

Vutrisiran

An Investigational RNAi Therapeutic for Transthyretin-Mediated (ATTR) Amyloidosis

Overview

- Vutrisiran (ALN-TTRSC02) is an investigational RNA interference (RNAi) therapeutic being evaluated for the treatment of ATTR amyloidosis, which encompasses both hereditary (hATTR) and wild-type (wt) amyloidosis.
- Vutrisiran works by inhibiting the production of disease-causing TTR proteins, leading to a reduction in the levels of TTR in a patient's bloodstream.
- Vutrisiran is subcutaneously administered (under the skin) and utilizes Alnylam's next-generation delivery platform known as the Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform.
- The ESC-GalNAc platform is designed for increased potency and high metabolic stability, as compared to prior GalNAc technologies. It also allows for a quarterly subcutaneous administered injection.
- Vutrisiran has been granted Orphan Drug designation in the United States (U.S.) and the European Union (EU) for the treatment of ATTR amyloidosis.

Clinical Development

- The safety and efficacy of vutrisiran are being evaluated in the HELIOS Phase 3 clinical program. HELIOS-A is a randomized, open-label, global multi-center Phase 3 study of 160 patients with hATTR amyloidosis with polyneuropathy.
 - ♦ Patients will receive either subcutaneous vutrisiran (25 mg every 3 months) (n=120) or IV patisiran (0.3 mg/kg every three weeks) (n=40) during the treatment period of 18 months.
 - ♦ Results from the vutrisiran arm will be compared to the placebo arm from the APOLLO study for most endpoints, which evaluated the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy.
 - ♦ Following the 18-month study period, all patients are eligible to receive vutrisiran during a treatment extension period.
- 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.
 - ♦ Key secondary endpoints at 9 months include 10-Meter Walk Test (10-MWT), modified Body Mass Index (mBMI), activity and social participation limitations in patients (R-ODS), and percent reduction in TTR levels. Additional efficacy analyses will be conducted at 18 months of frequency of death and hospitalizations in patients with or without cardiac involvement.
- Alnylam expects to report topline results from HELIOS-A in late 2020.
- Alnylam also plans to initiate HELIOS-B, a Phase 3 trial evaluating vutrisiran in patients with ATTR amyloidosis with cardiomyopathy, in late 2019.

About ATTR Amyloidosis

- ATTR amyloidosis is a rare, progressively debilitating and fatal disease caused by misfolded transthyretin (TTR) proteins that accumulate as amyloid deposits in multiple tissues including the nerves, heart and gastrointestinal (GI) tract. There are two types of ATTR amyloidosis: hereditary ATTR (hATTR) amyloidosis and wild-type (wt) amyloidosis.^{1,2,3}
 - ♦ hATTR amyloidosis is an inherited, progressive and multisystem type of the disease resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations.^{3,4,5} It is estimated to affect 50,000 people worldwide.⁶ This condition can have a debilitating impact on a patient's life and may lead to premature death within 4.7 years of diagnosis.⁷
 - ♦ wtATTR amyloidosis is a nonhereditary, progressive type of the disease with undefined etiology. It primarily manifests as cardiomyopathy, which leads to heart failure and mortality within 2 to 6 years.^{1,2,6} wtATTR affects an estimated 200,000-300,000 people worldwide.
- Alnylam is committed to developing multiple treatment options for people who are living with the various types of ATTR amyloidosis to help manage the debilitating and progressive nature of the disease.

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

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.

¹ Hanna. *Curr Heart Fail Rep* 2014;11:50-7

² Mohty et al. *Arch Cardiovasc Dis* 2013;106:528-40

³ Adams et al. *Neurology* 2015;85:675-82

⁴ Conceicao, et al. *Journal of the Peripheral Nervous System*. 2016;21:5-9

⁵ Shin, et al. *Mt Sinai J Med*. 2012;79(6):733-748

⁶ Hawkins, et al. *Ann Med* 2015;47:625-38

⁷ Swiecicki P, Zhen D, Mauermann M, et al. *Amyloid* 2015;22(2):123-131.