

Patisiran Clinical Development Programs

Patisiran is an intravenously administered, RNA interference (RNAi) therapeutic that is approved as ONPATTRO® (patisiran) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.* Patisiran is also being investigated for the treatment of ATTR amyloidosis with cardiomyopathy. ATTR amyloidosis is a rare, progressively debilitating and fatal disease that's caused by misfolded transthyretin (TTR) proteins that accumulate as amyloid deposits in multiple tissues, including the nerves, heart and gastrointestinal (GI) tract. There are two types of ATTR amyloidosis: hereditary (hATTR) and wild-type (wt) amyloidosis. The goal of the APOLLO clinical program is to evaluate the safety and efficacy of patisiran across the different types of this disease.

APOLLO-A (Completed in August 2017)¹

The APOLLO-A Phase 3 study (N=225) was a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in people with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy. The study was the largest controlled study of hATTR amyloidosis and was completed in August 2017. Patients who completed the trial were eligible to screen for the global open-label extension study, of which 99 percent enrolled.

APOLLO-A Endpoints

- The primary outcome measure of APOLLO-A was the difference between patisiran and placebo groups in the change from baseline of the modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months.
- Other endpoints included 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 outcomes included the Norfolk Quality of Life-Diabetic (QOL-DN) Score, timed 10-Meter Walk Test, Neuropathy Impairment Score (NIS)-weakness, Composite Autonomic Symptom Score (COMPASS) 31, modified Body Mass Index, Rasch-built Overall Disability Scale (R-ODS), and EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L).

APOLLO-A Results

- The study showed that ONPATTRO improved measures of polyneuropathy, quality of life, activities of daily living, ambulation, nutritional status and autonomic neuropathy symptoms relative to placebo in adult patients with hATTR amyloidosis with polyneuropathy. The primary endpoint of the APOLLO study was the modified Neuropathy Impairment Score +7 (mNIS+7), which assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure.
 - Patients treated with ONPATTRO had a mean 6.0-point decrease (improvement) in mNIS+7 score from baseline compared to a mean 28.0-point increase (worsening) for patients in the placebo group, resulting in a mean 34.0-point difference relative to placebo, after 18 months of treatment.
 - Fifty-six percent of ONPATTRO-treated patients at 18 months of treatment experienced reversal of neuropathy impairment (as assessed by mNIS+7 score) relative to their own baseline, compared to four percent of patients who received placebo.
 - Patients treated with ONPATTRO had a mean 6.7-point decrease (improvement) in Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) score from baseline compared to a mean 14.4-point increase (worsening) for patients in the placebo group, resulting in a mean 21.1-point difference relative to placebo, after 18 months of treatment.
 - As measured by Norfolk QoL-DN, 51 percent of patients treated with ONPATTRO experienced

improvement in quality of life at 18 months relative to their own baseline, compared to 10 percent of the placebo-treated patients.

- Additionally, patients treated with ONPATTRO experienced significant benefit versus placebo for all other secondary efficacy endpoints, including measures of activities of daily living, walking ability, nutritional status, and autonomic neuropathy symptoms.
- The most common adverse events that occurred more frequently with ONPATTRO than with placebo were upper respiratory tract infections and infusion-related reactions. To reduce the risk of infusion-related reactions, patients received premedication prior to infusion.

APOLLO-B²

The APOLLO-B study is a Phase 3, randomized, double-blind, placebo-controlled multicenter global study designed to evaluate the efficacy and safety of patisiran in patients with transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy, which enrolled 360 adult patients with ATTR amyloidosis (hereditary or wild-type) with cardiomyopathy.

APOLLO-B Study Design

- Study participants are randomized on a 1:1 basis to receive 0.3 mg/kg of patisiran or placebo intravenously administered every three weeks over a 12-month treatment period.
- The study consists of a 12-month, double-blind, placebo-controlled period and a 36-month open-label extension period (during which all patients receive patisiran).

APOLLO-B Endpoints

- The primary outcome measure of APOLLO-B is the change from baseline in the 6-minute walk test at 12 months.
- Key secondary and exploratory endpoints will evaluate the efficacy of patisiran compared to placebo on health status and health-related quality of life, patient mortality and hospitalizations, cardiac biomarkers and manifestations of cardiac amyloid involvement.

The APOLLO-B trial started in mid-2019 and enrollment was completed in May, 2021. The first top-line results are expected in mid-2022.

For more information on APOLLO-B ([NCT03997383](https://clinicaltrials.gov/ct2/show/NCT03997383)), please visit clinicaltrials.gov or contact media@alnylam.com.

**ONPATTRO was approved by the United States Food and Drug Administration on August 10, 2018. Patisiran is approved in >30 countries globally for hATTR amyloidosis with polyneuropathy; specific indications vary by country/region.*

¹ Adams D, Gonzalez-Duarte A, O’Riordan WD, et al. *N Engl J Med.* 2018; 379:11-21.

² National Institutes of Health: U.S. National Library of Medicine. 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). <https://clinicaltrials.gov/ct2/show/NCT03997383>. Accessed May 5, 2022.