Vutrisiran Clinical Development Program

Vutrisiran is an RNA interference (RNAi) therapeutic administered via subcutaneous injection once every three months (quarterly) for ATTR amyloidosis. It is marketed as AMVUTTRA® (vutrisiran) and it is approved in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults, and for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (CV) mortality, CV hospitalizations and urgent heart failure (HF) visits.

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-PN.[1]

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.[2]
- 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-PN.[2,3]

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.[1]

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.[1,4,5,6]
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.[7]
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.[8]
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.[3,9] 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.[2] A higher score indicates less disability.[3,10]
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.[1]

HELIOS-B

HELIOS-B was a Phase 3, global randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran in adult patients with ATTR-CM, including both hATTR and wild-type ATTR.[12]

Study Status

- The primary analysis was completed in May 2024.

Study Design

- Patients (N=654) were randomized 1:1 to receive either 25 mg of vutrisiran or placebo via subcutaneous injection once every three months for up to 36 months.

Primary Endpoint

The primary endpoint of HELIOS-B was the composite of all-cause mortality and recurrent CV events (hospitalizations and urgent HF visits) through 33-36 months. The primary endpoint was assessed separately in the overall population and in the monotherapy population (defined as the patients who were not receiving tafamidis at baseline).

Secondary Endpoints

Change from baseline in 6-minute walk test (6-MWT) at 30 months	An assessment of functional exercise capacity, measuring how far a patient can walk in six minutes along a prescribed course.[11, 12]
Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score at 30 months	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.[12]
All-cause mortality through up to 42 months	Death from any cause.[12]
Change from baseline in New York Heart Association (NYHA) class at 30 months	An assessment of the severity of clinical HF symptoms.[12]

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 March 2025.

[1] 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 January 9, 2025.
[2] Adams D, Tournev IL, Taylor MS, et al. *Amyloid.* 2023;30(1):18-26.
[3] Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. *N Engl J Med*. 2018;379(1):11-21.
[4] Obici L, Berk J, Gonzalez-Duarte A, et al. *Amyloid*. 2020;27(3):153-162.
[5] Vinik E, Hayes R, Oglesby A, et al. *Diabetes Technol Ther.* 2005;7(3):497-508.
[6] Vinik E, Vinik A, Paulson J, et al. *J Peripher Nerv Syst*. 2014;19(2):104-114.
[7] Palmer E. *Cinahl Information Systems*. 2015:1-6.
[8] Dyck P, Gonzalez-Duarte A, Obici L, et al. *J Neurol Sci*. 2019;405:116421:1-8.
[9] Suhr O, Danielsson A. *J Intern Med*. 1994;235:479-485.
[10] van Nes SI, Vanhoutte E, van Doorn P, et al. *Neurology*. 2011;76:337–345.
[11] Vita G, Stancanelli C, Gentile L, et al. *Neuromuscul Disord*. 2019;29:213-220.
[12] 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 January 9, 2025.