HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

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This study has been transitioned to CTIS with ID 2023-508365-33-00 check the CTIS register for the current data. To determine the efficacy of ALNTTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment. To…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON52839

Source
ToetsingOnline

Brief title
HELIOS-A

Condition

- Heart failures
- Neurological disorders congenital
- Gastrointestinal signs and symptoms

Synonym
Hereditary Transthyretin Amyloidosis

Research involving

Human

Sponsors and support

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

Intervention

Keyword: ALN-65492, ALN-TTRSC02, hATTR Amyloidosis, siRNA

Outcome measures

Primary outcome

To determine the efficacy of ALNTTRSC02 in patients with hATTR amyloidosis by

evaluating the effect on neurologic impairment.

Secondary outcome

To determine the efficacy of ALN-TTRSC02 on quality of life, gait speed,

neurological impairment, nutritional status, and disability

To demonstrate the noninferiority of ALNTTRSC02 compared to patisiran with

respect to serum TTR-levels.

Study description

Background summary

Hereditary transthyretin amyloidosis (hATTR) is a rare genetic disease that tends to run in some families. hATTR amyloidosis is caused by certain variations in the gene for a protein called transthyretin, or TTR. The liver is the main organ that produces TTR protein, and TTR then circulates in the blood stream. Abnormal TTR protein can gradually deposit in many tissues and organs of the body, in collections of proteins called amyloid fibrils. These amyloid fibril collections can often affect the function of important organs such as the nerves, the heart, and the gut. This leads to the symptoms of amyloidosis, including weakness, numbness, shortness of breath, lightheadedness, and diarrhea.
ALN-TTRSC02 is an investigational drug, which means it is not approved by the

Health Authority in the Netherlands, or Health Authorities of any other country, for the treatment of hATTR amyloidosis at this time.
ALN-TTRSC02 consists of a small interfering ribonucleic acid (siRNA) molecule attached to a sugar molecule which helps deliver the siRNA to the liver, where the TTR protein is made. The siRNA in ALN-TTRSC02 works by interfering with the ability of RNA (ribonucleic acid), a molecule that the cells use to produce proteins, to make TTR proteins in the liver. ALN-TTRSC02 therefore reduces the body*s TTR protein levels, which may in turn reduce the number of amyloid fibrils in the organs of patients with hATTR amyloidosis.

Study objective

This study has been transitioned to CTIS with ID 2023-508365-33-00 check the CTIS register for the current data.

To determine the efficacy of ALNTTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment. To determine the efficacy of ALN-TTRSC02 on quality of life, gait speed, neurologic impairment, nutritional status, and disability. To demonstrate the noninferiority of ALNTTRSC02 compared to patisiran with respect to serum TTR-levels.

To determine the effect of ALN- TTRSC02 on:
* disability and nutritional status
* Manifestations of cardiac amyloid involvement
* Other assessment of neurologic impairment
* Other assessments of quality of life
* Disease stage
* Performance of daily activities
* To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and patisiran on serum TTR and vitamin A levels
* To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran
* To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran

To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis

Study design

This is a global, Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran, a reference comparator. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs >=50).

The study will consist of a Screening Period of up to 42 days, an 18-month

Treatment Period, and an 42-month Randomized Treatment Extension Period (RTE) as of Amendment 4, in lieu of the 18-month Treatment Extension Period (hereafter referred to as the Legacy Treatment Extension Period). A Follow-up Period of up to 1 year will occur after the last dose of study drug.

Intervention

Eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as a subcutaneous (SC) injection once every 3 months or patisiran administered as an intravenous (IV) infusion once every 3 weeks. After approximately 18 months of treatment, patients will stop receiving patisiran and begin receiving ALN-TTRSC02 for the remainder of the study as part of the Randomized Treatment Extension period (approximately another 42 months). Patients who are given patisiran will have to receive required medications listed below prior to each dose of patisiran:
• Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
• Oral paracetamol (500 mg, or equivalent)
• Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
• Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

Study burden and risks

As ALN-TTRSC02 is designed to go to the liver, there is a potential for changes in liver function. Alcohol intake of >2 drinks/day is not allowed during the study
Treatment with ALN-TTRSC02 lowers vitamin A levels in your blood. As a precautionary measure, you will be asked to take a daily Vitamin A supplement during the study.
It is not known if the use of ALN-TTRSC02 in pregnant women might harm an unborn child. Women of child-bearing age should not be pregnant when starting treatment with ALN-TTRSC02 and must agree to use effective contraception during their participation in this study.

The comparator, patisiran may also cause side effects. The most common ones are infusion-related signs such as:
• Stomach pain
• Feeling sick (nausea)
• Body aches or pain, including pain in the back, neck, or joints
• Headache
• Feeling tired (fatigue)
• Chills
• Dizziness
• Cough, feeling short of breath, or other breathing problems
• Reddening of the face or body (flushing), skin warm, or rash
• Chest discomfort or chest pain
• Rapid heart rate

• Low or high blood pressure
• Pain, redness, burning sensation, or swelling at or near the infusion site
Other side effects of Patisiran or the pre-medication can occur. However, there may be side-effects that are still unknown.

It is not yet known whether the long-term reduction of blood TTR protein levels with ALN-TTRSC02 in patients with hATTR amyloidosis will favorably affect the course of the disease. Therefore, it is not known whether you will benefit from this treatment. Your participation may contribute to increased knowledge that may help in the future development of a new therapy for patients with hATTR amyloidosis.

In a phase 3 clinical study, patisiran was shown to improve neuropathy and quality of life in patients with hATTR amyloidosis and polyneuropathy, and on this basis has been approved for use as a treatment for patients with hATTR amyloidosis and polyneuropathy in the United States and Europe.
Participation in the study also means:
- Additional time
- Additional tests
- Instructions you need to follow

Contacts

Public
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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, with a documented TTR mutation, and a confirmed diagnosis of symptomatic hATTR amyloidosis with an NIS of 5 to 130 (inclusive), a PND score of <=3b, and KPS >=60%.

Exclusion criteria

Patients are excluded from the study if any of the following criteria apply:
Disease-specific Conditions
1. Has had a liver transplant or is likely, in the opinion of the Investigator, to undergo liver transplantation during the 18-month Treatment Period of the study
2. Has known other (non-hATTR) forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis
3. Has a New York Heart Association heart failure classification >2
Laboratory Assessments
4. Has any of the following laboratory parameter assessments:
a. ALT and/or AST >1.5× upper limit of normal reference range (ULN)
b. Total bilirubin >ULN (>1.5 ULN in patients with Gilbert's Syndrome)
c. International normalized ratio (INR) >1.2 (patients on anticoagulant therapy with an INR of <=3.5 will be allowed)
(Note: ALT, AST, and total bilirubin laboratory criteria must be met at both Screening Visit 1 and Screening Visit 2)
5. Platelet count <50,000/µL
6. Absolute neutrophil count (ANC) <1500 cells/mm³
7. Estimated glomerular filtration rate (eGFR) <=30 mL/min/1.73m2 (using the Modification of Diet in Renal Disease [MDRD] formula)
8. Has vitamin B12 levels below the lower limit of normal (LLN)
9. Has known human immunodeficiency virus (HIV) infection; or evidence of acute or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
Prior/Concomitant Therapy
10. Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (Day 1)

11. Received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR amyloidosis
12. Is currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to dosing (Day 1)
13. Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to dosing (Day 1)
Medical Conditions
14. Has other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease, monoclonal gammopathy) that the treating physician believes to be contributing to the neuropathy
15. Had acute coronary syndrome within the past 3 months
16. Has uncontrolled clinically significant cardiac arrhythmia or unstable angina
17. Has known type 1 diabetes
18. Has had type 2 diabetes mellitus for >=5 years
19. Has untreated hypo- or hyperthyroidism
20. Has had a major surgery within the past 3 months or has a major surgery planned during the study through Month 18
21. Has an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior dosing (Day 1)
22. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
23. Anticipated survival is less than 2 years, in the opinion of the Investigator
24. History of multiple drug allergies; or history of allergic reaction to an oligonucleotide or GalNAc; or had a prior severe reaction to a liposomal product or any component of patisiran (ALN-TTR02)
25. Is unable to take the required premedications (see Section 5.2.2.2)
26. History of intolerance to subcutaneous (SC) injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
27. Any condition (eg, medical concern), 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 through the Month 18 visit of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to hATTR identified by key laboratory abnormalities or medical history
Contraception, Pregnancy, and Breastfeeding
28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
29. Female patient is pregnant or breastfeeding
Alcohol Use
30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1

glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = * pint of beer [approximately 284 mL])
31. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-01-2020
Enrollment:	2
Type:	Actual

Ethics review

Approved WMO Date:	15-03-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-09-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2023
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
EU-CTR	CTIS2023-508365-33-00
EudraCT	EUCTR2018-002098-23-NL
CCMO	NL67887.000.19