Vutrisiran Clinical Development Program

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.

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 and HELIOS-B.

HELIOS-A

HELIOS-A is a Phase 3 global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran in patients with 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 questionnaire of 35 patients reported outcomes measures that is sensitive to the different features of diabetic neuropathy – a higher score indicates a worse outcome. Activities of daily living may be impacted by small fiber, and large fiber polyneuropathy, and autonomic nerve function[1,2]

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[3]
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[4]
Serum Transthyretin (TTR) Levels	A measure of TTR protein levels in ATTR patients

HELIOS-B

HELIOS-B is a global Phase 3, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran, in patients with ATTR amyloidosis with cardiomyopathy.

Study Design

- The randomized, double-blind, placebo-controlled trial is enrolling 600 patients with ATTR amyloidosis with cardiomyopathy in which patients will be randomized on a 1:1 basis to receive 25 mg of vutrisiran or placebo administered as a subcutaneous injection once every three months for up to 36 months. The study protocol includes an optional interim analysis to be conducted at the Company's discretion.

Primary Endpoint

The primary endpoint will evaluate the efficacy of vutrisiran versus placebo toward the composite outcome of reducing all-cause mortality and recurrent cardiovascular hospitalizations at 30 months.

All-cause mortality and cardiovascular (CV)-related hospitalizations	An evaluation on the reduction of all cases of morality and CV-related hospitalizations

Secondary Endpoints

Secondary endpoints include the change from baseline, measured by clinical evaluations including:

6-minute walk test (6-MWT)	An assessment of functional exercise capacity
Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS)	A 23-item self-administered questionnaire developed to independently measure the patient's perception of health status
Mean left ventricular (LV) wall thickness and global longitudinal strain	Assessment of cardiac structure and function by use of echocardiogram
All-cause mortality	Assessment of death
Recurrent CV hospitalizations	Assessment of cardiovascular hospitalization outcomes
N-terminal prohormone B-type natriuretic peptide (NT-proBNP)	A measure of the non-active prohormone that is released in response to changes in pressure inside the heart

For more information on HELIOS-A (NCT03759379) and HELIOS-B (NCT04153149) please visit www.clinicaltrials.gov or contact media@alnylam.com.

[1] Vinik, E. J., R. P. Hayes, et al. (2005). *Diabetes Technol Ther* 7(3): 497-508.
[2] Vinik, E. J., A. I. Vinik, et al. (2014). *J Peripher Nerv Syst* 19(2): 104-114.
[3] Suhr. *J Intern Med* 1994 235:479-485.
[4] van Nes SI. *Neurology* 2011 76:337–345.