Health Technology Briefing
January 2022

Vutrisiran for treating hereditary transthyretin amyloidosis

Company/Developer	Alnylam Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26998	NICE ID: 10727	UKPS ID: 664129

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Vutrisiran is in clinical development for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with polyneuropathy. hATTR amyloidosis is an inherited condition that is caused by mutations in a gene known as the transthyretin (TTR) gene. This causes the liver to produce an abnormal version of the TTR protein, which accumulates as deposits in the tissues of the body (amyloidosis). These accumulated deposits can disrupt the structure and damage the function of the affected tissues causing symptoms such as pain, loss of sensation and weakness in the hands, arms, legs or feet. The disease can also affect involuntary body functions such as blood pressure, heart rate, and digestion. The effects and complications of the condition can lead to death within 3 to 15 years of symptoms developing. Currently there are limited treatment options for this disease, and treatment involves regular intravenous infusions.

Vutrisiran is a medicine that is made of a small strand of synthetic genetic material that stops the gene for transthyretin from working and thereby blocks the production of transthyretin in the liver. Vutrisiran is administered by as an injection under the skin every 3 months, which is likely to reduce treatment burden compared to currently available therapies. If licensed, vutrisiran would provide an additional treatment option for hATTR amyloidosis in adult patients with polyneuropathy.

Proposed Indication

Vutrisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients.[1]

Technology

Description

Vutrisiran (ALN-TTRSC02) is an RNA interference (RNAi) therapeutic that inhibits the production of disease-causing transthyretin (TTR) protein by the liver, leading to a reduction in the level of TTR in the blood.[2] Vutrisiran uses the naturally occurring RNAi mechanism to specifically target and silence TTR messenger RNA (mRNA). This prevents the synthesis of TTR protein in the liver, which are the fundamental pathogenic proteins causing hereditary hATTR amyloidosis.[3]

Vutrisiran is in clinical development for the treatment of patients with hATTR amyloidosis. In the phase III clinical trial, vutrisiran is administered via subcutaneous (SC) injection as 25mg once every 3 months during the initial 18-month randomised treatment period and as 25mg once every 3 months or 50mg every 6 months during the 18-month randomised treatment extension period.[1,4]

Key Innovation

In patients with hATTR amyloidosis treatment options are limited.[5] Current options such as patisiran is administered via intravenous (IV) infusion every 3 weeks, whereas vutrisiran will be administered by SC injection every 3 months. Vutrisiran uses enhanced stabilisation chemistry designed for high metabolic stability to enable this infrequent SC dosing.[3] This will likely impact existing hATTR amyloidosis staffing and service provisions including homecare which are designed for IV therapy, as new patients will no longer require IV infusions every 3 weeks. Thus, vutrisiran may reduce burden on the NHS. Furthermore, vutrisiran offers greater budget predictability over patisiran with fixed dosing (not dependant on bodyweight).[a] Patients are likely to benefit from the less frequent SC dosing that vutrisiran offers, and reduced risk infusion-related reactions associated with IV administration of patisiran, therefore improving their quality of life and likely adherence to therapy.[6b]

Regulatory & Development Status

Vutrisiran does not currently have Marketing Authorisation in the EU/UK for any indication.

Vutrisiran is also in a phase III clinical trial for the treatment of patients with transthyretin-mediated amyloidosis (ATTR) amyloidosis with cardiomyopathy.[7]

Vutrisiran was granted an orphan drug designation in the EU in 2018 for the treatment of ATTR amyloidosis.[8]

[a] Information provided by Alnylam Pharmaceuticals Inc.
[b] Information provided by Alnylam Pharmaceuticals Inc.

Patient Group

Disease Area and Clinical Need

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 gastrointestinal tract. There are two types of ATTR amyloidosis: hATTR amyloidosis and wild-type ATTR (wtATTR) amyloidosis. hATTR amyloidosis is an inherited condition that is caused by variants (i.e., mutations) in the TTR gene.[2] Symptoms may include loss of sensation, limb weakness and pain; alternating episodes of diarrhoea, constipation, nausea, and vomiting; and heart-related issues.[9] In some cases hATTR amyloidosis can result in severe symptoms, such as arrhythmias, heart failure, progressive dementia, seizures, renal failure, cachexia, glaucoma, and sexual dysfunction.[10,11] While some people with hATTR may mainly have either polyneuropathy (the simultaneous malfunction of many peripheral nerves throughout the body) or cardiomyopathy symptoms, most patients seen in the NHS will have both over the course of the condition. The effects and complications of the disease can lead to death within 3-15 years of symptoms developing.[12]

It is estimated that there are approximately 50,000 patients with hATTR amyloidosis worldwide.[13] In the UK, there are thought to be around 150 people with the disease.[12] However, without effective treatment, patients with the most common variant in the UK have a median survival of only 3.4 years from diagnosis.[14] The condition can have a severely debilitating impact on a patient's life, is progressive and eventually fatal. Some people whose symptoms begin at a younger age may live for only a few years after diagnosis, while older patients with slowly progressive disease can live for many years.[15] In 2020-21, there were 611 finished consultant episodes (FCE) and 537 admissions with primary diagnosis of amyloidosis unspecified (ICD-10 E85.9) which resulted in 664 FCE bed days.[16]

Recommended Treatment Options

NICE recommends the following treatment options for hATTR amyloidosis:[17]

- Patisiran
- Inotersen

Clinical Trial Information

Trial	**HELIOS-A;** NCT03759379; 2018-002098-23; A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) **Phase III –** Active, not recruiting **Location(s):** 11 EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2020
Trial Design	Randomised, parallel assignment, open label
Population	N = 164; Subjects with hATTR amyloidosis with TTR mutation and polyneuropathy disability; aged 18 to 85 years old
Intervention(s)	Vutrisiran (SC injection) during the treatment and treatment extension periods
Comparator(s)	Patisiran (IV infusion) during the treatment period, with switch to vutrisiran (SC) during the treatment extension period

Outcome(s)	Primary outcome measure: Change from baseline in the modified neurologic impairment score +7 at month 9 [Time frame: baseline, month 9] See trial record for full list of other outcomes
Results (efficacy)	Vutrisiran met its primary and secondary endpoints at nine months. The reduction of neurologic impairment and improvement in quality of life in patients with hATTR amyloidosis with polyneuropathy observed as early as nine months are maintained at 18 months. In addition, patients treated with vutrisiran showed quantitative improvements across a number of exploratory endpoints.[18]
Results (safety)	Vutrisiran demonstrated an encouraging safety and tolerability profile.[18]

Estimated Cost

The cost of vutrisiran is not yet known.

Relevant Guidance

NICE Guidance

- NICE highly specialised technologies guidance. Patisiran for treating hereditary transthyretin amyloidosis. (HST10). August 2019.
- NICE highly specialised technologies guidance. Inotersen for treating hereditary transthyretin amyloidosis. (HST9). May 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for diagnostic service for amyloidosis (All Ages).

Other Guidance

- Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. Canadian Journal of Neurological Sciences. 2021.[19]
- Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases. 2013.[15]

Additional Information

References

1 Clinicaltrials.gov. *HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)*. *Trial ID: NCT03759379*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03759379 [Accessed 07 December 2021].

2 Alnylam Pharmaceuticals. *Vutrisiran*. 2021. Available from: https://www.alnylam.com/wp-content/uploads/pdfs/Vutrisiran-Fact-Sheet.pdf [Accessed 07 December].
3 Habtemariam BA, Karsten V, Attarwala H, Goel V, Melch M, Clausen VA, et al. Single-Dose Pharmacokinetics and Pharmacodynamics of Transthyretin Targeting N-acetylgalactosamine-Small Interfering Ribonucleic Acid Conjugate, Vutrisiran, in Healthy Subjects. *Clin Pharmacol Ther*. 2021;109(2):372-82. Available from: https://doi.org/10.1002/cpt.1974.
4 Alnylam Pharmaceuticals Inc. *Vutrisiran Clinical Development Program*. 2020. Available from: https://www.alnylam.com/wp-content/uploads/pdfs/HELIOS-Fact-Sheet.pdf [Accessed 04 January 2022].
5 Hattrguide. *hATTR Amyloidosis Treatment Overview*. 2021. Available from: https://www.hattrguide.com/hattr-amyloidosis-treatment/ [Accessed 07 December 2021].
6 FAP News Today. *Vutrisiran Now Under Review for Approval in Europe for FAP Treatment*. 2021. Available from: https://fapnewstoday.com/2021/09/20/vutrisiran-under-review-europe-fap-treatment/ [Accessed 07 December 2021].
7 *HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy*. *Trial ID: NCT04153149*. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04153149 [Accessed 04 January 2021].
8 European Medicines Agency (EMA). *Public summary of opinion on orphan designation*. 2018. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/18/2026-public-summary-opinion-orphan-designation-synthetic-double-stranded-sirna-oligonucleotide_en.pdf [Accessed 07 December 2021].
9 Alnylam Pharmaceuticals. *Understanding Hereditary ATTR Amyloidosis*. 2022. Available from: https://www.alnylam.com/patients/amyloidosis/ [Accessed 04 January 2022].
10 Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care. *Therapeutics and clinical risk management*. 2020;16:109-23. Available from: https://doi.org/10.2147/TCRM.S219979.
11 Conceição I, González-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9. Available from: https://doi.org/10.1111/jns.12153.
12 National Cancer Institute of Health and Care Excellence (NICE). *Patisiran for treating hereditary transthyretin amyloidosis* (*hst10)*. Available from: https://www.nice.org.uk/guidance/hst10/resources/patisiran-for-treating-hereditary-transthyretin-amyloidosis-pdf-50216252129989 [Accessed 17 January 2022].
13 Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care*. 2017;23(7 Suppl):S107-s12.
14 Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SD, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J*. 2012;33(9):1120-7. Available from: https://doi.org/10.1093/eurheartj/ehr383.
15 Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon B-G, Ikeda S-i, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet Journal of Rare Diseases*. 2013;8(1):31. Available from: https://doi.org/10.1186/1750-1172-8-31.
16 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 04 January 2022].
17 National Cancer Institute of Health and Care Excellence (NICE). *Transthyretin amyloidosis*. 2021. Available from: https://pathways.nice.org.uk/pathways/endocrine-nutritional-and-metabolic-conditions#path=view%3A/pathways/endocrine-nutritional-and-metabolic-conditions/metabolic-conditions.xml&content=view-node%3Anodes-transthyretin-amyloidosis [Accessed 07 December 2021].

18 Businesswire. *Alnylam Reports Positive Topline 18-Month Results from HELIOS-A Phase 3 Study of Vutrisiran in Patients with hATTR Amyloidosis with Polyneuropathy*. 2021. Available from: https://www.businesswire.com/news/home/20211027005869/en/Alnylam-Reports-Positive-Topline-18-Month-Results-from-HELIOS-A-Phase-3-Study-of-Vutrisiran-in-Patients-with-hATTR-Amyloidosis-with-Polyneuropathy [Accessed 07 December 2021].

19 Alcantara M, Mezei MM, Baker SK, Breiner A, Dhawan P, Fiander A, et al. Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2021:1-12. Available from: https://doi.org/10.1017/cjn.2021.34.

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