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Newcastle University

Health Technology Briefing
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Eplontersen for treating transthyretin amyloid cardiomyopathy

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28554	NICE ID: Not available	UKPS ID: 672865

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Eplontersen is in clinical development for the treatment of adults with transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-CM occurs due to a build-up of abnormal proteins in the heart. These protein deposits can cause thickening and stiffening of the heart muscle, leading to heart failure. There are two types of ATTR, namely the hereditary and wild-type forms. Wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) is an underrecognized cause of heart failure due to misfolded wild-type transthyretin (TTRwt) myocardial deposition. Hereditary ATTR amyloidosis is caused by a mutation in the gene for TTR, inherited from one parent. The disease therefore runs in families, though the timing, development and severity of the disease can vary greatly. Wild-type ATTR-CM is the more common form of the condition. It is primarily seen in older men and often in conjunction with other age-related cardiac diseases. Current treatment options act by slowing the progress of the disease but no cure is available. There is a need for more treatments with increased effectiveness because the current options are limited.

Eplontersen works by reducing the production of transthyretin (TTR) protein to treat ATTR-CM. It also reduces the amount of protein being deposited in the tissues. Eplontersen is self-administered subcutaneously, with injections once per month. If licensed, Eplontersen would offer a new treatment option for people with ATTR-CM with the advantages of lower and less frequent dosing in comparison to other approved agents.

Proposed Indication

Treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) in adults aged 18 Years and older.[1,2]

Technology

Description

Eplontersen (ION-682884, IONIS-TTR-LRx, AKCEA-TTR-LRx)[2] is a ligand-conjugated antisense (LICA) drug in development for the treatment of hATTR and wATTR, a fatal disease caused by mutations in the TTR gene.[3] Eplontersen targets the TTR pre-messenger ribonucleic acid (pre-mRNA) through Watson-Crick base pairing.[4] The binding of eplontersen to TTR mRNA causes ribonuclease H1-mediated degradation, therefore preventing production of both mutant and wild-type TTR protein. This results in a reduction of serum TTR protein and TTR protein deposits in tissues.[5]

Eplontersen is currently in clinical development for the treatment of ATTR-CM in adults and older adults (aged 18 to 90 years). In the phase III clinical trial (ATTR-CM, NCT04136171), 1438 participants were randomly assigned to receive subcutaneous (SC) injections of either eplontersen or placebo once every 4 weeks. Additionally, participants also received daily supplemental doses of the recommended daily allowance of vitamin A.[2]

Key Innovation

Eplontersen demonstrated an increase in pharmacological potency compared with inotersen, a currently approved antisense medicine for the treatment of hATTR. Based on the pathogenesis of ATTR, it is likely that preventing TTR from being synthesized would eliminate the origin of misfolded protein and subsequent amyloid fibril deposition, thus leading to the improvement of symptoms of ATTR, including cardiomyopathy and polyneuropathy.[3] The advanced design of eplontersen increases drug potency to allow for lower and less frequent dosing. With a potential to yield an approximate 20–30-fold increase in potency, compared to parent antisense oligonucleotide inhibitors such as inotersen, that permits substantial reduction in systemic exposure and an improved safety and tolerability profile.[3] Additionally, there is some evidence of a statistically significant reduction in volumetric heart and lung ratio when treated with eplontersen, compared to treatment-naïve control group, in patients with hATTR-CM.[6]

If licensed, eplontersen could offer the potential to reduce the disease burden of hATTR with lower and less frequent dose than the parent compound.

Regulatory & Development Status

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

Eplontersen is also in the phase II/III clinical development for the following indications:[7]

- hereditary transthyretin-mediated amyloid polyneuropathy (ATTR-PN)

Eplontersen has the following regulatory designation:[8]

- the US FDA approval for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in December 2023

Patient Group

Disease Area and Clinical Need

ATTR is a systemic disease. Due to amyloid deposition in extracardiac tissues, patients often have associated extracardiac signs and symptoms. However, isolated cardiac involvement has been reported as well.[9] ATTR-CM occurs from the accumulation of unstable TTR protein in the myocardium.[10] These TTR deposits in the heart muscle lead to thickening and stiffening of the heart, often leading to heart failure.[11] There are two subtypes of ATTR-CM; hereditary (hATTR) and wild-type (wATTR), both of which have different risk factors, gender prevalence and major clinical symptoms.[10] Diagnosis of these patients can be difficult as both types of ATTR can mimic cardiovascular disease caused by high blood pressure. Both types of ATTR can be asymptomatic, hereditary is less common due to the frequency of the mutations and the penetrance and wild-type is more common due to an aging population.[11,12] wATTR-CM is the more common type of ATTR-CM and primarily seen in older men. Several autopsy studies have shown that the incidence of wATTR deposits increases with advancing age. It is often seen in conjunction with other cardiac diseases associated with aging, like aortic stenosis, atrial fibrillation, and heart failure with preserved ejection fraction.[9] Symptoms of ATTR-CM can include shortness of breath, palpitations and abnormal heart rhythms, most frequently atrial fibrillation or atrial flutter, ankle swelling, fatigue, fainting and chest pain.[11] Management of ATTR-CM includes appropriate treatment for heart failure for symptomatic relief, prevention of arrhythmias and heart transplantation for non-responders.[10]

Data from the National Amyloidosis Centre in the UK reports that about 1,000 new cases of amyloidosis

(including all different types) are diagnosed each year.[13] In the UK, it is estimated that wATTR-CM mostly affects older individuals and more men than women. Median survival is 3.6 years for people with wATTR. hATTR-CM affects people born with inherited mutations in the TTR gene. These variants are thought to be less stable than the wildtype and so are more likely to form amyloid fibrils. The most prevalent TTR variants in the UK are Vall112Ile and T60A. The Val122Ile variant is mostly associated with isolated cardiomyopathy without neuropathy. Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant3 and 3.4 years for people with the T60A variant.[14] Transthyretin amyloid cardiomyopathy is a rare but severe cause of restrictive cardiomyopathy, caused by the accumulation of transthyretin fibrils in the myocardium.[10] In England in 2022-2023, there were 95 finished consultant episodes (FCE) and 61 hospital admissions for other restrictive cardiomyopathy (ICD-10 code I42.5) which resulted in 694 FCE bed days and 18 day cases.[15]

Recommended Treatment Options

Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care such as diuretics.[16] Liver transplantation, which prevents the formation of additional amyloid deposits by removing the main source of abnormal TTR production, or heart transplantation, are options for some people with ATTR-CM and a specific genetic mutation. However, this mutation is uncommon in England, and transplantation can only take place early in the course of the disease, so it is very rarely used in England.[16] There are currently no pharmacological therapies recommended by NICE for the treatment of ATTR-CM.[17]

Clinical Trial Information		
Trial	NCT04136171, 2019-002835-27; CARDIO-TTRansform: A phase 3 global, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ION-682884 in patients with transthyretin-mediated amyloid cardiomyopathy (ATTR CM) **Phase III –** Active, not recruiting **Location(s):** Twelve EU countries, UK, USA, Canada, and other countries **Primary completion date:** June 2025	NCT05667493, 2022-000826-74; An open-label extension study to assess the long term safety of eplontersen (ION-682884) in patients with transthyretin-mediated amyloid cardiomyopathy (ATTR-CM) **Phase III –** Recruiting **Location(s):** Eight EU countries, USA, Canada, and other countries **Primary completion date:** April 2029
Trial Design	Randomised, double-blind, placebo-controlled, parallel assignment	Single group, open label
Population	N=1438 (actual); all sexes; subjects aged 18 years to 90 years (adult, older adult) with amyloid deposits in cardiac or non-cardiac tissue confirmed by Congo Red (or equivalent) staining OR technetium scintigraphy (99mTc -3,3-diphosphono-1,2- propanodicarboxylic acid [DPD-Tc], 99m Tc-pyrophosphate [PYP-Tc], or 99m Tc-hydroxymethylene-diphosphonate [HMDP-Tc]) with Grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio, centrally confirmed, end-diastolic interventricular septum thickness of > 12 (mm) on Screening echocardiogram	N=1400 (estimated); aged 18 years and older (adult, older adult); with satisfactory completion of treatment period and the end of treatment visit of the index study (ion-682884-cs2) or diagnosis of ATTR-CM and satisfactory participation on ISIS 420915-cs101 study as judged by the investigator and sponsor
Intervention(s)	Eplontersen subcutaneous injections once every 4 weeks. Participants will also receive daily vitamin A supplementation.	Eplontersen subcutaneous injections once every 4 weeks for up to 36 months or 6 months after eplontersen is approved and available in the site's country, whichever occurs first. Participants will also receive daily vitamin A supplementation.
Comparator(s)	Matched placebo	None
Outcome(s)	Primary outcome measure: • Composite outcome of cardiovascular (CV) mortality and recurrent CV clinical events up to week 140	Primary outcome measures: • Number of participants with adverse events and serious adverse events up to 36 months • Change from baseline in platelet count up to 36 months

	• Change from baseline on the 6-minute walk test (6MWT) at week 61 See trial record for full list of other outcomes.	• Change from baseline in estimated glomerular filtration rate up to 36 months • Change from baseline in urine protein ratio up to 36 months • Change from baseline in AST up to 36 months • Change from baseline in ALT up to 36 months • Number of participants with clinically significant changes from baseline in electrocardiogram parameters up to 36 months • Number of participants with clinically significant changes from baseline in thyroid-stimulating hormone up to 36 months • Percentage of participants with anti-drug antibodies up to 36 months See trial record for full list of other outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

The cost of eplontersen is not yet known.

Relevant Guidance

NICE Guidance

- NICE health technology appraisal guidance. Eplontersen for treating hereditary transthyretin-related amyloidosis. (ID6337). Expected August 2024.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

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Additional Information

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