APOLLO Phase 3 Clinical Trial Overview

Alnylam is conducting a Phase 3 clinical trial called, APOLLO (NCT01960348), examining the investigational drug patisiran in people with hereditary ATTR amyloidosis (hATTR amyloidosis) with polyneuropathy. hATTR amyloidosis is caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple sites including the nerves, heart, and gastrointestinal tract.[1]

About hATTR amyloidosis

hATTR amyloidosis is an inherited, rapidly progressive, life-threatening disease. It is a multisystemic disease with a heterogeneous clinical presentation that includes sensory and motor, autonomic (e.g., diarrhea, hypotension, erectile dysfunction) and cardiac symptoms. hATTR amyloidosis has an aggressive course and can lead to significant morbidity, disability and can potentially lead to mortality within two to 15 years.[1]

The disease continuum of hATTR amyloidosis includes patients who present with predominantly polyneuropathy symptoms, historically known as familial amyloidotic polyneuropathy (FAP), as well as patients who present with predominantly cardiomyopathy symptoms, historically known as familial amyloidotic cardiomyopathy (FAC). However, many patients suffer from both polyneuropathy and cardiomyopathy symptoms. Due to the constellation of the disease presentation and progression, hATTR amyloidosis is often initially misdiagnosed. Many specialists are typically seen over the course of many years during a patient's path to diagnosis. Treatment options for the disease are limited.[2]

About the APOLLO Study

Objective

To evaluate the efficacy and safety of patisiran in patients with hereditary ATTR amyloidosis (hATTR amyloidosis) with polyneuropathy.

Design

- APOLLO is being conducted in 50 clinical centers in 21 countries worldwide.
- All participants are between 18-85 years old, diagnosed with hATTR amyloidosis with polyneuropathy, a documented TTR mutation, have adequate cardiac function, have not had a liver transplant and have met other eligibility criteria.
- The study is randomized, double-blinded and placebo controlled, meaning that neither the physicians nor the participants know which participants are receiving patisiran or placebo.
- 225 participants were randomly assigned to receive patisiran or placebo; two out of three participants in the study were randomly assigned to receive patisiran and one out of three participants were assigned to receive placebo.
- Patisiran or placebo is administered by IV infusion once every three weeks.
- At nine and 18 months, participants will be assessed to see if and how patisiran is affecting their disease (refer to endpoints listed below).

- After 18 months, patients who complete the study may be eligible to continue treatment with patisiran as part of a clinical trial open label extension study, APOLLO-OLE (NCT02510261).

Primary Endpoint

The primary outcome measure of this study is the difference between treated and placebo groups in the change from baseline of the modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months. The mNIS+7 is a composite neurologic impairment score that provides a robust and reproducible outcome measure assessing all aspects of the neuropathy, including sensory, motor and autonomic manifestations. An increase in mNIS+7 score over time means the disease is worsening.

Other Select Endpoints

Other select endpoints include the difference between patisiran and placebo groups in the change from baseline after 18 months in terms of quality of life, motor function and autonomic function. Clinical evaluations of these outcome measures include:

- **Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Score:** This is a comprehensive and validated tool designed to capture the full spectrum of neuropathy on patient perceptions about their quality of life, including symptoms in the extremities, subtle loss of function, such as fine motor impairments and slight sensory changes, unique problems with proprioception (the sense of position of self and movement) and balance and a variety of autonomic symptoms.[3]
- **NIS-weakness:** This tool evaluates weakness within a broad group of muscles, including those of the head and limbs.[1]
- **Modified Body Mass Index (mBMI):** This is used to evaluate nutritional status of patients.
- **Timed 10-meter walk:** This is a test of mobility, in which time is measured while a patient walks a specific distance.
- **Composite Autonomic Symptom Score (COMPASS) 31:** This tool provides a concise score of autonomic (involuntary) functions including orthostatic, vasomotor and gastrointestinal measurements.[4]
- **Rasch-built Overall Disability Scale (R-ODS):** Assesses activity and social participation limitations in patients comprised of a 24-item linearly weighted scale.

Timing

- Initiated in November 2013
- Enrollment completed in January 2016
- Results expected in mid-2017

For more information, please contact media@alnylam.com or visit the clinicaltrials.gov page for each study: APOLLO and APOLLO-OLE.

1. Suanprasert N, et al. J Neurol Sci. 2014;344:121–128. 19.
2. Hawkins PN, et al. Annals of Medicine. 2015;625–638.
3. Vinik EJ, et al. Diabetes Technol Ther. 2005;7:497-508.
4. Sletten DM, et al. Mayo Clin Proc. 2012;87:1196-201.