A Phase 1/2, Single-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose Safety, Tolerability, Pharmacokinetic and Pharmacodynamics Study of Subcutaneously Administered ALN-GO1 in Healthy Adult Subjects, and Patients with Patients with Primary Hyperoxaluria Type 1

Published: 11-08-2016
Last updated: 31-12-2024

Primary* Evaluate the safety and tolerability of single- and multiple-ascending doses of ALN-GO1, respectively, in healthy adult subjects and in patients with PH1Secondary* Characterize the pharmacokinetics (PK) of ALN-GO1* Evaluate the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON47017

Source
ToetsingOnline

Brief title
ALN-GO1

Condition

- Inborn errors of metabolism

Synonym
Primary Hyperoxaluria Type 1

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALN-GO1, Primary Hyperoxaluria Type 1

Outcome measures

Primary outcome

Primary

* The primary endpoint is the incidence of adverse events. Safety will also be evaluated through vital signs, electrocardiograms, clinical laboratory assessments, and physical examinations.

Secondary outcome

Secondary Endpoints for Part B

o PK parameters including, but not limited to, Cmax, tmax, AUC, t*, fe/F, and CLR

o Urinary oxalate excretion (oxalate concentration in 24-hour urine collection)

o Urinary glycolate excretion (glycolate concentration in 24-hour urine collection)

o Plasma glycolate concentration

o Calculated creatinine clearance

Study description

Background summary

Currently, there are no approved therapies for the treatment of PH1. Disease management is based on supportive measures, including high fluid intake, potassium citrate (to increase urinary oxalate solubility), Vitamin B6, and treatment of complications such as urinary tract stones and infections. Therefore, there is a high unmet medical need for additional treatments for patients with PH1.

Study objective

Primary
* Evaluate the safety and tolerability of single- and multiple-ascending doses of ALN-GO1, respectively, in healthy adult subjects and in patients with PH1
Secondary
* Characterize the pharmacokinetics (PK) of ALN-GO1
* Evaluate the pharmacodynamics (PD) of ALN-GO1
Exploratory
* Characterize exploratory biomarkers of PH1
* Characterize the PK of metabolites of ALN-GO1

Study design

This is a randomized, single-blind, placebo-controlled study of subcutaneously administered ALN-GO1. Subjects and patients will be randomized in a 3:1 ratio to receive either ALN-GO1 or placebo. The study is designed to evaluate the safety, tolerability, PK, and PD of single- and multiple-ascending doses of ALN-GO1 and will be conducted in 2 parts:
* Part A: SAD part in healthy adult subjects
* Part B: MAD part in adult and pediatric patients with PH1
In Part A, subjects in each cohort will be randomized to receive 1 dose of ALN-GO1 or placebo.
In Part B, patients will be enrolled in up to 6 sequential dose cohorts to receive ALN-GO1 or placebo monthly or quarterly. Patients dosed monthly will receive 3 doses of ALN-GO1 or placebo. After completion of the blinded portion of the study, patients dosed monthly will be unblinded on or after Day 78. Patients who initially received placebo will then receive 3 doses of open-label ALN-GO1 dosed monthly at the same dose administered to the cohort into which they were initially randomized and will follow the same assessment schedule. Patients dosed quarterly will receive either ALN-GO1 or placebo on Day 1. All patients in quarterly dosing cohorts, including those initially randomized to placebo, will receive open-label ALN-GO1 on Day 85 at the same dose

administered to the cohort into which they were initially randomized. Up to 2 expansion cohorts in Part B may be enrolled based on available safety and PD data; these patients will all receive open-label ALN-GO1, not placebo.

After the dosing period, patients will return to the clinical study center for continued safety, tolerability, PK, and PD monitoring for at least 12 weeks (84 days) following the last dose of study drug. Following completion of the 12-week postdose follow-up period, patients will be invited to participate in an open-label extension study.

For patients who do not enroll in the open-label extension study, safety and PD follow up will continue until 24-hour urinary oxalate is >80% of baseline, and plasma glycolate is <20% above baseline or = the ULN. If an investigator wishes to discontinue follow-up after completion of the postdose follow-up period and prior to oxalate and glycolate recovery, the Safety Review Committee (SRC) must agree based upon consideration of emerging data on the safety of ALN-GO1 knockdown and the individual patient*s safety and PD data.

A Safety Review Committee (SRC) will perform ongoing reviews of safety, tolerability, and available PD data, with the primary purpose of protecting the safety of subjects/patients participating in this clinical study.

Intervention

ALN-GO1 is a synthetic, double-stranded small interfering RNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA that is covalently linked to a ligand containing 3 N-acetylgalactosamine residues. ALN-GO1 will be supplied as a sterile solution for subcutaneous (SC) injection at a targeted concentration of 200 mg/mL.

Study burden and risks

ALN-GO1 is designed to reduce hepatic production of oxalate. The potential benefit of this treatment is the amelioration of the clinical course of PH1 in patients across the spectrum of disease, irrespective of age and disease stage; however, patients with PH1 in this study may not receive treatment for a sufficient duration, or at an adequate dose, to experience clinical benefit. The potential benefit to children enrolled in this study includes possible reduction in oxalate production during the study period, which may have a temporarily ameliorating effect on their disease. In addition, experience in children with this disease under carefully controlled conditions will provide data that may enhance the future development of this therapeutic. Moreover, since evaluation of safety and PD effects in children will be important in the design of future studies, it is considered important and appropriate to enroll children in the current study.

Contacts

Public
Alnylam Pharmaceuticals, Inc

Third Street 300
Cambridge 02142 MA
US
Scientific
Alnylam Pharmaceuticals, Inc

Third Street 300
Cambridge 02142 MA
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female subjects aged 18-64 years (or age of legal consent, whichever is older), inclusive (Part A) and 6-64 years, inclusive (Part B).
2. Women of child bearing potential must have a negative pregnancy test, cannot be breastfeeding, and must be willing to use contraception.
3. Willing to provide written informed consent and to comply with study requirements.
Additional Inclusion Criteria for Part B:
4. confirmation of PH1 disease.
5. 24-hour urinary oxalate excretion of >0.7 mmol/1.73m2/day.
6.Estimated GFR of >45 mL/min/1.73m2.
7. If taking Vitamin B6 (pyridoxine), must have been on stable regimen

for at least 90 days .

Exclusion criteria

1. Any uncontrolled or serious disease, or any medical or surgical condition (with the exception of PH1 for patients in Part B) that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to the Investigator's judgment) if he/she participates in the clinical study.
2. Mental illness, alcoholism, drug abuse, or heavy smokers and users of nicotine
3. History of multiple drug allergies or intolerance to subcutaneous injection
4. Received an investigational agent within 3 months before the first dose of study drug or are in follow-up of another clinical study
5. Known history of allergic reaction to an oligonucleotide or GalNAc
6. History of intolerance to SC injection or relevant abdominal scarring
7. Women who are pregnant or breast feeding

Part B only

8. Echocardiography (ECHO) assessment of normal left ventricular systolic function, defined as left ventricular ejection fraction <55% at screening
9. Troponin I > the upper limit of normal (ULN) at screening

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-01-2018

Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	11-08-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2018

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	EUCTR2015-004407-23-NL
CCMO	NL58243.000.16

Study results

Date completed:	12-10-2018
Results posted:	24-07-2019
Actual enrolment:	2

First publication
18-07-2019