A Placebo-Controlled, Single-Blind, Single-Center Phase 1 Study in Normal Healthy Volunteers and Open-Label Multi Center Study in Patients with Primary Hyperoxaluria to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of DCR PHXC Solution for Injection (subcutaneous use)

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Objectives:Primary:* To evaluate the safety and tolerability of single doses of DCR-PHXC Solution for Injection (SC use) (*DCR-PHXC*) inNHV (Group A) and in patients with primary hyperoxaluria (PH) (Group B).Secondary:* To characterize the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal and urinary tract disorders congenital
Study type	Interventional

Summary

ID

NL-OMON46435

Source
ToetsingOnline

Brief title
A 2-part study in NHV and PH patients

Condition

- Renal and urinary tract disorders congenital
- Renal disorders (excl nephropathies)

Synonym
Over production of Oxalate, primary hyperoxaluria

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Minors, Phase I, Primary hyperoxaluria, Synthetic RNA

Outcome measures

Primary outcome

Safety analysis will be based on the Safety Analysis Set, which will include

all volunteers and patients who received a

full or partial dose of DCR-PHXC. This will be the primary analysis population

for safety evaluation.

Secondary outcome

* PK analysis will be based on the PK Analysis Set, which will include all

volunteers and patients who received a full

dose of DCR-PHXC and have sufficient data for at least 1 post-dose PK

assessment.

* PD analysis will be based on the PD Analysis Set, which will include all PH

patients who received a full dose of

DCR-PHXC and have at least 1 post-dose PD assessment.

Study description

Background summary

Dicerna pharmaceuticals Inc, are the company sponsoring this clinical trial, Dicerna have designed a drug called DCR-PHXC which is proposed to be a treatment for primary hyperoxaluria.

Primary hyperoxaluria is an ultra-rare autosomal recessive disease, that is typically diagnosed during childhood or early adulthood, and is thought to affect around 5000 people in Europe. However, the real number of patients is thought to be higher due to the disease sometimes being misdiagnosed.

Primary hyperoxaluria (PH) is categorised into three genetically distinct diseases. PH 1, 2 and 3. PH1 is the most common form of the disease and effects around 80% of those with PH. PH is the result of the liver over producing oxalate, which is highly insoluble compound and is removed from the body by the kidneys. However, due to excessive amounts of oxalate in patients with PH, the kidneys struggle to cope and this means oxalate builds up in the kidneys, causing the production of kidney stones. In addition, the excess oxalate is deposited elsewhere in the body and causes a number of other issues, such as recurrent urinary tract infections.

As there are no effective treatments available at present patients will PH must follow strict guidelines in respect to high water intake and minimising their dietary intake of oxalate rich foods. However, even with their best efforts many people reach end stage renal failure by their mid-30s. Kidney and liver transplants are an option but these themselves present a number of complications, such as the body rejecting the donor organ.

There is an unmet need to find a treatment for this rare yet life threatening disease. DCR-PHXC is proposed to work by silencing the gene that produces a key enzyme called lactate dehydrogenase A (LDHA). In addition, DCR-PHXC is supposed to be beneficial as it is very specific to hepatocyte cells (found in the liver). Silencing the gene that produces LDHA means that the amount of the enzyme produce is reduced, normally the LDHA enzyme has been shown to be key in the production of oxalate, and Dicerna have demonstrated in animal models that reducing the amount of LDHA has a direct reduction of the amount of oxalate produced. In fact, in animal models this approach demonstrated reductions of oxalate to normal or near normal levels. By reducing oxalate in PH patients, the drug may then go on to prevent the damage to kidneys and other organs

caused by oxalate accumulation.

Study objective

Objectives:

Primary:
* To evaluate the safety and tolerability of single doses of DCR-PHXC Solution for Injection (SC use) (*DCR-PHXC*) in
NHV (Group A) and in patients with primary hyperoxaluria (PH) (Group B).

Secondary:
* To characterize the pharmacokinetics (PK) of single doses of DCR-PHXC in NHV and patients with PH.
* To evaluate the pharmacodynamic (PD) effects of single doses of DCR-PHXC in NHV and patients with PH on
biochemical markers including, but not limited to, changes in plasma oxalate and glycolate, and urine oxalate, and
glycolate concentrations.

Exploratory (Group A only):
* To evaluate the onset and magnitude of change in urine oxalate concentration (Screening, Day 1, 15, 29) in NHV after a
single SC dose of DCR-PHXC after ingestion of 20 g of gelatin.

Exploratory (Group B only):
* To evaluate the pharmacodynamic (PD) effects of single doses of DCR-PHXC in patients with PH on changes in plasma glyoxalate.
* To establish a minimum effective dose (MED) of DCR-PHXC in adults

Study design

This study, to be conducted in two parts at approximately 7 study sites in the European Union (EU) and United States is a single ascending-dose (SAD) study of DCR PHXC in Normal Healthy Volunteers (NHV- Group A) and patients with Primary Hyperoxaluria (PH- Group B) (lagging Group A by at least 1 dose level cohort).

In both groups, a Safety Review Committee (SRC) will convene to review safety data at pre-defined decision points and upon the occurrence of any potential DLTs to ensure the acceptability of continued dosing within each cohort and dose escalation to subsequent cohorts.

Group A: Single Ascending-Dose (SAD) Study in Normal Healthy Volunteers This part of the study will consist of a screening period and a 28-day observational period following DCR-PHXC or placebo administration. Within each dosing cohort, 5 subjects (3 active, 2 placebo) will be enrolled.

- Day 0: Eligible subjects will be admitted
- Day 1: First two subjects will be administered 1 DCR-PHXC and 1 placebo
- Day 3: If study drug is well tolerated by first two subjects then enrol and administer next 3 subjects 2 DCR-PHXC and 1 placebo.
- Days 8 (±1), 15 (±1), 22 (±1), and Day 29/EOS (±1)): Monitoring at specified time points through day 29.

After dosing all subjects in each SAD cohort, the SRC will review at least 3 days of post-dose safety and tolerability data from all subjects in the current cohort before authorizing escalation to the next dose level.

Group B: SAD study in patients with PH (lagging Group A by at least 1 dose level cohort)
This part of the study will consist of a screening period and a 57-day observational period following administration of DCR-PHXC.
Within each dosing cohort, 4 patients will be enrolled and all will receive a single dose of DCR-PHXC. Oonly part B will run in the Netherlands.

- Day 0: Eligible patients will be admitted (one adult PH patient)
- Day 1: One adult PH patient will receive a single dose of DCR-PHXC. Patients will be discharged from the clinical study site on Day 3 after completing the post-dose assessments. Patients will be given the option to return home following completion of all protocol-specified visit procedures at the end of Day 0, Day 1 and Day 2 and to return the following morning.
- Day 8 : If study drug is well tolerated by the first patient through at least day 8, then enrol and administer dose to the remaining patients in the cohort.
- (Days 8 (±1), 15 (±1), 29 (±1), 43 (±1), and 57/EOS (±3). Monitoring at specified time points through day 57.

Within each dosing cohort, up to 5 patients will be enrolled and all will receive a single dose of DCR PHXC. Patients with PH will be enrolled such that enrolment in Group B is lagging behind enrolment in Group A by at least one dose level and occurs only after demonstration of an acceptable safety profile at the same dose level in Group A. Each cohort will include at least one patient with PH1.

Patients with PH participating in Group B will be allowed to participate in the next study, a Multiple-Dose Study of DCR-PHXC, if they meet required eligibility criteria.

Intervention

Group B (PH patients): up to 18 patients with either PH1 or PH2 (assuming 3 planned cohorts: low, medium, and high dose and one optional cohort, not to exceed the 6mg/kg dose).

All doses will be administered at a dose concentration of 170 mg/mL.

The starting dose proposed in patients is 1.5 mg per kg of body weight. This part of the study will have up to 4 dose levels with a maximum of 6.0 mg per kg. The dose levels will gradually increase in each group of up to 5 patients. However, progression to the next dose level will only occur if the safety results from the previous group are considered as satisfactory and the same dose level was tolerated well in normal healthy volunteers

Please see protocol section 3.2.

Study burden and risks

Benefit/Risk Assessment
An expanded risk-benefit analysis is provided in the IB. In brief, no benefit is expected from participation in this study. Measures to minimize the risks to healthy subjects and patients with PH have been incorporated into the following study design elements:

Clinical Laboratory Monitoring: At time of study entry, study participants are required to have safety laboratory values within acceptable ranges. Serial measurements of safety lab parameters (CBC, platelet count, creatinine, cytokines, liver function tests) and coagulation parameters are planned with interim review as defined in the SRC charter.

Study Eligibility: Section 3.10 describes the selection of eligibility criteria intended to
reduce the risk of reactions to an oligonucleotide-based therapy.

Overall Dosage: The dose range and multiples proposed for this study are justified based on the safety profile of such doses in nonclinical toxicity studies. In addition, a sentinel dosing strategy will be employed to ensure that no more than one healthy volunteer is exposed to active drug at the start of each new dose level.
*
Total blood volume collected: The following blood volumes will be collected during the trial:
o NHV: A total of ~120 mL
o Adult PH patients: A total of ~ 129.64 mL

No specific significant toxicities were identified in nonclinical pharmacology and toxicology studies at doses equivalent to and substantially greater than those in the planned study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

PH patients must meet all of the following criteria to be eligible for participation in this study.
1. Patient
a. Understands the full nature and purpose of the study, including possible risks and side effects.
b. Is willing and able to comply with all study procedures including collection of 24-hr urine samples.
c. Provides informed consent.

2. Male or female, at least 18 years of age at the time of obtaining informed consent. ;3. Documented diagnosis of PH1 or PH2, confirmed by genotyping (historically available genotype information is acceptable for study eligibility).
4. 24-hr urine oxalate excretion >=0.7 mmol on at least one of the two assessments

conducted in the screening period, with less than 30% variation between both oxalate measurements.

5. eGFR >=30 mL/min normalized to 1.73 m2 BSA calculated using the Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 1999; National Kidney Foundation, 2002).

6. Males, female patients of childbearing potential and female partners of male patients of childbearing potential must be willing to use a highly effective and approved contraceptive method(s) from the date of informed consent until 12 weeks after the last dose of IMP. A highly effective method of contraception is defined as fulfilling at least one of the following:
a. Strict abstinence: When this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.]
b. Surgically sterile (having undergone one of the following surgical procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization.
c. Combined hormonal oral contraceptive (estrogen and progesterone), implanted, or injectable contraceptive on a stable dose for at least 1 month prior to the screening visit plus a barrier method. Combined hormonal contraception is considered a highly effective method of contraception only if it is associated with inhibition of ovulation. If associated with inhibition of ovulation, progesterone-only hormonal contraception is also considered a highly effective method of contraception.
d. Intrauterine devices plus condoms. Hormonal IUD inserted at least 1 month prior to the screening visit.
e. Vasectomized partner (at least 6 months post-procedure) prior to the screening visit.
f. Postmenopausal females: defined as 12 months with no menses prior to screening and a serum FSH >26 IU/L at screening. ;7. For WOCP: a negative pregnancy test at screening and Day 0 ;8. Patients with PH1 receiving pyridoxine at stable doses at least 4 weeks prior to study entry must be willing to remain on the same stable dose during the study. In the unlikely event that a patient with PH2 is receiving pyridoxine, this should be discontinued at least 4 weeks prior to study entry

Exclusion criteria

PH patients meeting any of the following criteria will be excluded from this study:
1. Prior renal and/or hepatic transplantation.
2. Currently receiving dialysis.
3. Documented evidence of clinical manifestations of systemic oxalosis.
4. Participation in any clinical study where they received an investigational medical product within 4 months before enrollment. For IMPs with the potential to reduce Uox and/or plasma oxalate, these concentrations must have returned to historical baseline levels.
a. If patient participated in an earlier cohort in this study (DCR-PHXC-101), a minimum of 8 weeks must have elapsed prior to re-enrollment and urinary oxalate excretion must have returned to >=80% of baseline.

5. Presence of any medical condition or co-morbidities that would interfere with study compliance or data interpretation or potentially impact patient safety including, but not restricted to:
a. severe intercurrent illness
b. routine vaccination within 30 days prior to dosing and through EOS visit
c. known causes of active liver disease/ injury or transaminase elevation (e.g., alcoholic liver disease, Nonalcoholic fatty liver disease/ steatohepatitis (NAFLD/NASH)
d. physician concerns about excess alcohol consumption
e. routine or chronic use of more than 3 grams of acetaminophen daily.
6. History of alcohol consumption exceeding more than 21 units in males, 14 units in females, per week as determined by the Investigator. See Section 5 for details.
7. Women who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days after last dosing of IMP.
8. Liver function test (LFT) abnormalities: ALT and/or AST >1.5 times ULN for age and gender.
9. History of one or more of the following reactions to an oligonucleotide-based therapy a. Severe thrombocytopenia
b. Hepatotoxicity
c. Severe flu-like symptoms leading to discontinuation of therapy
d. Localized skin reaction from the injection (Grade 3 or higher) leading to discontinuation of therapy.
e. Coagulopathy/ clinically important prolongation of clotting time

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	26-03-2018
Enrollment:	5
Type:	Anticipated

Ethics review

Approved WMO Date:	20-02-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-04-2019
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	EUCTR2017-003534-89-NL
ClinicalTrials.gov	NCT03392896
CCMO	NL64762.000.18