HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Published: 03-02-2020
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This study has been transitioned to CTIS with ID 2024-518318-25-00 check the CTIS register for the current data. Primary: • To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and cardiovascular (CV)-related...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52969

Source
ToetsingOnline

Brief title
HELIOS-B

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Transthyretin Amyloidosis with Cardiomyopathy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ATTR Amyloidosis with Cardiomyopathy, siRNA, Vutrisiran

Outcome measures

Primary outcome

Primary outcome is a composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in both the overall population and the vutrisiran monotherapy subgroup (defined as patients not on tafamidis at study baseline).

Secondary outcome

The following secondary endpoints will be defined in both the overall population and the vutrisiran monotherapy subgroup:

• Change from baseline in 6-minute walk test (6-MWT)

• Change from baseline in the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS)

• All-cause mortality

• Change from baseline in NYHA class

Study description

Background summary

(also see research protocol section 1.5)
ATTR amyloidosis is a rare, serious, life-threatening, multisystemic disease encompassing hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis, which result from either hereditary (genetic mutation) or nonhereditary (aging) causes, respectively.
TTR, also known as prealbumin, is a tetrameric protein produced by hepatocytes, the choroid plexus, and retina.[Liz 2010] More than 95% of TTR in the circulation is derived from the liver. The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A), which involves TTR binding to the retinol binding protein (RBP): vitamin A complex. However, there is evidence to suggest that vitamin A transport and tissue uptake can occur in the absence of circulating RBP.
Previously, the sponsor developed patisiran. Patisiran is a siRNA targeting hepatic TTR mRNA developed by the Sponsor. Patisiran, which is formulated as a lipid nanoparticle (LNP), is administered every 3 weeks (q3w) by intravenous (IV) infusion, and requires use of premedications in order to prevent infusion-related reactions. It is approved for use in patients with hATTR amyloidosis with polyneuropathy in a number of regions, including Canada, the EU, Japan, and the US. These approvals were based on the results of a large, randomized, double-blind, placebo-controlled, Phase 3, Study ALN-TTR02-004 (APOLLO).[Adams 2018] This study demonstrated that patisiran treatment significantly improved neuropathy, quality of life, and a range of disease manifestations relative to placebo in hATTR amyloidosis patients with polyneuropathy across a broad range of disease severity and TTR genotypes.
Presently, the sponsor is developing vutrisiran for SC administration for the treatment of ATTR amyloidosis, inlcuding the treatment of patients with ATTR amyloidosis with cardiomyopathy. Vutrisiran utilizes a mechanism similar to patisiran in that RNAi is used to selectively target and degrade TTR mRNA, thus preventing the synthesis of both wt and mutant TTR in the liver, the primary source of circulating TTR.

Study objective

This study has been transitioned to CTIS with ID 2024-518318-25-00 check the CTIS register for the current data.

Primary: • To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and cardiovascular (CV)-related hospitalizations

Secondary: To evaluate the efficacy of vutrisiran compared with placebo treatment on:
• Functional capacity
• Patient-reported health status and health-related quality of life
• All-cause mortality
• Severity of clinical heart failure symptoms

Exploratory: To evaluate the efficacy of vutrisiran compared with placebo treatment on:
• Severity of clinical heart failure symptoms
• Additional cardiac biomarkers and biomarker-based risk assessments
• Nutritional Status
• Assessments of quality of life

PD and PK:
• To characterize the PD effect of vutrisiran on transthyretin (TTR)
• To characterize plasma pharmacokinetics (PK) of vutrisiran
• To assess presence of antidrug antibodies (ADA) against vutrisiran

Safety:
• To evaluate the safety and tolerability of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy

Study design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in approximately 600 patients with ATTR amyloidosis with cardiomyopathy. Approximately 20% of the study population is anticipated to have hereditary ATTR (hATTR) and 80% wild-type ATTR (wtATTR) amyloidosis with cardiomyopathy.
At baseline, patients are either:
• Tafamidis-naïve (see inclusion criterion #3 for definition); or
• Currently receiving tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication in the country of use). This group will be capped at 30% of total enrollment in the study.
The study consists of 3 periods (Figure 1):
1. Screening Period: Up to 45 days during which patients will undergo screening assessments to determine eligibility.
2. Double-Blind Period (DB Period):
• At the start of the DB Period, eligible patients will be randomized in a 1:1 ratio to receive 25 mg of vutrisiran or placebo administered as a subcutaneous (SC) injection once every 3 months (q3M; every 12 weeks ±7 days) for up to 36 months. Study drug will be administered at the clinic during scheduled study assessment visits.
* In addition to study drug, all patients will take the recommended daily allowance of vitamin A during their DB Period and Follow-up Period (see below).
• An individual patient*s DB Period will end after they complete their Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, the length of each patient*s intended treatment during the DB Period may vary from 30 to 36 months.
• The primary analysis will be conducted after the last patient has completed the Month 30 Visit or otherwise discontinued.
3. Follow-Up Period after the last dose of vutrisiran on study:
• Following their last dose of vutrisiran in the DB Period, patients will

commence safety follow-up visits every 12 weeks for the durations outlined below.
• Prior to unblinding, the duration of the Follow-up Period for a patient will be 1 year from their last dose of study drug. For women of child-bearing potential, the duration of the Follow-up Period will be 18 months from their last dose of study drug. Patients will continue vitamin A supplementation during their Follow-up Period.
• After unblinding, all patients who were on placebo, and patients who received vutrisiran whose serum TTR level has returned to >=80% of baseline or who have completed the Follow-up Period, whichever comes first, may discontinue further follow-up and stop taking vitamin A; all patients will be followed for a minimum of 3 months.
• For any patient who starts a TTR lowering treatment as part of clinical care, and has completed a minimum of 3 months of safety follow-up, further follow-up will be discontinued.

Intervention

Vutrisiran is a subcutaneously (SC) administered N-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA), which targets liver-expressed messenger RNA (mRNA) for transthyretin (TTR).
Study drug (vutrisiran or placebo) will be administered using a pre-filled syringe and a needle safety device. The outside of the pre-filled syringe barrel will be masked in such a way as to hide the identity of the study drug contained within.
Starting on Day 1, patients will receive 25 mg of vutrisiran or placebo administered as a SC injection once every 3 months (q3M; every 12 weeks; ±7 days) for up to 36 months. Study drug will be administered under the supervision of the Investigator or designee.

Reference Treatment, Dose, and Mode of Administration
The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration), which will be administered at the same dosing interval and volume as the study drug.

Duration of Treatment and Study Participation
The planned duration of treatment for each patient is up to 36 months (approximately 3 years).
The estimated total time on study for each patient is up to approximately 4 years, including a Screening Period of up to 45 days, a DB Period of up to 36 months, and a Follow-up Period of up to 1 year (18 months for women of child-bearing potential).

Study burden and risks

These adverse effects/discomforts/side effects are common (may affect up to 1

in 10 people):

• Injection site reactions
• Pain in joints (arthralgia)
• Shortness of breath (dyspnea)

• Blood draw: Drawing blood may be painful or cause some bruising. We will take at each visit, 3 - 40.7 mL blood each time from the subject. This amount does not cause any problems in adults. To compare: a blood donation involves 500 ml of blood being taken each time.
• Echocardiogram (ECHO): the subject will have gel applied to the chest (this could feel cold) to help sound waves sent to the heart from a probe passed over the chest *echo* back to the probe. The sound waves create a picture of the heart. the subject may be asked to move or hold his/her breath briefly to get better pictures.
• Electrocardiogram (ECG): the subject will have small sticky pads placed on different areas of the body. Wires connected to the pads will send information on the electrical activity back to a machine for recording and measuring. Minor skin irritation could develop from the adhesive used on the pads.

Injection Site Reactions
Vutrisiran will be given under your skin (subcutaneous) in your abdomen, arm, or thigh, and you could develop a reaction at the site of the injection, known as injection site reaction (ISR). It is possible that you could develop pain, tenderness, redness, swelling, itching, formation of sores, skin color changes, or other reactions around an injection site. These reactions usually resolve by themselves. In the phase 1 study, mild and transient ISRs were seen in 4 out of 60 (7%) healthy volunteers given vutrisiran; in the phase 3 study, ISRs were reported in 5 out of 122 (4.1%) patients given vutrisiran and in 5 out of 629 (0.8%) doses of vutrisiran administered.
During the study, the study staff will check the site of injection for any reactions. If you have a reaction, a dermatologist (skin doctor) may examine you. This examination may include taking photographs, collecting a skin sample (biopsy) or other laboratory testing. The photographs will, whenever possible, be taken in such a way as to prevent disclosure of your identity. The Sponsor may want to have the biopsy sample evaluated by a pathologist who is specialized in skin reactions. If you agree, the Sponsor may perform additional testing on the biopsy tissue to increase the understanding of vutrisiran and the reactions at the injection site.

Low Vitamin A
Treatment with vutrisiran lowers vitamin A levels in your blood. Decreases in Vitamin A levels in the blood are not expected to have medical consequences based on studies in animals and in people (healthy volunteers and patients) who received similar siRNA drugs that lowered vitamin A. Your vitamin A levels will be followed with blood tests during the study and, as a precautionary measure,

you will be asked to take a daily Vitamin A supplement during the study and for up to 12-18 months after your final dose of study treatment. Tell your doctor if you experience eye symptoms such as decrease in night vision, dry eyes, poor vision, hazy or cloudy vision, which could be related to low vitamin A levels.

Reproductive Health
It is not known if the use of vutrisiran in pregnant women might harm an unborn child. Data from animal studies are insufficient to determine the risk to the unborn child. It is unknown if breastfeeding while taking vutrisiran may cause harm to the child.
Vitamin A is needed for the normal development of an unborn child. Levels of vitamin A that are too high or too low can harm the normal development of an unborn child. The effects of reduction in a mother*s TTR protein and vitamin A caused by vutrisiran and the effects of vitamin A supplementation on an unborn child are unknown.

Are there any risks with using vutrisiran in combination with other drugs?
The side effects of using vutrisiran in combination with other drugs are not known at this time, but vutrisiran may increase or decrease the level of other drugs that the subject takes. It is very important to tell the study doctor or his/her study staff about any drugs the subject is taking, discuss any dose changes before they happen, any drugs the subject has taken in the past, and any drugs the subject may start taking while in the study, including drugs obtained without a prescription. Drugs that the subject takes that require their levels to be followed may need to have their levels checked more frequently.

Contacts

Public
Alnylam Pharmaceuticals, Inc.

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US
Scientific
Alnylam Pharmaceuticals, Inc.

Third Street 300
Cambridge 02142
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age 18 (or age of legal consent per local regulations, whichever is older) to 85 years, inclusive.
2. Documented diagnosis of ATTR amyloidosis with cardiomyopathy, classified as either hATTR amyloidosis with cardiomyopathy or wtATTR amyloidosis with cardiomyopathy
3. Medical history of HF with at least 1 prior hospitalization for HF (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker) OR clinical evidence of HF (with or without hospitalization) manifested by signs and symptoms of volume overload or elevated intracardiac pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that currently requires treatment with a diuretic.
4. Patient meets one of the following criteria: a. Tafamidis-naïve and not actively planning to commence treatment
with tafamidis during the first 12 months following randomization (per exclusion criterion #7); or
b. On tafamidis (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)
5. Patient is clinically stable, with no CV-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.
6. Screening NT-proBNP >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500ng/L.
7. Able to complete >=150 meters on the 6-MWT at Screening.
8. Have a Karnofsky performance status of >=60%.

Exclusion criteria

1. Has known primary amyloidosis (AL amyloidosis) or leptomeningeal amyloidosis.
2. NYHA Class IV heart failure; or NYHA Class III heart failure AND ATTR Amyloidosis Disease Stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 ml/min)
3. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk due to polyneuropathy, or is wheelchair bound) at the Screening visit.
4. Has any of the following laboratory parameter assessments at Screening:
a. AST or ALT levels >2.0 × ULN,
b. Total bilirubin >2.0 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN)
c. International normalized ratio (INR) >1.5 (unless patients were on anticoagulant therapy in which case excluded if INR >3.5)
5. Has eGFR <30 mL/min/1.73 m2 (using the modification of diet in renal disease [MDRD] formula) at Screening.
6. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.
7. Tafamidis-naïve patients (per inclusion criteria #4a) for whom the Investigator
actively plans or anticipates commencing treatment with tafamidis either during the screening period or the first 12 months following randomization, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
8. Received prior TTR-lowering treatment (including revusiran, patisiran or inotersen) or participated in a gene therapy trial for hATTR amyloidosis.
9. Is currently taking diflunisal; if previously on this agent, must have at least a 30-day wash-out prior to dosing (Day 1).
10. Is currently taking doxycycline or tauroursodeoxycholic acid or ursodeoxycholic acid; if
previously on any of these agents, must have completed a 30-day washout prior to dosing (Day 1).
11. Unwilling to avoid any concurrent treatment with diflunisal, ursodeoxycholic acid/tauroursodeoxycholate/doxycycline, or TTR lowering agents (eg,
patisiran, inotersen)
12. 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). In the case of investigational TTR stabilizer drugs, washout for 3 months prior to dosing (Day 1) is required; this does not apply to patients who are on

tafamidis at baseline (per inclusion criterion #4).
13. Requires treatment with or is unwilling to avoid any concurrent treatment with nondihydropyridine calcium channel blockers (eg, verapamil, diltiazem).
14. Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (eg, prior myocardial infarction with documented history of cardiac enzymes and ECG changes) that the Investigator feels is a significant contributor or the predominant cause of the patient's heart failure.
15. Unstable congestive heart failure (CHF) (including patients who require adjustment of existing diuretics or addition of new diuretics at time of screening for purposes of achieving optimal management of CHF).
16. Had acute coronary syndrome or unstable angina within the past 3 months.
17. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
18. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
19. Has persistent elevation of systolic (>170 mmHg) or diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
20. Has untreated hypo- or hyperthyroidism.
21. Has an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior to dosing (Day 1).
22. Prior or anticipated (during the first 12 months after randomization) heart, liver or other organ transplant or implantation of left-ventricular assist device.
23. History of multiple drug allergies; or history of allergic reaction to any component of or excipient in the study drug.
24. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability.
25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
26. Is not willing to comply with the contraceptive requirements during the study period.
27. Female patient is pregnant, planning a pregnancy, or breast-feeding.
28. Unwilling or unable to limit alcohol consumption throughout the course of the study.
29. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.
30. History of illicit drug abuse within the past 5 years that in the opinion of the Investigator would interfere with compliance with study procedures or follow-up visits.

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:	Recruiting
Start date (anticipated):	09-11-2020
Enrollment:	22
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	03-02-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	22-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2022
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:	18-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2024
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	CTIS2024-518318-25-00
EudraCT	EUCTR2019-003153-28-NL
CCMO	NL71235.000.20