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

Published: 01-09-2020
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This study has been transitioned to CTIS with ID 2023-508364-29-00 check the CTIS register for the current data. To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6 minute walk test [6-MWT]) in patients...

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

Summary

ID

NL-OMON56106

Source
ToetsingOnline

Brief title
APOLLO-B

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Transthyretin Amyloidosis with Cardiomyopathy (ATTR)

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, Patisiran, siRNA

Outcome measures

Primary outcome

Change from baseline at Month 12 in 6 MWT .

Secondary outcome

• Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire

Overall Summary (KCCQ OS) score

• Composite endpoint of all-cause mortality, frequency of cardiovascular (CV)

events (CV hospitalizations and urgent HF visits) and change from baseline in

6-MWT over the 12 month double-blind period

• Composite endpoint of all-cause mortality and frequency of all-cause

hospitalizations and urgent HF visits over the 36-month double-blind period

Study description

Background summary

Transthyretin (TTR)-mediated amyloidosis (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 (ageing) causes, respectively. In ATTR amyloidosis, deposition of TTR in various organs results in progressive, chronically debilitating morbidity and mortality. The most common

manifestations of ATTR amyloidosis are polyneuropathy and cardiomyopathy (ie, ATTR amyloidosis with cardiomyopathy).

The treatment of ATTR amyloidosis requires a multidisciplinary approach primarily involving cardiology, neurology, and gastroenterology specialties. While there are treatments for polyneuropathy that are available to hATTR amyloidosis patients, for most regions no treatments are currently available for the cardiomyopathy phenotype for either the hATTR or wtATTR forms. Palliative/symptomatic therapies directed at specific symptoms, including volume control and treatment of cardiac arrhythmias and conduction system disturbances, including cardiac pacemakers where appropriate, have been the mainstay of treatment despite their limited effectiveness.

Patisiran is a small interfering RNA (siRNA) specific for TTR, which is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[Akinc 2010] The patisiran drug product (ALN-TTR02; patisiran-LNP, hereafter referred to as *patisiran*) is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with ATTR amyloidosis.

Study objective

This study has been transitioned to CTIS with ID 2023-508364-29-00 check the CTIS register for the current data.

To evaluate the efficacy of patisiran compared with placebo treatment on functional capacity (6 minute walk test [6-MWT]) 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 patisiran in approximately 300 patients with ATTR amyloidosis (hereditary or wt) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hATTR and 80% wtATTR. In addition, at baseline, patients are either:
• Tafamidis naïve; or
• Currently on tafamidis (for >=6 months), with disease progression in the opinion of the Investigator. This group will be capped at 30% of total enrollment in the study.
The study consists of a screening period of up to 45 days, a 12-month, double-blind, placebo-controlled period, a 36-month, open-label extension period (during which all patients will receive patisiran), and a 28-day follow-up period.
After screening, during the 12-month double-blind period, eligible patients

will be randomized to receive intravenous (IV) treatment every 3 weeks with either patisiran or placebo. Prior to receiving randomized, double-blind study drug (patisiran or placebo), to reduce the potential for an infusion related reaction (IRR) with patisiran, all patients will receive premedications at least 60 minutes before the start of their infusion. Study drug will be administered as an approximately 80 minute IV infusion.
During the 36-month open-label extension period, all patients will receive treatment with open label patisiran.
Study drug administration at a location other than the study center (eg, at home) may be administered as follows:
• Double-blind period: Patients who have received >=2 doses of study drug at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have study drug administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Study drug administration will be performed by a healthcare professional, trained on the protocol and on administration of premedications and study drug infusion, with oversight of the Investigator.
• 36-month open-label extension period: Patients who have received >=2 doses of open label patisiran at the study center with no evidence of IRRs or other drug-related adverse effects that impact safety and tolerability of the infusion may have patisiran administered at a location other than the study center (eg, at home), where applicable country and local regulations allow. Patisiran administration will be performed by a healthcare professional trained on the protocol and on administration of premedications and patisiran infusion, with oversight of the Investigator.
To evaluate the efficacy of treatment with patisiran versus placebo in patients with ATTR amyloidosis with cardiomyopathy, the change from baseline in 6-MWT will be assessed at Month 12 (Weeks 52-53) as the primary endpoint; this assessment will also be performed at Month 6 (Weeks 25-26) and Month 9 (Weeks 37-38) in the double-blind period, and during the open-label extension period.
The first secondary endpoint will assess change from baseline at Month 12 in the KCCQ-OS score. In situations where an efficacy study visit at Months 6, 9, and/or 12 is unable to be completed at the study center due to the Coronavirus disease 2019 (COVID-19) pandemic impacting activities at the study center or patient ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 6, 9, and/or 12 efficacy assessments. After consultation with the Medical Monitor, efficacy assessments may be extended for that visit as follows: Month 6 up to Day 214; Month 9 up to Day 319; Month 12, up to Day 417, but prior to the first dose of open-label patisiran. Patients may continue to receive double-blind study drug until the Month 12 efficacy assessment is performed.
Safety will be assessed throughout the double-blind and open-label extension periods of the study.

Intervention

Patisiran is a ribonucleic acid (RNA) interference (RNAi) therapeutic consisting of a double-stranded small interfering RNA (siRNA) targeting TTR mRNA formulated in a lipid nanoparticle (LNP). The patisiran drug product is a sterile formulation of ALN-18328 (siRNA targeting TTR) formulated as LNPs with lipid excipients (1,2-Dilinoleyloxy-N,N-dimethylpropylamine [DLin-MC3-DMA], 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-C-DMG) in isotonic phosphate buffered saline.
All patients will receive premedications prior to study drug administration to reduce the risk of IRRs.
An IV infusion of double-blind study drug (patisiran 0.3 mg/kg or placebo) will be administered under the supervision of the site personnel once every 3 weeks ±3 days. Dosing is based on actual body weight. For patients weighing >=100 kg, the maximum recommended patisiran dose is 30 mg.
The last dose of double-blind study drug will be at Week 51 and the first dose of open-label patisiran will be 3 weeks later (at Week 54) and thereafter every 3 weeks (±3 days) for the remainder of the study. Open-label patisiran will be administered per the schedule and dose as is described above for double-blind patisiran.

Reference Treatment, Dose, and Mode of Administration
The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier (or, if necessary, by a local supplier, with prior Sponsor approval).

Study burden and risks

These side effects are very common (occur 1 in 10 people or more):
• Swelling of the arms or legs (peripheral edema)

These side effects are common (occur in up to 1 in 10 people):
• Pain in the joints (arthralgia)
• Muscle spasms
• Indigestion (dyspepsia)
• Shortness of breath (dyspnea)
• Redness of the skin (erythema)
• Feeling dizzy or faint (vertigo)
• Stuffy or runny nose (rhinitis)
• Irritation or infection of the airways (sinusitis, bronchitis)
• infusion-related reaction
• low Vitamin A
Patisiran may also cause side effects that are unknown. If significant new risks develop during the course of the study that might affect your willingness to participate, information will be reported to you as soon as possible.

Tests
• Blood draw: Blood collections may cause pain or bruising. The amount of blood that will be taken from you during a single visit will be between about 4 mL and 16 mL. In total, we will collect approximately 147 mL blood from the subject. This amount should not cause any problems in adults. In comparison: at the blood bank, 500 mL of blood is collected at one time
• Make a heart trace (ECG): the subject will have pads stuck to their chest, arms, and legs so their heart*s electrical activities can be measured. Minor skin irritation could develop from the sticky glue used on the patches
• Echocardiogram (ECHO): the subject will have gel applied to your chest (this could feel cold) and a probe passed over your chest. Minor discomfort could be felt from having to lie in one position during the test.

Potential side effects of pre-medications
In order to decrease the risk of having an infusion-related reaction, teh subject will receive 4 types of medications at least 60 minutes before the dose of study drug. They are approved for use in the Netherlands and have been shown to reduce the chance of having an infusion reaction when given before other drugs that are known to cause such reactions

Infusion-related reactions
Infusion-related reactions are very common (may affect more than 1 in 10 people).
• 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, rash, or itching
• Chest discomfort or chest pain
• Rapid heart rate
• Low or high blood pressure
• Fainting
• Pain, redness, burning sensation, or swelling at or near the infusion site

Low Vitamin A
Treatment with patisiran lowers the amount of vitamin A in your blood. You will be required to take a vitamin supplement every day. You should not take more than the recommended daily allowance of vitamin A. Your vitamin A levels will be measured by a blood test before starting the study.

Thinning of the bones
Patients with ATTR amyloidosis may be at risk for thinning of the bones (osteoporosis), which can lead to an increased risk of breaking a bone.

Long-term use of dexamethasone may have additional effects on the bone. As part of your overall medical care for ATTR amyloidosis, your study doctor may recommend therapy for the prevention and early treatment of osteoporosis.

Contacts

Public
Alnylam Pharmaceuticals, Inc

Third Street 300
Cambridge 02142
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, 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:
Hereditary ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:
a. TTR pathogenic mutation consistent with hATTR.

b. Evidence of cardiac involvement by echocardiography with an enddiastolic interventricular septal wall thickness >12 mm (based on central echocardiogram reading at screening).
c. Amyloid deposits in cardiac or noncardiac tissue (eg, fat pad aspirate, salivary gland, median nerve connective sheath) confirmed by Congo Red (or equivalent) staining OR technetium (99mTc) scintigraphy (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], 99mTc-pyrophosphate [PYP-Tc], or 99mTc-hydroxymethylene diphosphonate (HMDP]) with Grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.
d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.
Wild-type ATTR amyloidosis with cardiomyopathy diagnosed based on meeting all of the following criteria:
a. Absence of pathogenic TTR mutation.
b. Evidence of cardiac involvement by echocardiography with an enddiastolic interventricular septal wall thickness >12mm (based on central echocardiogram reading at screening).
c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, OR technetium (99mTc) scintigraphy (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], 99mTc-pyrophosphate [PYP-Tc] or 99mTc-hydroxymethylene diphosphonate [HMDP]) with Grade 2 or 3 cardiac uptake, if MGUS has been excluded.
d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry
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; in addition to patients who have never taken tafamidis, those who have been on tafamidis for <=30 days total and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.
b. Currently on tafamidis (for >=6 months) and has demonstrated disease progression, as determined by the Investigator. (At the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis for the treatment of ATTR amyloidosis with cardiomyopathy at the approved 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. Able to complete >=150 m on the 6-MWT at screening.
7. 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 <8500 ng/L.

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent; and patient agrees to sign the medical records release form for collection of vital status.

Exclusion criteria

1. Has known primary amyloidosis (AL) or leptomeningeal amyloidosis.
2. NYHA Class III AND ATTR amyloidosis disease Stage 3 (defined as both NT-proBNP >3000 ng/L and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m2).[Gillmore 2018]
3. NYHA Class IV at the Screening visit.
4. Has a polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the Screening visit.
5. Has any of the following laboratory parameter assessments at screening:
a. Aspartate transaminase (AST) or alanine transaminase (ALT) levels>2.0 × the upper limit of normal (ULN).
b. Total bilirubin >2 × ULN.
c. International normalized ratio (INR)>1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR>3.5).
6. Has eGFR <30 mL/min/1.73 m2 (using the modification of diet in renal disease [MDRD] formula).
7. Has known human immunodeficiency virus infection; or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.
8. Tafamidis naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference and/or commercial availability of tafamidis.
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, ursodeoxycholic acid or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day wash-out prior to dosing (Day 1).
11. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for hATTR amyloidosis.
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 6 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 chronic treatment with non-dihydropyridine 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 electrocardiogram [ECG] changes).
15. Has non-amyloid disease affecting exercise testing (eg, severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).
16. Recent or planned orthopedic procedure during the double-blind period (eg, lower extremity or back surgery) that could impact 6-MWT.
17. Unstable congestive heart failure (CHF) (eg, no adjustment of diuretics at time of screening required to achieve optimal treatment of CHF).
18. Had acute coronary syndrome or unstable angina within the past 3 months.
19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.
20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.
21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.
22. Has untreated hypo- or hyperthyroidism.
23. Prior or planned heart, liver, or other organ transplant.
24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.
26. Has a history of severe hypersensitivity (eg. anaphylaxis) to any of the excipients in patisiran. Also see exclusion Criterion 11, which excludes all patients with prior TTR-lowering treatment including patisiran.
27. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
28. Female patient is pregnant or breast-feeding.
29. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, more than 14 units of alcohol per week; for males, more than 21 units of alcohol per week [unit: 1
glass of wine [125 mL] = 1 measure of spirits = * pint of beer]);
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):	15-03-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	01-09-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2023
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)

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	CTIS2023-508364-29-00
EudraCT	EUCTR2019-001458-24-NL
CCMO	NL74788.000.20