Patisiran Clinical Development Program

APOLLO[1]

APOLLO was a global, randomized, double-blind, multicenter, placebo-controlled Phase 3 study designed to evaluate the efficacy and safety of patisiran in adult patients with the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis. The study was the largest controlled study in hATTR amyloidosis.

Study Status

- The study was completed in August 2017, with an enrollment of 225 patients.

Study Design

- Patients were randomized on a 2:1 basis to receive 0.3 mg/kg of patisiran or placebo intravenously administered once every three weeks over an 18-month treatment period.
- Patients who completed the 18-month trial were eligible to screen for the global open-label extension study, of which 99% enrolled.

Primary Endpoint

The primary endpoint of APOLLO was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months. The mNIS+7 assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure. It has a score range from 0-304 points, with higher scores representing a greater severity of disease.[1,2]

Secondary Endpoints

Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) Score at 18 months	The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that is sensitive to the different features of diabetic neuropathy – small fiber, large fiber, and autonomic nerve function, symptoms and activities of daily living – which may impact quality of life. It is validated for hATTR amyloidosis with polyneuropathy. The Norfolk QoL-DN has a total score range from -4 to 136, with higher scores representing greater impairment.[3-5]
Change from baseline in Neuropathy Impairment Score-weakness (NIS-W) at 18 months	NIS-W is a component of mNIS+7 that quantifies motor strength. The score ranges from 0 to 192, with higher scores indicating more impairment.[1]
Change from baseline in Rasch-built Overall Disability Scale (R-ODS) at 18 months	R-ODS is a 24-item linearly weighted scale that specifically captures activity and social participation limitations. The minimum and maximum values are 0 and 48, respectively. A higher score indicates less disability.[1,6]
Change from baseline in timed 10-Meter Walk Test (10-MWT) at 18 months	A test of ambulatory function that measures a patient's speed in walking 10 meters.[7]
Change from baseline in modified Body Mass Index (mBMI) at 18 months	A measure of nutritional status calculated as the product of body mass index and serum albumin.[1,8] Lower mBMI indicates worse nutritional status.
Change from baseline in Composite Autonomic Symptom Score 31 (COMPASS 31) at 18 months	The COMPASS 31 is a composite score that quantifies autonomic symptoms. The minimum and maximum values are 0 and 100, respectively, with higher scores indicating more autonomic neuropathy symptoms.[1,3]

Select Exploratory Endpoint

Change from baseline in EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) score at 18 months	A patient-reported, standardized five-dimension instrument that measures health outcomes, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels of severity.[3]

APOLLO-B[9-11]

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

Study Status

- The double-blind period of the study was completed in June 2022, with an enrollment of 360 patients. The open-label extension period is expected to complete in June 2025.

Study Design

- Study participants were 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).

Primary Endpoint

The primary endpoint of APOLLO-B was the change from baseline in the 6-Minute Walk Test (6-MWT) at 12 months. The 6-MWT measures distance walked over a period of 6 minutes; a decrease in the distance walked indicates a decline in functional capacity.

Secondary Endpoints

Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score at 12 months	The KCCQ is a 23-item self-administered questionnaire quantifying 6 domains (symptoms, physical function, quality of life, social limitation, self-efficacy and symptom stability) and 2 summary scores (clinical and overall summary [OS]). Scores are transformed to a range of 0-100, in which higher scores reflect better health status.[9]
Composite endpoint of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent heart failure [HF] visits) and change from baseline in 6-MWT up to 12 months	This composite endpoint was analyzed using the win ratio method. This method combines all-cause mortality, frequency of CV events (CV hospitalizations and HF visits) and change from baseline in 6-MWT in a hierarchical fashion. The method uses pairwise comparisons for all possible active/placebo patient pairs. A 'win' represents a patient doing better based on the hierarchical comparison. The win ratio is the total number of 'winners' divided by the total number of 'losers' in the active group.[9]
Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits up to 12 months	The hazard rate of all-cause mortality and all-cause hospitalizations and urgent HF visits was compared between treatment groups using an Andersen-Gill model.[9]

Select Exploratory Endpoints

Change from baseline in N-terminal prohormone B-type natriuretic peptide (NT-proBNP) and troponin I at 12 months	Biomarkers for the severity of heart failure, cardiac stress and cardiac injury.[10]

For more information on APOLLO (**NCT01960348**) and APOLLO-B (**NCT03997383**), please visit clinicaltrials.gov or contact **media@alnylam.com**.

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