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Health Technology Briefing
July 2023

Eplontersen for hereditary transthyretin-mediated amyloid polyneuropathy

Company/Developer	AstraZeneca UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28555	NICE TSID: Not available	UKPS ID: 668929

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Eplontersen is currently in development for the treatment of hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN). Hereditary transthyretin amyloidosis with polyneuropathy (formerly known as Familial Amyloid Polyneuropathy) is a rare disease caused by mutations in the gene that codes for transthyretin and is characterised by a multisystem extracellular deposition of amyloid (abnormal fibrous, extracellular, proteinaceous deposits found in organs and tissues), leading to the dysfunction of different organs and tissues. Therefore, hATTR-PN is a debilitating disease that can cause life-threatening situations.

Eplontersen is an investigational antisense medicine designed to reduce the production of transthyretin protein at its source to treat hATTR-PN. Eplontersen is administered by subcutaneous (under the skin) injection and is expected to halt the progression of neuropathy (nerve damage) in patients with hATTR-PN, by sustaining reduced transthyretin levels, resulting in an improved patients' quality of life. If licenced, eplontersen may provide another treatment option for patients with hATTR-PN.

Proposed Indication

Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (hATTR-PN).[1,2]

Technology

Description

Eplontersen is a ligand-conjugated antisense medicine designed to reduce the production of transthyretin protein at its source to treat hATTR-PN. Eplontersen is conjugated to a triantennary N-acetyl galactosamine moiety. This moiety acts as a ligand for productive receptor-mediated uptake by the high-capacity asialoglycoprotein receptors (ASGR) expressed by hepatocytes, which are the principal source of systematically circulating transthyretin (TTR).[3-5] The subcutaneous injection of Eplontersen to patients with hATTR-PN is expected to halt the progression of neuropathy, by sustaining reduced transthyretin levels, resulting in an improved patients' quality of life.[6]

Eplontersen is currently in phase III clinical development for the treatment of hATTR-PN[1,2] In the phase III clinical trial (NCT04136184; NEURO-TTRansform), eplontersen was administered by subcutaneous injection once every 4 weeks.[6]

Key Innovation

hATTR-PN is a debilitating disease that leads to peripheral nerve damage with motor disability within five years of diagnosis and, without treatment, is generally fatal within a decade.[7] Eplontersen belongs to a chemically-modified antisense oligonucleotide that is conjugated to a triantennary N-acetyl galactosamine moiety. This mediates asialoglycoprotein receptor-mediated uptake by the hepatocytes maximising liver targeting, increasing drug potency, and allowing for lower and less frequent doses.[8] A recent phase 1 study has confirmed a 30-fold increase in the potency of eplontersen compared to an unconjugated antisense oligonucleotide product in reducing TTR concentration, with no significant side effects.[9] Additionally, targeted receptor-mediated delivery eliminates the need for a full phosphorothioate-modified backbone to facilitate tissue distribution and cell uptake. Based on prior clinical experience with GalNAc3-conjugated antisense oligonucleotides, eplontersen is expected to support lower, less frequent dosing and achieve an improved safety and tolerability profile compared with an unconjugated antisense oligonucleotide product.[9] If licenced, eplontersen may provide a new treatment option for hereditary transthyretin-mediated amyloid polyneuropathy.

Regulatory & Development Status

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

Eplontersen was awarded an Orphan Drug designation by the US FDA in 2022 for the treatment of transthyretin-mediated amyloidosis.[10]

Eplontersen is also in phase III development for the treatment of Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM).[11]

Patient Group

Disease Area and Clinical Need

hATTR-PN (formerly known as Familial Amyloid Polyneuropathy) is a rare disease that occurs due to mutations in the gene encoding transthyretin and is characterised by multisystem extracellular deposition of amyloid, leading to dysfunction of different organs and tissues.[12] The signs and symptoms of the disease are divided into stages; in stage 1, typically mild sensory manifestations start in the lower limbs, and unassisted walking is preserved; in stage 2, the patient needs assistance for walking due to the progressive weakness that affects muscles of the lower limbs; in stage 3, sensory manifestations are severe, and due to the severe weakness or flaccid paralysis of all limbs, the patient is wheelchair-bound or bedridden.[13].[13]

The prevalence of polyneuropathy caused by hATTR is estimated to be less than 1 in 100,000 people in the general European population.[14] In the UK there are thought to be around 230 people with the disease eligible for treatment.[15].

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following pharmacological treatment options for hATTR-PN.[16]

- Inotersen for treating stage 1 and stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis.
- Patisiran for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy.
- Vutrisiran for treating hereditary transthyretin-related amyloidosis in adults with stage 1 or stage 2 polyneuropathy.

Clinical Trial Information

Trial	**NEURO-TTRansform**; NCT04136184, EudraCT 2019-001698-10; A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. **Phase III** – Active, not recruiting **Location(s):** Eight EU countries, Australia, Canada, US and others **Primary completion date:** April 2023
Trial Design	Randomized, open-label, crossover assignment, active comparator controlled.
Population	N= 168 (actual); adults aged 18 to 82 with hereditary transthyretin-mediated polyneuropathy
Intervention(s)	Subcutaneous injection of eplontersen once every 4 weeks
Comparator(s)	Subcutaneous injection of inotersen once weekly for 34 weeks
Outcome(s)	**Primary outcome measure:** • Change from baseline in mNIS+7 at Week 66 [Time Frame: Baseline, Week 66] • Change from baseline in the Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Questionnaire at Week 66 [Time Frame: Baseline, Week 66]

	• Percent change from baseline in serum TTR concentration at Week 66 [Time Frame: Baseline, Week 66] • Percent change from baseline in serum transthyretin (TTR) concentration at Week 35 [Time Frame: Baseline, Week 35] • Change from baseline in modified neuropathy impairment score plus 7 (mNIS+7) at Week 35 [Time Frame: Baseline, Week 35] See trial record for a full list of other outcomes.
Results (efficacy)	At 66 weeks, patients treated with eplontersen demonstrated consistent and sustained benefit on the three co-primary endpoints of serum transthyretin (TTR) concentration, neuropathy impairment and quality of life (QoL). Eplontersen also achieved statistically significant improvements in all secondary endpoints versus the external placebo group.[6]
Results (safety)	The rate of treatment emergent adverse events in the eplontersen group was comparable or similar to the external placebo group across all major categories.[6]

Clinical Trial Information

Trial	NCT05071300, EudraCT 2021-001427-40; An Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of ION-682884 in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy. **Phase III** - Recruiting **Location(s):** Six EU countries, Australia, Canada, US and others
Trial Design	Interventional, single group assignment, open label, no control.
Population	N= 140 (estimated); adults aged 18 and above who previously completed the NCT04136184 trial
Intervention(s)	Subcutaneous injection of eplontersen once every 4 weeks for up to 3 years
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measure:** Change from baseline in platelet count [Time frame: baseline to week 181]. See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost for eplontersen is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Vutrisiran for treating hereditary transthyretin-related amyloidosis (TA868). February 2023.
- 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

No relevant guidance identified.

Other Guidance

- Alcantara, M., Mezei, M., Baker, S., Breiner, A., Dhawan, P., Fiander, A., Bril, V. (2022). Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. 2022.[17]
- 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. 2020.[12]
- Welsh Health Specialised Services Committee. Treatment options for Transthyretin Amyloidosis (Specialised Services Policy Position PP187). 2020.[18]
- Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Planté-Bordeneuve V, Rapezzi C, Said G, Salvi F. Guideline of transthyretin-related hereditary amyloidosis for clinicians. 2013.[19]

Additional Information

References

1 ClinicalTrials.gov. *A Study to Assess the Long-Term Safety and Efficacy of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy*. *Trial ID: NCT05071300*. 2021. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT05071300 [Accessed 04 June, 2023].

2 ClinicalTrials.gov. *NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy*. *Trial ID: NCT04136184*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04136184 [Accessed 09 June 2023].

3 Coelho T, Ando Y, Benson MD, Berk JL, Waddington-Cruz M, Dyck PJ, et al. Design and Rationale of the Global Phase 3 NEURO-TTRansform Study of Antisense Oligonucleotide AKCEA-TTR-LRx (ION-682884-CS3) in Hereditary Transthyretin-Mediated Amyloid

Polyneuropathy. *Neurology and Therapy*. 2021;10(1):375-89. Available from: https://doi.org/10.1007/s40120-021-00235-6.

4 Viney NJ, Guo S, Tai LJ, Baker BF, Aghajan M, Jung SW, et al. Ligand conjugated antisense oligonucleotide for the treatment of transthyretin amyloidosis: preclinical and phase 1 data. *ESC Heart Fail*. 2021;8(1):652-61. Available from: https://doi.org/10.1002/ehf2.13154.

5 AstraZeneca. *Eplontersen met co-primary and secondary endpoints in interim analysis of the NEURO-TTRansform Phase III trial for hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN)*. 2022. Available from: https://www.astrazeneca.com/media-centre/press-releases/2022/eplontersen-phase-iii-trial-met-co-primary-endpoints.html [Accessed 04 June 2023].

6 AstraZeneca. *NEURO-TTRansform Phase III results presented at AAN showed eplontersen demonstrated consistent and sustained improvement in all measures of disease and quality of life through 66 weeks*. 2023. Available from: https://www.astrazeneca.com/media-centre/press-releases/2023/neuro-ttransform-phase-iii-results-presented-at-aan-showed-eplontersen-demonstrated-consistent-and-sustained-improvement.html#:~:text=The%20positive%20results%20being%20presented%20today%20in%20an,this%20fatal%20disease%20with%20significant%20unmet%20need.%201 [Accessed 09 June 2023].

7 Cortese A, Vegezzi E, Lozza A, Alfonsi E, Montini A, Moglia A, et al. Diagnostic challenges in hereditary transthyretin amyloidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereditary neuropathy. *Journal of Neurology, Neurosurgery & Psychiatry*. 2017;88(5):457-8. Available from: https://doi.org/10.1136/jnnp-2016-315262.

8 Obici L, Mussinelli R. Current and Emerging Therapies for Hereditary Transthyretin Amyloidosis: Strides Towards a Brighter Future. *Neurotherapeutics*. 2021;18(4):2286-302. Available from: https://doi.org/10.1007/s13311-021-01154-y.

9 Viney NJ, Guo S, Tai L-J, Baker BF, Aghajan M, Jung SW, et al. Ligand conjugated antisense oligonucleotide for the treatment of transthyretin amyloidosis: preclinical and phase 1 data. *ESC Heart Failure*. 2021;8(1):652-61. Available from: https://doi.org/10.1002/ehf2.13154.

10 AstraZeneca. *Eplontersen granted Orphan Drug Designation in the US for transthyretin amyloidosis*. 2022. Available from: https://www.astrazeneca.com/media-centre/medical-releases/eplontersen-granted-orphan-drug-designation-in-the-us-for-transthyretin-amyloidosis.html#:~:text=Eplontersen%20has%20been%20granted%20Orphan%20Drug%20Designation%20%28ODD%29,transthyretin-mediated%20amyloidosis%2C%20a%20systemic%2C%20progressive%20and%20fatal%20condition. [Accessed 09 June 2023].

11 ClinicalTrials.gov. *CARDIO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM). Trial ID: NCT04136171*. 2019. Status: Recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04136171 [Accessed 11 July 2023].

12 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.

13 Sequeira VCC, Penetra MA, Duarte L, Azevedo FR, Sayegh RSR, Pedrosa RC, et al. Hereditary transthyretin-mediated amyloidosis with polyneuropathy: baseline anthropometric, demographic and disease characteristics of patients from a reference center. *Arquivos de Neuro-Psiquiatria*. 2022;80(3):262-9. Available from: https://doi.org/10.1590/0004-282x-anp-2020-0590.

14 Orpha.net. *Prevalence of rare diseases: Bibliographic data. In: National Institute for Health and Care Excellence (NICE). Proposed Highly Specialised Technologies Evaluation: Patisiran*

for treating hereditary transthyretin-related amyloidosis - Draft scope (pre-referral). 2017. Available from: https://www.nice.org.uk/guidance/hst10/documents/draft-scope-pre-referral [Accessed 28 June 2023].

15 National Institute for Health and Care Excellence (NICE). *Putting NICE guidance into practice: Resource impact report: Vutrisiran for treating hereditary transthyretin related amyloidosis (TA868)*. 2023. Available from: https://www.nice.org.uk/guidance/ta868/resources/resource-impact-report-pdf-11374791085 [Accessed 11 July 2023].

16 National Institute for Health and Care Excellence (NICE). *Hereditary transthyretin amyloidosis*. 2019. Available from: https://www.nice.org.uk/search?q=hereditary+transthyretin+amyloidosis [Accessed 09 June 2023].

17 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*. 2022;49(1):7-18. Available from: https://doi.org/10.1017/cjn.2021.34.

18 Committee WHSS. *Treatment options for Transthyretin Amyloidosis: Specialised Services Policy Position PP187* 2020. Available from: https://whssc.nhs.wales/commissioning/whssc-policies/all-policy-documents/pp187-treatment-options-for-transthyretin-amyloidosis-in-adults-pdf [Accessed 09 June 2023].

19 Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet Journal of Rare Diseases*. 2013;8:31. Available from: https://doi.org/10.1186/1750-1172-8-31.

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