Inotersen (Ionis TTRRx) for hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) – first line

NIHR HSRIC ID: 8601

Lay summary

Inotersen is a new drug to treat hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), which is a rare disease caused by the abnormal build-up of proteins in the tissues of the body. Inotersen is delivered by injection under the skin. It stops a protein called transthyretin being made, and therefore stops it from building-up in body tissues.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Adult hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), previously referred to as Familial Amyloid Polyneuropathy (FAP): stage 1 and 2, with or without concomitant cardiomyopathy — first line.

TECHNOLOGY

DESCRIPTION

Inotersena (IONIS TTRRx; ISIS 420915; ISIS-GSK1Rx; ISIS-TTRRx) is a second-generation antisense oligonucleotide (ASO) drug that inhibits transthyretin (TTR) production, including wild-types and all known mutant forms of transthyretin. In a phase III clinical trial, inotersen is administered as 300mg of inotersen sodium (equivalent to 284mg inotersen) via subcutaneous (SC) injection three times on alternate days for the first week, and then once-weekly for 64 weeks.

Inotersen does not currently have marketing authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, inotersen will offer an additional treatment option for patients with hATTR-PN who currently have few effective therapies available.

DEVELOPER

Ionis Pharmaceuticals. GlaxoSmithKline have an option to commercialise this product.

AVAILABILITY, LAUNCH OR MARKETING

Inotersen is a designated orphan drug in the EU.

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

hATTR-PN is an autosomal dominant genetic disorder with the extracellular deposition of misfolded proteins as insoluble fibrils that progressively disrupt tissue structure and function. It is characterised by progressive sensory, motor, and autonomic polyneuropathy which results in death. TTR is a plasma transport protein for thyroxine and vitamin A that is synthesised predominantly by the liver (90%), but also in the retina and choroid plexus.

In addition to hATTR-PN, transthyretin amyloidosis (ATTR) can present as an infiltrative cardiomyopathy (hereditary ATTR with cardiomyopathy [hATTR-CM]). Typically in patients who have a predominant polyneuropathy, sensory neuropathy begins in the lower extremities, and is followed within a few years by motor neuropathy. In some patients,

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a Inotersen is a proposed as an international non-proprietary name (INN).
particularly those with early onset disease, autonomic neuropathy is the first manifestation of the disease, resulting in orthostatic hypotension, constipation alternating with diarrhoea, nausea and vomiting, sexual impotence, and urinary incontinence. In later stages, patients can experience muscle atrophy, sensory loss, weakness in their hands and feet, foot drop and wrist drop.

Diagnosis can be challenging as the disease presents in many different forms with considerable phenotypic variation across individuals and geographical locations. In patients from Portugal and Japan with a particular genetic mutation (Val30Met), the disease usually begins in the third to fifth decade; onset is usually later in persons from other geographical areas. ATTR can lead to significant morbidity, disability, and mortality. Patients with hATTR-PN typically have a life expectancy of 5 to 15 years from symptom onset. The mean survival in patients with FAP is approximately 2.5 years.

**CLINICAL NEED and BURDEN OF DISEASE**

The population affected by hATTR-PN is very small. hATTR-PN is rare in most parts of the world, and in the general European population the prevalence of hATTR-PN is estimated to be less than 1 in 100,000 individuals. In 2014-15 in England, there were 24 hospital admissions for neuropathic heredofamilial amyloidosis (ICD-10 E85.1), resulting in 34 bed days and 25 finished consultant episodes.

The population likely to be eligible to receive inotersen could not easily be estimated from available routine published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- No relevant guidance identified.

**NHS England Policies and Guidance**

**Other Guidance**

**CURRENT TREATMENT OPTIONS**

Current treatment options for patients with hATTR-PN are limited and there are no nationally reimbursed medicinal products available for patients with hATTR-PN in England. Current disease management of ATTR mainly focuses on palliation. Palliative and supportive care can include pain management, nutritional and mobility support and mitigation of the effects of the disease on hearing, the kidney function and vision.
Liver transplant is a therapeutic option for a subset of patients with early onset Val30Met mutations. The aim of liver transplantation is to prevent the formation of additional amyloid deposits by removing the main source of abnormal TTR production. This procedure removes approximately 95% of the production of variant TTR and can slow or halt the progression of the disease. An average of 120 patients worldwide receive a liver transplant for the treatment of hATTR-PN each year. Current data indicates a 5 year post-transplant survival rate of 82% in patients with a Val30Met mutation versus 59% for patients with a non-Val30Met mutation.

Liver transplantation has a number of limitations, including a shortage of donors, a requirement for surgery for both the recipient and any living donors, and significant risks of adverse events. In addition, a large number of patients are not good transplant candidates because of their age and/or advanced disease status. Furthermore, progression of cardiac amyloidosis following transplantation can occur because TTR continues to be produced due to synthesis in the retina and choroid plexus.

Tafamidis (Vyndaqel) is a disease-modifying agent that kinetically stabilises TTR and may limit TTR amyloid fibril formation. It is licensed in the EU for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy. Tafamidis is not routinely commissioned in the NHS based on an Advisory Group for National Specialised Services (AGNSS) recommendation, which found the available evidence was insufficient to support clinical effectiveness.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>IONIS-TTRRx, NCT01737398; ISIS 420915-CS2; IONIS-TTR Rx vs placebo; phase III.</th>
<th>IONIS-TTRRx, NCT02175004; IONIS-TTRRx; phase III extension.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Ionis Pharmaceuticals, Inc.</td>
<td>Ionis Pharmaceuticals, Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^1), manufacturer.</td>
<td>Trial registry(^1).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Participants</td>
<td>n=172; aged 18-82 years; stage 1 and stage 2 FAP; modified Neuropathy Impairment Score (mNIS) &gt;10 and &lt;30; documented transthyretin variant by genotyping; documented amyloid deposit by biopsy.</td>
<td>Estimated maximum n=172; satisfactory completion of dosing and efficacy assessments in ISIS 420915-CS2.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to 284mg inotersen SC on days 1, 3 and 5 and then once a week; or placebo SC on days 1, 3 and 5 and then once a week.</td>
<td>Patients receive 284mg inotersen SC once a week</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 64 weeks; follow up 6 months.</td>
<td>Follow-up for 78 weeks.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Modified NIS +7 (mNIS+7); Norfolk Quality of Life Diabetic Neuropathy questionnaire (Norfolk QOL-DN).</td>
<td>Adverse events; blood pressure; heart rate; body weight; routine laboratory test panel; number of concomitant medications used; QT interval; visual acuity; light detection ability.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Modified Body Mass Index (mBMI) and Body Mass Index (BMI); individual</td>
<td>mNIS+7; Norfolk QOL-DN; polyneuropathy disability score (PND);</td>
</tr>
</tbody>
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### ESTIMATED COST and IMPACT

#### COST

The cost of inotersen is not yet known.

The estimated cost associated with liver transplant procedures is £20,501, and the subsequent cost in the first 6-month cycle after the transplant is £22,232 followed by a 6-monthly cost of transplant after 1st year of £814.  

Tafamidis is administered daily at a dose of 20 mg, with an estimated annual cost of £130,000.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Improved quality of life for patients or carers.
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services: *weekly SC injections*.
- Decreased use of existing services: *potential slowing of disease progress, reduction in hospital stays*.
- Re-organisation of existing services
- Need for new services
- None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs
- Other: *more patients potentially eligible for treatment*.
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified
- None identified

#### REFERENCES