A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias (ENVISION)

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Primary:Evaluate the effect of subcutaneous (SC) givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home in patients with acute...

Ethical review	Approved WMO
Status	Completed
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON50649

Source
ToetsingOnline

Brief title
ENVISION

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Acute hepatic porphyrias

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Acute hepatic porphyrias

Outcome measures

Primary outcome

Primary

Annualized rate of porphyria attacks requiring hospitalization, urgent

healthcare visit, or home hemin administration during the 6-month double-blind

treatment period.

Secondary outcome

Secondary

All secondary endpoints will be measured over the 6-month double-blind

treatment period

*Percentage change from baseline in urinary ALA levels

*Percentage change from baseline in urinary PBG levels

*Annualized number of administered hemin doses

*Attack-free days (days without porphyria attacks requiring hospitalization,

urgent healthcare visit or home hemin administration)

*Daily worst pain score as measured by Brief Pain Inventory-Short Form (BPI-SF)

numeric rating scale (NRS)

*Daily worst nausea score as measured by NRS

*Daily worst fatigue score as measured by Brief Fatigue Inventory - Short Form

(BFI-SF) NRS

*Change from baseline in the Physical Component Summary (PCS) of the 12-item

Short-Form Health Survey (SF-12)

Study description

Background summary

The acute hepatic porphyrias (AHPs) are a family of rare, serious and life-threatening metabolic disorders predominantly caused by a genetic mutation in one of the 8 enzymes responsible for heme synthesis.
Over 75% of acute porphyria attacks require urgent medical care and/or hospitalization or intravenous hemin. Patients are initially treated with supportive care and intravenous (IV) glucose, analgesics and antiemetics, along with the removal of known precipitating triggers, such as certain medications or dieting. Pain relief typically requires opioids until porphyria-specific therapy takes effect. In patients with moderate to severe attacks, or who fail to respond to supportive measures, treatment with IV hemin is used. After 2 to 5 days of hemin treatment, urinary ALA and PBG levels approach normalization accompanied by improvement in attack symptoms. However, in some patients attacks can last several weeks, requiring prolonged hemin use and hospitalization. Hemin administration can result in significant acute side effects such as severe headache, nausea, flu-like symptoms, fatigue and thrombophlebitis. There are no approved treatments for the prevention of acute attacks of hepatic porphyria, and there is little evidence published on how best to manage AHP patients with recurrent attacks.
AHP is associated with significant morbidity and mortality, and negatively affects activities of daily living as well as the quality of life of patients.
There is a clear unmet need for novel therapeutics with favorable safety profiles that effectively and durably decrease the frequency of debilitating attacks, diminish the chronic symptoms in between attacks, and improve patients* quality of life.

Based on the available nonclinical and clinical data, givosiran, administered subcutaneously as a once-monthly dose regimen, may be able to offer dose-dependent, potent and sustained suppression of ALAS1, thereby decreasing the accumulation of the neurotoxic heme intermediates ALA and PBG. This may, in turn, potentially prevent the occurrence of acute porphyria attacks, as well as potentially ameliorate chronic porphyria symptoms that patients experience

between attacks, including pain, nausea and fatigue.

Study objective

Primary:
Evaluate the effect of subcutaneous (SC) givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home in patients with acute intermittent porphyria (AIP)

Secondary:
*Evaluate the effect of givosiran, compared to placebo, on urinary aminolevulinic acid (ALA) levels in patients with AIP
*Evaluate the effect of givosiran, compared to placebo, on urinary porphobilinogen (PBG) levels in patients with AIP
*Evaluate the effect of givosiran, compared to placebo, on hemin usage in patients with AIP
*Evaluate the effect of givosiran, compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP
*Evaluate the effect of givosiran, compared to placebo, in patients with AIP on the symptoms of pain, nausea and fatigue
*Evaluate the effect of givosiran, compared to placebo, in patients with AIP on the physical Component Summary (PCS) of the 12-item Short-Form health survey (SF-12)
*Evaluate the safety and tolerability of givosiran in patients with any AHP

Exploratory:
_Evaluate the effects of givosiran, compared to placebo, in patients with AIP and in patients with any AHP over the 6-month treatment period on:
__Rate of all porphyria attacks (requiring hospitalization, urgent healthcare visit, IV hemin administration at home, or treatment at home without IV hemin)
__Urinary aminolevulinic acid synthase (ALAS1) messenger RNA (mRNA) levels
__Analgesic usage
__Additional quality of life (QOL) measures, including missed days of work/school
*Assess the within-patients treatment effect of givosiran during the open-label extension (OLE) period in patients with AIP and in patients with any AHP who had previously been randomized to placebo treatment
*Assess the long-term treatment effect of givosiran in patients with AIP and in patients with any AHP
*characterize the pharmacokinetics (PK) and assess the antidrug antibodies (ADA) of givosiran in patients with any AHP

Study design

This is a 2-part multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of givosiran in adults and adolescents (*12 years of age) with a documented diagnosis of AIP. The efficacy and safety of givosiran will also be investigated in the other AHPs types, including Hereditary Coproporphyria (HCP), Variegate Porphyria (VP) and ALA dehydratase deficient porphyria (ADP).

Patients who are on hemin prophylaxis prior to enrollment will be eligible to participate if they meet the attack entry criteria. In this study, patients may be given hemin for the treatment of acute attacks if clinically indicated, but may not use hemin prophylactically. Hemin prophylaxis is not permitted in this study because givosiran is intended as monotherapy to prevent attacks and the regular co-administration of hemin could confound efficacy and safety signals related to givosiran.

in the first part of the study, consenting (and assenting, where applicable) patients who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 2.5mg/kg givosiran or placebo monthly for a 6-month treatment period (double blind); both givosiran and placebo will be administered subcutaneously. Randomization into treatment groups will be stratified at study entry by AHP type (AIP [with mutation in the HMBS gene] versus HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene); all patients in the AIP group will be further stratified by each patient's use of hemin prophylaxis regimen at the time of screening and by each patient's historical annualized attack rate. Patients on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <7 attacks versus *7 attacks in the past 12 months. Patients who were not on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <12 attacks versus *12 attacks in the past 12 months.
No additional stratification factors will be considered for patients with HCP, VP, ADP or any AHP without identified mutation in a porphyria-related gene.

During the 6-month treatment period, patients will undergo efficacy and safety assessments every 2 weeks for the first month and monthly thereafter. After month 6 visit procedures are completed in the treatment period, patients from both the givosiran and placebo arms will begin the second part of the study, the OLE period during which they will be treated with givosiran for up to 30 months.

Patients who crossed over to the OLE period prior to the implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving a 2.5 mg/kg once monthly givosiran dose will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran. After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25 mg/kg treatment group who experience inadequate disease control may be allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month

13 Study Visit (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg) based on discussion and agreement by the Investigator and medical monitor, demonstration of tolerability to givosiran and fulfillment of ALA and clinical activity criteria. Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity.

For particular study visits, as specified in the Schedule of assessments, and where applicable country and local regulations and infrastructure allow, study procedures, including study drug administration, may be conducted by a qualified home healthcare professional. Patients must demonstrate the ability to tolerate doses of the study drug at the study center before dosing at a location other than the study center is permitted. If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, givosiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations.

Patients or caregivers will be provided with an electronic diary (eDiary) to record severity of daily pain, nausea, and fatigue, as well as analgesic usage. Potential porphyria attacks will be reported by patients and caregivers through the eDiary when they occur; study centers will be notified when potential porphyria attacks are reported in the eDiary. In instances when the eDiary is not used to report potential porphyria attacks, study centers may be notified by telephone by patients, caregivers, or other healthcare providers. All potential porphyria attacks will be confirmed by the Investigator.

Intervention

Monthly Givosiran/Placebo 2.5mg/kg subcutaneously administered during the blinded 6 month treatment period

Monthly Givosiran 1.25 mg/kg or 2.5mg/kg subcutaneously administered during the open-label extension period.

Study burden and risks

41 visits to the study center (where applicable country and local regulations and infrastructure allow, about 24 of the study visits can be performed by a home healthcare professional)

Blinded 6-month treatment period:

- 6x physical examination
- 9x vital signs
- 1x Single 12-Lead ECG
- 3x Triplicate 12-Lead ECG
- 8x pregnancy test
- 9x Urine samples for ALA and PBG
- 3x Questionnaire of Life to fill out
- Daily Electronic Diary Entries

Monthly administration of the study drug/placebo (subcutaneously)

Open-Label Extension period (Month 6through Month 18):
- 5x physical examination
- 10x vital signs
- 1x Triplicate 12-Lead ECG
- 9x pregnancy test
- 10 urine samples for ALA en PBG
- 3x Questionnaire of Life to fill out
- first 6 months, daily Electronic Diary Entries, from month 13 on only when potential attacks occur

Monthly administration of the study drug (subcutaneously)

Open-Label Extension period (Month 19 through End of Study):
- 4x physical examination
- 7x vital signs
- 2 Single 12-Lead ECG
- 13x pregnancy test
- 7x urine sample for ALA and PBG
- 3x Questionnaire of Life to fill out
- Electronic Diary Entries only when potential attacks occur

Monthly administration of study drug (subcutaneously) except during the visit in month 36 (End of Study) and during the Safety FU visit.

Risk: Possible side effects of the study drug and study procedures

Contacts

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US
Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study:
1. Age *12 years
2. Documented diagnosis of AIP, HCP, VP or ADP based on clinical features (eg. acute attacks of abdominal, back, chest, extremities and/or limb pain), at least one documented urinary or plasma PBG or ALA value *4x upper limit of normal (ULN) within the past year prior to Screening, and one of the following:
* documented genetic evidence of mutation in a porphyria-related gene, defined as any of the following: _AIP: mutation in the hydroxmethylbilane synthase gene (HMBS; also referred to as the porphobilibnogen deaminase [PBGD] gene); _HCP: mutation in the coporphyrinogen oxidase (CPOX) gene; _VP: mutation in the protoporphyrinogen oxidase (PPOX) gene; _ADP: mutation in the aminolevulinic acid dehydratase (ALAD) homozygous or compound heterozygous genes
*Or if the results of a patient's genetic testing do not identify a mutation in a porphyria-related gene (<5% of cases), a patient may be eligible for the study if they have both clinical features and diagnostic biochemical criteria consistent with AHP
3. Have active disease, with at least 2 porphyria attacks requiring

hospitalization, urgent healthcare visit or treatment with IV hemin at home within the 6 months prior to screening
4. willing to discontinue and/or not initiate use of prophylactic hemin at the time of screening and for the duration of the study
5. have adequate venous access for study sample collection as judged by the investigator
6. be willing to comply with the contraceptive requirements during the study period
7. be willing and able to comply with the study requirements and to provide written informed consent and assent in the case of patients under the age of legal consent, per local and national requirements

Exclusion criteria

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study:
1. Any of the following laboratory parameter assessments at Screening:
* Alanine aminotransferase (ALT) >2xULN
* Total bilirubin >&.5xULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2xULN
* International normalized ratio (INR)>1.5 (patients on an anticoagulant [eg. warfarin] with an INR<3.5 will be allowed)
2. Estimated Glomerular Filtration Rate (eGFR) <30mL/min/1.73m² using the Modification of Diet in Renal Disease (MDRD) formula
3. on an active liver transplantation waiting list, or anticipated to undergo liver transplantation during the blinded study treatment period
4. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to N-acetylgalactosamine (GalNAc)
5. History of intolerance to subcutaneous injection(s)
6. Known active HIV infection; or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
7. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer) since ending another investigational device or drug study(s), or receiving other investigational agent(s)
8. Females who are pregnant, breast-feeding, or planning to become pregnant during the study
9. Any condition (eg. medical concern or alcohol or substance abuse), which in the opinion of the Investigator, would make the patient unsuitable for dosing or which could interfere with the study compliance, the patient's safety and/or the patient's participation in the 6-month treatment period of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to porphyria identified by key laboratory abnormalities or medical

history
10. History of recurrent pancreatitis, or acute pancreatitis with disease activity within the past 12 months prior to screening
11. Has planned elective major surgery scheduled to occur during the study
12. History of serious infection within one month prior to screening
13. Had a malignancy within 5 years prior to screening, except for basal or squamous cell carcinoma of the skin, cervical in-situ carcinoma, or breast ductal carcinoma, that has been successfully treated

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-07-2018
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO

Date:	12-12-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	21-06-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2020
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	EUCTR2017-002432-17-NL
ClinicalTrials.gov	NCT03338816
CCMO	NL63599.000.17

Study results

Date completed:	13-04-2021
Results posted:	23-12-2021
Actual enrolment:	1

First publication
23-11-2021