Patisiran Clinical Development Program

**APOLLO**

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-SD-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-B9-11

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

<table>
<thead>
<tr>
<th>Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score at 12 months</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Composite endpoint of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits up to 12 months</td>
<td>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</td>
</tr>
</tbody>
</table>

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.