Vutrisiran Clinical Development Program

Vutrisiran (ALN-TTRsc02) is an investigational subcutaneously administered (under the skin) RNA interference (RNAi) therapeutic being evaluated for the treatment of ATTR amyloidosis, which encompasses both hereditary ATTR (hATTR) and wild-type (wt) amyloidosis. Vutrisiran is being studied in the Phase 3 HELIOS clinical program, consisting of two clinical trials, HELIOS-A (currently underway) and HELIOS-B (expected to initiate in late 2019), to evaluate the safety and efficacy of vutrisiran in patients with ATTR amyloidosis.

HELIOS-A

HELIOS-A is a Phase 3 global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran in patients with hereditary ATTR (hATTR) amyloidosis with polyneuropathy.

Study Design

- The randomized global, open-label trial is enrolling 160 people diagnosed with hATTR amyloidosis with polyneuropathy, between the ages of 18 and 85, in which 120 patients will receive 25mg of vutrisiran subcutaneously every 12 weeks over an 18-month period, and 40 patients will receive a 0.3 mg/kg IV infusion of patisiran once every three weeks as a reference comparator. In addition, results from the vutrisiran arm will be compared to the placebo arm results from the APOLLO Phase 3 study for most endpoints, which evaluated the efficacy and safety of patisiran in people with hATTR amyloidosis with polyneuropathy.
- Following the 18-month study period, all patients are eligible to receive vutrisiran during a treatment extension period.

Primary Endpoints

The co-primary endpoints of HELIOS-A are the change from baseline in the modified Neurologic Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Total Score at 9 months.

modified Neuropathy Impairment Score+7 (mNIS+7)	A composite neurologic impairment score, including sensory, motor, and autonomic manifestations – an increase in mNIS+7 score over time means a patient's level of impairment from his or her neuropathy is worsening
Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Score	A comprehensive quality of life questionnaire for patients that includes activities of daily living that may be impacted by both small and large fiber polyneuropathy

Secondary Endpoints

Key secondary endpoints include the change from baseline at 9 and 18 months, measured by clinical evaluations including:

Timed 10-meter walk (10-MWT)	A test of mobility that measures the time it takes for a patient to walk 10 meters
modified Body Mass Index (mBMI)	A measure of nutritional status that combines serum albumin and body mass index
Rasch-built Overall Disability Scale (R-ODS)	A tool to assess activity and social participation limitations in patients comprised of a 24-item linearly weighted scale
Serum Transthyretin (TTR) Levels	A measure of TTR protein levels in ATTR patients

Topline results from the HELIOS-A study are expected in late 2020.

For more information on HELIOS-A (NCT03759379), please visit www.clinicaltrials.gov or contact media@alnylam.com.

HELIOS-B

HELIOS-B will evaluate the efficacy and safety of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy. Initiation of this trial is expected in late 2019.

Vutrisiran has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

[1] ONPATTRO [package insert]. Cambridge, MA; Alnylam Pharmaceuticals, Inc; 2018.
[2] Suhr. *J Intern Med* 1994 235:479-485
[3] van Nes SI. *Neurology* 2011 76:337–345