating requirement for dialysis during the study period
- Plasma oxalate > 30 *mol/L
- Documented evidence of clinical manifestations of systemic oxalosis (including pre-existing retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations).
- Liver function test (LFT) abnormalities: Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 times upper limit of normal (ULN) for age and gender.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	26-08-2020
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	07-02-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	10-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003098-91-NL
CCMO	NL68734.000.19