Health Technology Briefing
April 2024

Vutrisiran for treating transthyretin amyloidosis with cardiomyopathy

Company/Developer	Alnylam Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28653	NICE ID: Not applicable	UKPS ID: 672001

Licensing and Market Availability Plans

Currently in Phase II/III clinical trials.

Summary

Vutrisiran is a medicinal product that is in development for the treatment of adults with transthyretin amyloidosis with cardiomyopathy (ATTR-CM). ATTR-CM is classified as either wildtype transthyretin (wtATTR) amyloidosis with cardiomyopathy (wtATTR-CM) or hereditary transthyretin (hATTR) amyloidosis with cardiomyopathy (hATTR-CM). ATTR-CM occurs when a protein called transthyretin (TTR) becomes defective and aggregates, forming amyloid deposits in the heart and other organs. Amyloid deposits can damage the structure and function of the organs, leading to the thickening and stiffening of heart tissues (cardiomyopathy), which can cause severe disease and be fatal. The wtATTR form results from the normal functioning TTR protein becoming defective with ageing. In contrast, the hATTR form occurs due to a faulty gene that runs in families and can be passed down from biological parents to their children. ATTR-CM is a poorly recognised condition with delayed diagnosis and poor prognosis, and treatment options are limited to best supportive care to the management of symptoms.

Vutrisiran is a 'small interfering RNA' (siRNA). This very short piece of synthetic genetic material that has been designed to attach to and block the genetic material of the cells responsible for producing transthyretin. This reduces production of defective transthyretin, thereby reducing the formation of amyloids and relieving symptoms. Vutrisiran is administered through an injection under the skin every three months. If licensed, vutrisiran will offer a treatment option for adults with hereditary or wildtype ATTR-CM.

Proposed Indication

Adults with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) classified as either hereditary ATTR-CM or wildtype ATTR-CM.[1]

Technology

Description

Vutrisiran (Amvuttra, ALN-TTRSC02) is a chemically stabilised double-stranded small interfering RNA (siRNA) that specifically targets hereditary and wild-type transthyretin messenger RNA (mRNA). Transthyretin (TTR) is a tetrametric protein synthesised mainly by the liver. TTR proteins can misfold, either as a result of gene variants in *TTR* or as an ageing-related phenomenon, and deposit as amyloid fibrils in the heart and peripheral nerves, which can result in ATTR.[2] Vutrisiran is covalently linked to a ligand containing three *N*-acetylgalactosamine residues to enable delivery of the siRNA to hepatocytes. Through a natural process called RNA interference (RNAi), vutrisiran causes the catalytic degradation of transthyretin mRNA in the liver, reducing misfolded and defective TTR proteins circulating in the blood.[3]

Vutrisiran is in development for adults with wildtype or hereditary ATTR-CM.[1] In the ongoing phase III trial (NCT04153149), 25mg of vutrisiran is administered as a subcutaneous (SC) injection once every three months.[1]

Key Innovation

ATTR-CM is a poorly recognised disease with delayed diagnosis and poor prognosis.[4] Current treatment options for wild-type or hereditary ATTR-CM are limited to managing symptoms and best supportive care.[5] siRNA technologies such as vutrisiran have been shown to be effective for the reduction of TTR expression in the liver in humans.[2] When compared to other treatments for patients with a similar condition called hATTR amyloidosis with polyneuropathy, vutrisiran demonstrated promising treatment effects at 18 months.[6]

If licensed, vutrisiran will provide a treatment option for adults with wildtype or hereditary ATTR-CM, who currently have no approved pharmacological treatment options available.

Regulatory & Development Status

Vutrisiran currently has Marketing Authorisation in the EU/UK for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[3] Vutrisiran is in phase II/III clinical development for hereditary transthyretin amyloidosis with polyneuropathy.[7]

Vutrisiran has the following regulatory designations/awards:

- An orphan drug in the UK for the treatment of transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.[8]
- An orphan drug in the EU in 2018 for the treatment of transthyretin-mediated amyloidosis.[9]

Patient Group

Disease Area and Clinical Need

Transthyretin amyloidosis is a rare, life-threatening disease resulting from aggregation and deposition of TTR amyloid fibrils in various tissues and organs. There are two predominant phenotypic presentations of the disease: hATTR with polyneuropathy, which primarily affects the peripheral nerves, and ATTR-CM, which primarily affects the heart and includes both wild-type and hereditary forms.[10] Hereditary ATTR-

CM is characterised by a single amino acid substitution caused by a point mutation in the *TTR* gene that is genetically inherited in an autosomal dominant manner and present from birth.[11,12] People with African or Caribbean family backgrounds are more likely to have hereditary ATTR-CM because of the increased prevalence of the TTR variant Val112Ile in this group.[13] Wildtype ATTR-CM is a non-hereditary form of the disease that occurs due to ageing-related processes.[11,14] The typical age of symptom onset for hereditary ATTR-CM is variable and can range between 30 to 80 years, compared to wildtype ATTR-CM, which predominantly presents in later life, with an average age of onset reported as 74 years.[13] Wildtype ATTR-CM occurs more frequently in males than females.[11,12] Common symptoms of ATTR-CM may mimic symptoms of heart failure and can include shortness of breath, swelling in the leg, confusion, and irregular heartbeat or palpitations.[15] Carpal tunnel syndrome is a common symptom seen in people with wildtype ATTR-CM while numbness or tingling in the hands and feet is a common symptom in people with hereditary ATTR-CM.[15]

Since diagnosing ATTR-CM is challenging and often missed, the true prevalence remains unknown.[16] In the UK, there are thought to be around 600 people with wildtype ATTR-CM and 200 people with hereditary ATTR-CM.[5] The number of new diagnoses made each year, particularly for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of non-invasive diagnostic tests.[5] In England (2022-23), there were 2,302 finished consultant episodes (FCE) and 1,681 admissions for organ-limited amyloidosis (ICD-10 code E85.4). This resulted in 7,322 FCE bed days and 1,239 day cases.[17]

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for hereditary or wildtype ATTR-CM.[18]

Clinical Trial Information

Trial	**HELIOS-B**, NCT04153149, EudraCT-2019-003153-28; HELIOS-B: A Phase 3, Randomised, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy) **Phase III** – Ongoing **Location(s)** Sixteen EU countries, UK, USA, Canada and other countries **Primary completion date**: February 2024
Trial Design	Randomised, parallel assignment, quadruple-blind
Population	N=655 (actual); subjects with transthyretin amyloidosis with cardiomyopathy; aged 18 to 85 years old.
Intervention(s)	Vutrisiran 25mg administered by SC injection every 3 months.
Comparator(s)	Placebo comparator
Outcome(s)	**Primary outcome**: Composite endpoint of all-cause mortality and recurrent cardiovascular (CV) events (CV hospitalisations and urgent heart failure visits) [Time frame: 30-36 months]. See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

Estimated Cost

Vutrisiran is marketed in the UK for the treatment of hereditary transthyretin-related amyloidosis in adults with stage 1 or 2 polyneuropathy; one prefilled disposable injection (25mg/0.5ml) costs £95,862.36.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Acoramidis for treating transthyretin-mediated amyloidosis cardiomyopathy (TSID 11904). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (ID 6327). Expected June 2024.
- NICE technology appraisal. Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA696). May 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for cardiology: Inherited cardiac conditions (All ages). A09/S/c.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages). E13/S(HSS)/c.

Other Guidance

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Additional Information

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