Vutrisiran Clinical Development Program

Vutrisiran is an RNA interference (RNAi) therapeutic administered via subcutaneous injection once every three months (quarterly) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. Where it is approved, it is marketed as AMVUTTRA® (vutrisiran).

Vutrisiran is also being evaluated as an investigational therapy in the HELIOS-B[1] Phase 3 study for the treatment of adult patients with transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy, including both hATTR and wild-type ATTR (wtATTR) amyloidosis.

HELIOS-A

HELIOS-A was a Phase 3 global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran in adult patients with hATTR amyloidosis with polyneuropathy.[2]

Study Status

- The primary analysis was completed in November 2020.

Study Design

- Patients (N=164) were randomized 3:1 to receive either 25 mg 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 group), for 18 months.[3]
- For the primary and most secondary and exploratory efficacy endpoints, the vutrisiran arm was compared to an external placebo group from another study composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis.[3,4]

Primary Endpoint

The primary endpoint of HELIOS-A was the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months. The mNIS+7 has a total score range from 0 to 304 points, with higher scores representing a greater severity of disease.

Secondary Endpoints

Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Score at 9 and 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.[5,6,7]
Change from baseline in timed 10-meter walk test (10-MWT) at 9 and 18 months	A test of ambulatory function that measures a patient's speed in walking 10 meters.[8]
Change from baseline in modified Neuropathy Impairment Score+7 (mNIS+7) at 18 months	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, with higher scores representing a greater severity of disease.[9]
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.[4,10] Lower mBMI indicates worse nutritional status.
Change from baseline in Rasch-built Overall Disability Scale (R-ODS) at 18 months	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.[3] A higher score indicates less disability.[4,11]
Percentage reduction in serum transthyretin (TTR) levels through 18 months	Unlike other endpoints, for this measure the vutrisiran arm was compared to the within-study patisiran arm.[2]

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).[1]

Study Status

- Enrollment is complete with 655 patients.

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) in the overall study population and in the vutrisiran monotherapy population (defined as the group of patients not on tafamidis at study baseline) at 33-36 months.

Secondary Endpoints

The following secondary endpoints will be evaluated in both the overall study population and the vutrisiran monotherapy population:

Change from baseline in 6-minute walk test (6-MWT)	An assessment of functional exercise capacity, measuring how far a patient can walk in six minutes along a prescribed course.[1, 12]
Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS)	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.[1]
All-cause mortality	Death from any cause.[1]
Change from baseline in New York Heart Association (NYHA) class	A clinical assessment of symptoms resulting from HF.[1]

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

Current information as of May 2024.

[1] 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 April 29, 2024.
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