APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)

Published: 20-08-2014
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This study aims to demonstrate the clinical efficacy of patisiran and to establish the safety of chronic dosing in ATTR patients with FAP.The primary objective of the study is to determine the efficacy of patisiran by evaluating the difference...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON44756

Source
ToetsingOnline

Brief title
APOLLO

Condition

- Neurological disorders congenital
- Neurological disorders NEC

Synonym

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familial ATTR, FAP (familial amyloidotic polyneuropathy)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALN-TTR02, Familial amyloidotic polyneuropathy, patisiran, RNAi therapeutic

Outcome measures

Primary outcome

The primary objective of the study is to determine the efficacy of patisiran by evaluating the difference between the patisiran and placebo groups in the change from baseline of modified NIS+7 (mNIS+7) score at 18 months.

Secondary outcome

The secondary objectives of the study are to determine the effect of patisiran on various clinical parameters by assessing the difference between patisiran and placebo in the change from baseline in the following measurements at 18 months:

- Quality of Life

- Motor function

- Autonomic function

Study description

Background summary

Transthyretin-mediated amyloidosis (ATTR) is an inherited, autosomal dominant,

systemic disease caused by a mutation in the transthyretin (TTR) gene, leading to destabilization of the tetrameric form of TTR and tissue deposition of amyloid fibrils. The particular TTR mutation and site of amyloid deposition determines the clinical manifestations of the disease, which include sensory and motor neuropathy, autonomic neuropathy, and/or cardiomyopathy. ATTR is a progressive disease associated with severe morbidity, with a life expectancy limited to 5 to 15 years from symptom onset. There are over 100 reported TTR mutations which are associated with 2 clinical syndromes: familial amyloidotic polyneuropathy (FAP) and familial amyloidotic cardiomyopathy (FAC). The estimated worldwide prevalence of FAP is 5,000 to 10,000, with the majority of cases in Portugal, Sweden, France, Japan, Brazil, and the United States.
There are multiple lines of evidence demonstrating that reduction of circulating TTR improves outcomes in patients with ATTR. Because the liver is the primary source of wildtype and mutant TTR, orthotopic liver transplantation is the current standard of care in patients with minimal neuropathy symptoms and no cardiac involvement. It is estimated that approximately two-thirds of FAP patients are not transplant-eligible. Nonsurgical options that are used for the treatment of FAP include tafamidis (Vyndaqel®; only approved in the EU for early-stage FAP) and diflunisal (completed a phase III clinical trial). Due to the restricted use of liver transplantation and tafamidis in patients with early stage of disease, and the non-standard use of diflunisal among practitioners, there remains an unmet medical need for a potent and effective therapy for FAP that will have an impact on patients across a broad range of neurologic impairment, regardless of their mutation.
Patisiran (ALN-TTR02) is being developed for the treatment of ATTR patients with symptomatic FAP. Patisiran is a short interfering RNA (siRNA) specifically targeting TTR, and is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration. Following LNP-mediated delivery to the liver, patisiran targets TTR mRNA for degradation, resulting in the potent and sustained reduction of mutant and WT TTR protein via the RNA interference (RNAi) mechanism. It is postulated that the suppression in both WT and mutant TTR observed upon administration of patisiran once every 21 days may result in clinical benefit in FAP patients with polyneuropathy.

Study objective

This study aims to demonstrate the clinical efficacy of patisiran and to establish the safety of chronic dosing in ATTR patients with FAP.

The primary objective of the study is to determine the efficacy of patisiran by evaluating the difference between the patisiran and placebo groups in the change from baseline of modified NIS+7 (mNIS+7) score at 18 months.

The secondary objectives of the study are to determine the effect of patisiran on various clinical parameters by assessing the difference between patisiran and placebo in the change from baseline in the following measurements at 18 months:

- Quality of Life
- Motor function
- Autonomic function

Study design

This is a multicenter, multinational, randomized, double-blind study comparing patisiran to placebo in ATTR patients with symptomatic Familial Amyloidotic Polyneuropathy (FAP).
Consented eligible patients will be randomized to receive either 0.3 mg/kg patisiran or placebo in a blinded manner. Patients will receive patisiran or placebo for 78 weeks.

Intervention

Consented eligible patients will be randomized to receive either 0.3 mg/kg patisiran or placebo in a blinded manner. Patients randomized to the active treatment group will receive 0.3 mg/kg patisiran administered as an IV infusion by a controlled infusion device.
Patients randomized to placebo will receive IV normal saline (0.9%).

Study burden and risks

Patients are required to visit the hospital more often than during standard treatment, and will need to discontinue tafamidis or diflunisal if presently used. The patient's participation in this study will last for approximately 78 weeks. Efficacy and safety testing will be performed. Visits involve the administration of study medication and standard safety tests.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female of 18 to 85 years of age (inclusive);
- Have a diagnosis of FAP;
- Have a Neuropathy Impairment Score of 5 to 100;
- Have a Karnofsky performance status *60%;
- Have adequate complete blood counts and liver function tests;
- Have adequate cardiac function;
- Have negative serology for hepatitis B virus (HBV) and hepatitis C virus (HCV);

Exclusion criteria

- Had a prior liver transplant
- Has untreated hypo- or hyperthyroidism;
- Has known human immunodeficiency virus (HIV) infection;
- 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;
- Recently received an investigational agent or device ;
- Is currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid;

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:	Recruitment stopped
Start date (anticipated):	25-06-2015
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	20-08-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-12-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-07-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-08-2016
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-11-2016
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	EUCTR2013-002987-17-NL
ClinicalTrials.gov	NCT01960348
CCMO	NL46180.000.14