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

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Primary objective:To evaluate the safety and tolerability of a single dose of DCR-PHXC in patients with PH3Secondary objectives:To characterize the plasma PK of a single dose of DCR-PHXC in patients with PH3To assess the efficacy of a single dose of...

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

Summary

ID

NL-OMON49809

Source
ToetsingOnline

Brief title
PHYOX4 Study

Condition

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

Synonym
Hyperoxaluria, PH3

Research involving
Human

Sponsors and support

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

Intervention

Keyword: DCR-PHXC, Primary Hyperoxaluria Type 3, Safety, Tolerability

Outcome measures

Primary outcome

• Incidence and severity of treatment-emergent AEs, SAEs, and AESI

• Changes from baseline in clinical laboratory test results, including

hematology, serum chemistry, and urinalysis

• Changes from baseline in vital signs measurements

• Changes from baseline in 12-lead ECG findings

• Incidence and nature of treatment-emergent clinically significant physical

examination findings

All the primary end points will be evaluated from baseline to end of study.

Secondary outcome

1. Plasma PK parameters of DCR-PHXC and its metabolites, including Cmax,

AUC(0-t), and AUC(0-inf), if estimable

2. The proportion of participants achieving a > 30% decrease from baseline in

24-hour Uox on 2 consecutive visits

Study description

Background summary

Primary hyperoxaluria type 3 was first genetically characterized in 2010. Approximately 50% to 65% of individuals with PH3 present with a stone prior to the age of 5. Although the frequency and severity of stone activity appear to abate in adolescence and adulthood, stone formation can occur throughout life.

Nephrocalcinosis has been reported only occasionally in individuals with PH3. Over time, kidney function may become compromised from frequent stones and/or nephrocalcinosis, resulting in chronic kidney disease (CKD). Kidney function does appear to remain better preserved among individuals with PH3 compared with those with PH1 or PH2.To date, only one individual with PH3 has been reported to progress to end-stage renal disease (ESRD). In this 8-year-old patient, stone removal procedures and urinary tract obstruction may have contributed to the loss of kidney function.

At present, no therapies are approved by regulatory authorities for the treatment of patients with PH3. A number of supportive therapies are used in an attempt to mitigate some of the effects of the disease. Current medical management before renal failure develops is underpinned by hyperhydration, with fluid intake recommendations of at least 3 liters per day per square meter of BSA, e.g., 5 L/day for a 70-kg adult. These regimens can be problematic in infants and toddlers, necessitating placement of a gastrostomy tube to ensure adequate nighttime fluid administration. Affected patients are at considerable risk of serious complications during periods of increased fluid loss (fever, diarrhea/vomiting, and urinary tract infections) or when oral hydration is compromised (following surgical procedures). Oral potassium citrate administration is used to inhibit crystallization and alkalinize the urine.

Study objective

Primary objective:
To evaluate the safety and tolerability of a single dose of DCR-PHXC in patients with PH3

Secondary objectives:
To characterize the plasma PK of a single dose of DCR-PHXC in patients with PH3
To assess the efficacy of a single dose of DCR PHXC in reducing oxalate burden in patients with PH3

Study design

A placebo-controlled, double-blind, multicenter study

Intervention

single dose of DCR-PHXC

Study burden and risks

At present, no therapies are approved for the treatment of PH. DCR-PHXC is being evaluated in 5 ongoing studies in healthy volunteers (HV) and patients with PH1 or PH2. No significant safety findings have emerged from these ongoing studies. DCR-PHXC has been well tolerated by both healthy volunteers and participants with PH1 and PH2

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.

Side effects observed to date in a completed and ongoing phase I studies with DCR-PHXC in healthy volunteers and PH patients.
In the completed phase I study the majority of side effects were mild and disappeared without treatment. There were no severe side effects which were attributed to taking the study drug.
The following side effects have been reported in participating subjects receiving DCR-PHXC:
• an injection site reaction: mild reddening, sensitive/painful feeling, itching or swelling at the place where the study drug was injected;
• gastrointestinal symptoms: nausea, vomiting, abdominal pain, or sensitivity round the liver;
• urological symptoms: frequent urination;
• other symptoms such as: fatigue, fever, rash, back pain/kidney pain, headache, lack of energy, menstrual pain, prickling feeling of the skin of the lower abdomen, sniffling (nose), earache, nosebleed.

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

1. At least 6 years of age at the time of signing the informed consent/assent
Type of Participant and Disease Characteristics
2. Documented diagnosis of PH3, confirmed by genotyping (historically available genotype information is acceptable for study eligibility)
3. 24-hour Uox excretion >= 0.7 mmol (adjusted per 1.73 m2 BSA in participants < 18 years of age) in both collections performed in the screening period

The full list of inclusion criteria is provided in the EudraCT Application Form

(and the research protocol)

Exclusion criteria

1. Prior renal or hepatic transplantation; or planned transplantation within the study period
2. Currently receiving dialysis or anticipating requirement for dialysis during the study period
3. Plasma oxalate > 30 µmol/L

The full list of exclusion criteria is provided in the EudraCT Application Form (and the research protocol)

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2020
Enrollment:	2
Type:	Anticipated

Ethics review

Approved WMO

Date:	28-09-2020

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-10-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2020
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	EUCTR2020□000344□67-NL
ClinicalTrials.gov	NCT04555486
CCMO	NL74676.000.20

Study results

First publication
05-01-2022