Vutrisiran

An Investigational RNAi Therapeutic for ATTR Amyloidosis

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.

Overview

- Vutrisiran is an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis, which encompasses both hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis.[1, 2]
- Vutrisiran inhibits the production of disease-causing transthyretin (TTR) protein by the liver, leading to a reduction in the level of TTR in the blood.[1, 2]
- Vutrisiran is administered subcutaneously (under the skin) and utilizes one of Alnylam's delivery platforms known as the Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform.[1, 2]
- Vutrisiran is administered every three months.[2]
- Vutrisiran is under review by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Brazilian Health Regulatory Agency (ANVISA). Vutrisiran has been granted Orphan Drug Designation in the U.S. and the European Union (EU) for the treatment of ATTR amyloidosis. Vutrisiran has also been granted a Fast Track designation in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults. In the U.S. vutrisiran has received an action date under the Prescription Drug User Fee Act (PDUFA) of April 14, 2022. The Company received orphan drug designation in Japan. Alnylam has global commercial rights to vutrisiran, assuming regulatory approvals.

Clinical Development

- A Phase 1 clinical study of vutrisiran was conducted in 80 healthy volunteers (60 received vutrisiran and 20 received placebo). Vutrisiran demonstrated an acceptable safety profile and a single dose reduced serum TTR for a period of at least 90 days.[2]
- The safety and efficacy of vutrisiran are being evaluated in the HELIOS Phase 3 clinical program, currently consisting of two clinical trials: HELIOS-A and HELIOS-B.
  - **HELIOS-A** is a randomized, open-label, global multi-center Phase 3 study of 164 adult patients with hATTR amyloidosis with polyneuropathy.[1]
    - The primary endpoint of HELIOS-A is change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) at 9 months.
    - Secondary endpoints at 9 months include the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Total Score and the 10-Meter Walk Test (10-MWT).
    - The 9-month endpoints will be analyzed at 18 months with the addition of other secondary endpoints.
  - **HELIOS-B** is a randomized, double-blind, placebo-controlled Phase 3 study of 655 adult patients with ATTR amyloidosis with cardiomyopathy (including both hATTR and wtATTR amyloidosis).[3]
    - The primary endpoint will evaluate the efficacy of vutrisiran versus placebo for the composite outcome of all-cause mortality and recurrent cardiovascular (CV) events (CV hospitalizations and urgent heart failure (HF) visits) at 30-36 months.
    - Secondary endpoints include the change from baseline in the 6-minute walk test (6-MWT), health status measured using the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS), echocardiographic assessments of mean left ventricular wall thickness and global longitudinal strain, the N-terminal prohormone B-type natriuretic peptide (NT-proBNP) as a cardiac biomarker, and all-cause mortality, rate of recurrent CV events, and composite of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits at month 30 or 30-36 months.

About ATTR Amyloidosis

- ATTR amyloidosis is a rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR that accumulates as amyloid fibrils in multiple tissues including the nerves, heart, and GI tract. There are two types of ATTR amyloidosis: hATTR amyloidosis and wtATTR amyloidosis.[4,5,6]
    - hATTR amyloidosis is an inherited condition that is caused by variants (i.e., mutations) in the transthyretin (TTR) gene.[5,7,8] TTR protein is produced primarily in the liver and is normally a carrier of vitamin A.[9] The variant results in misfolded TTR proteins that accumulate as amyloid deposits in multiple tissues, including the nerves, heart and gastrointestinal (GI) tract.[5, 6, 7] It is a multisystem disease that can include sensory and motor, autonomic, and cardiac symptoms. The condition can have a debilitating impact on a patient's life and may lead to premature death with a median survival of 4.7 years following diagnosis.[8,10] It is estimated that there are approximately 50,000 patients with hATTR amyloidosis worldwide.[11]
    - wtATTR amyloidosis is a non-hereditary condition that occurs when misfolded wild-type TTR accumulates as amyloid deposits in multiple organs. It predominantly manifests as cardiac symptoms, but other systems are also involved, and commonly leads to heart failure and mortality within 2.5 to 5.5 years.[12,13,14,15,16,17,18,19] wtATTR amyloidosis affects an estimated 200,000-300,000 people worldwide.[20]
- Alnylam is committed to developing multiple treatment options for people who are living with ATTR amyloidosis to help manage the debilitating and progressive nature of the disease.

For more information about vutrisiran, please contact media@alnylam.com.

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 November 2021.

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 October 21, 2021.
2 Habtemariam BA, Karsten V, Attarwala H, et al. *Clin Pharmacol Ther.* 2021;109(2):372-382.
3 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 October 21, 2021.
4 Hanna M. *Curr Heart Fail Rep.* 2014;11:50-57.
5 Mohty D, Damy T, Cosnay P,et al. *Arch Cardiovasc Dis.* 2013;106:528-540.
6 Adams D, Coelho T, Obici L, et al. *Neurology*. 2015;85(8):675-682.
7 Conceicao I, Gonzalez-Duarte A, Obici L, et al. *J Peripher Nerv Syst.* 2016;21:5-9.
8 Shi SC and Robinson-Papp J. *Mt Sinai J Med.* 2012;79(6):733-748.
9 National Institutes of Health: Department of Health and Human Services. Genetics Home Reference. Transthyretin amyloidosis. https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis#inheritance. Accessed October 21, 2021.
10 Swiecicki PL, Zhen DB, Mauermann ML, et al. *Amyloid.* 2015;22(2):123-131.
11 Gertz MA. *Am J Manag Care.* 2017;23(7):S107-S112.
12 Ruberg F, Maurer M, Judge D, et al. *Am Heart J.* 2012;64:222-228.
13 Connors L, Sam F, Skinner M, et al. *Circulation.* 2016;133:282-290.
14 Grogan M, Scott C, Kyle R, et al. *J Am Coll Cardiol.* 2016;68:1014-1020.
15 Pinney J, Whelan C, Petrie A, et al. *J Am Heart Assoc.* 2013;2:e000098.
16 Siepen F, Bauer R, Voss A, et al. *Clin Res Cardiol.* 2018;107:158-169.
17 Givens R, Russo C, Green P, et al. *Aging Health.* 2013;9:229-235
18 Gillmore J, Damy T, Fontana M, et al. *Eur J Heart.* 2018;39:2799-2806.
19 Lane T, Fontana M, Martinez-Naharro A, et al. *Circulation.* 2019;140:16-26.
20 Data on file.