

# 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 is an investigational RNAi therapeutic, administered subcutaneously every three months, in development for the treatment of transthyretin-mediated (ATTR) amyloidosis, which encompasses both hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis. Vutrisiran is under evaluation in the Phase 3 HELIOS clinical program, currently consisting of two pivotal clinical trials: HELIOS-A<sup>1</sup> and HELIOS-B.<sup>2</sup>

## HELIOS-A

HELIOS-A is a Phase 3 global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran in adult patients with hATTR amyloidosis with polyneuropathy.<sup>1</sup>

### Study Status

- Enrollment is complete with 164 patients.

### Study Design

- Patients were randomized 3:1 to receive either 25mg of vutrisiran via subcutaneous injection once every three months or 0.3 mg/kg of patisiran via IV infusion once every three weeks (as a reference comparator), for 18 months. Thereafter, all patients will receive vutrisiran during a treatment extension period.<sup>3</sup>
- For the primary and most secondary and exploratory efficacy endpoints, the vutrisiran arm will be compared to the placebo arm of the APOLLO Phase 3 study.<sup>4</sup>

### Primary Endpoint

The primary endpoint of HELIOS-A is the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months.

### Secondary Endpoints

See below for descriptions of secondary endpoints.

<b>Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Score at 9 and 18 months</b>	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 minimum and maximum values are -4 and 136, respectively. <sup>5</sup> A higher score indicates a worse outcome. <sup>6,7</sup>
<b>Change from baseline in timed 10-meter walk test (10-MWT) at 9 and 18 months</b>	A test of ambulatory function that measures a patient's speed in walking 10 meters. <sup>8</sup>
<b>Change from baseline in modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months</b>	The mNIS+7 is a composite score that quantifies motor, sensory, and autonomic neurologic impairment due to injury of large and small nerves. The minimum and maximum values are 0 and 304, respectively. A higher score indicates a worse outcome. <sup>9</sup>
<b>Change from baseline in modified Body Mass Index (mBMI) at 18 months</b>	A measure of nutritional status calculated as the product of body mass index and serum albumin. <sup>4,10</sup> Lower mBMI indicates worse nutritional status.
<b>Change from baseline in Rasch-built Overall Disability Scale (R-ODS) at 18 months</b>	R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations. The minimum and maximum values are 0 and 48, respectively. <sup>4</sup> A higher score indicates a better outcome. <sup>4,11</sup>
<b>Percentage reduction in serum Transthyretin (TTR) Levels through 18 months</b>	Unlike other endpoints, for this measure the vutrisiran arm will be compared to the within-study patisiran arm. <sup>1</sup>

## HELIOS-B

HELIOS-B is a global, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran in adult patients with ATTR amyloidosis with cardiomyopathy (including both hATTR and wtATTR amyloidosis).<sup>2</sup>

### Study Status

- Enrollment is ongoing. The trial is planned to enroll ~600 patients with ATTR amyloidosis with cardiomyopathy.

### Study Design

- Patients will be randomized on a 1:1 basis to receive either 25 mg of vutrisiran or placebo administered as a subcutaneous injection once every three months for up to 36 months.

### Primary Endpoint

The primary endpoint will evaluate the efficacy of vutrisiran versus placebo on the composite endpoint of all-cause mortality and recurrent cardiovascular (CV) events (CV hospitalizations and urgent heart failure (HF) visits) at 30-36 months.

### Secondary Endpoints

Secondary endpoints include:

<b>Change from baseline in 6-minute walk test (6-MWT) at 30 months</b>	An assessment of functional exercise capacity, measuring how far a patient can walk in six minutes along a prescribed course. <sup>2,12</sup>
<b>Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) at 30 months</b>	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. <sup>2</sup>
<b>Change from baseline in mean left ventricular (LV) wall thickness and global longitudinal strain at 30 months</b>	Echocardiographic assessments of cardiac structure and function. <sup>2</sup>
<b>Composite endpoint of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits at 30-36 months</b>	All-cause mortality, recurrent all-cause hospitalizations and urgent HF visits. <sup>2</sup>
<b>All-cause mortality at 30-36 months</b>	Deaths from any cause. <sup>2</sup>
<b>Recurrent CV events at 30-36 months</b>	Recurrent CV events (CV hospitalizations and urgent HF visits). <sup>2</sup>
<b>Change from baseline in N-terminal prohormone B-type natriuretic peptide (NT-proBNP) at 30 months</b>	A biomarker for the severity of heart failure. <sup>2,13</sup>

For more information on HELIOS-A ([NCT03759379](https://clinicaltrials.gov/ct2/show/NCT03759379)) and HELIOS-B ([NCT04153149](https://clinicaltrials.gov/ct2/show/NCT04153149)) please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) or contact [media@alnylam.com](mailto:media@alnylam.com).

Current information as of January 5, 2021.

<sup>1</sup> National Institutes of Health : U.S. National Library of Medicine. HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis). <https://clinicaltrials.gov/ct2/show/NCT03759379>. Accessed December 17, 2020.

<sup>2</sup> National Institutes of Health : U.S. National Library of Medicine. HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy. <https://clinicaltrials.gov/ct2/show/NCT04153149>. Accessed December 17, 2020.

<sup>3</sup> Data on file.

<sup>4</sup> Adams D, et al. *N Engl J Med*. 2018;378(27).

<sup>5</sup> Obici, Laura, et al. *Amyloid* 2020;27(3):153-162. 10.1080/13506129.2020.1730790. Accessed November 20, 2020.

<sup>6</sup> Vinik, E. J., R. P. Hayes, et al. *Diabetes Technol Ther* 2005;7(3):497-508.

<sup>7</sup> Vinik, E. J., A. I. Vinik, et al. *J Peripher Nerv Syst* 2014;19(2):104-114.

<sup>8</sup> Palmer, Ellenore. Cinahl Information Systems. November 2015;1-6.

<sup>9</sup> Dyck, P. James, et al. *J Neurol Sciences* 2019;405(116424).

<sup>10</sup> Suhr. *J Intern Med* 1994;235:479-485.

<sup>11</sup> van Nes SI. *Neurology* 2011;76:337-345.

<sup>12</sup> Vita, G. L., et al. *Neuromuscular Disorders* 29 2019;213-220.

<sup>13</sup> Solomon, S. et al. *Circulation* 2019;139:431-443.