Patisiran for polyneuropathy in patients with hereditary transthyretin-related amyloidosis

NIHR HSRIC ID: 8003

Lay summary

Patisiran is a new drug for the treatment of hereditary transthyretin-related amyloidosis. Amyloidosis is a rare disease caused by abnormal accumulation of proteins in the tissues of the body. The most common protein to cause hereditary amyloidosis is transthyretin. Patisiran is delivered straight into the blood. It targets the cause of this disease by preventing the disease-causing transthyretin protein from being made.

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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Polyneuropathy: hereditary amyloidosis; transthyretin-related.

TECHNOLOGY

DESCRIPTION

Patisiran (ALN-TTR02) is an RNA interference (RNAi) agent, designed to suppress liver production of both wild-type and all mutant forms of transthyretin (TTR). In phase III clinical trials, patisiran is administered by intravenous (IV) injection at 0.3mg/kg every 3 weeks. Patisiran does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, patisiran will offer a new treatment option for polyneuropathy in patients with hereditary transthyretin-related amyloidosis that may target and suppress the underlying disease process.

DEVELOPER

Alnylam Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Amyloidosis is caused by the extracellular deposition of misfolded proteins as insoluble amyloid fibrils that progressively disrupt tissue structure and function. Most hereditary amyloidoses are due to TTR mutations. 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. The extracellular deposition of TTR amyloid fibrils causes accumulation in multiple tissues, including nerves, the heart and gastrointestinal tract. Damage to body organs and tissues results in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy.

TTR amyloidosis can present as a progressive axonal sensory, sensory and/or autonomic neuropathy (familial amyloid polyneuropathy, FAP), or as an infiltrative cardiomyopathy (familial amyloid cardiomyopathy, FAC). Diagnosis can be challenging as the disease presents in many different forms, with considerable phenotypic variation across individuals and geographic locations. In patients from Portugal and Japan, the disease usually begins in the third to fifth decade; onset is usually later in persons from other geographical areas. Typically, sensory neuropathy begins in the lower extremities, and is followed within a few years by motor neuropathy. In some patients, 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. TTR amyloidosis can lead to significant morbidity, disability, and mortality within two to 15 years.

**CLINICAL NEED and BURDEN OF DISEASE**

There are over 100 different mutations described in the TTR gene, the most common being Val30Met, which can affect 1 in 500 people in some regions of Northern Portugal and is primarily associated with neuropathy. FAP is rare in most parts of the world, with an estimated 1 in 100,000 people affected in the USA and Europe. TTR amyloid polyneuropathy is more common in some parts of Sweden, Japan, Brazil, Majorca and Ireland. It is estimated that FAP affects approximately 10,000 people worldwide, and FAC affects at least 40,000 people worldwide. Cardiomyopathy is the predominant feature in mutations of Val122Ile, Ile68Leu, Thr60Ala and Leu111Met. The Val122Ile mutation is a low penetrance variant present in 3-4% of African Americans.

Patients with FAP typically have a life expectancy of five to 15 years from symptom onset. The mean survival in patients with FAC is approximately 2.5 years.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- No relevant guidance identified.

**NHS England Policies and Guidance**

- No relevant guidance identified.

**Other Guidance**


**CURRENT TREATMENT OPTIONS**

Current treatment options for patients with TTR amyloidosis are limited. For patients with TTR-FAP who have mild or moderate disease, liver transplant is the current standard of care for patients under the age of 50 years. 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 FAP each year. Current data indicates a 10-year survival rate of 74% in patients with a Val30Met mutation versus 44% for patients with a non-Val30Met mutation, who have received a liver transplant. This data suggests that there are differences in the mutation-specific utility of liver transplant for TTR-FAP. Prognosis after liver transplant is influenced by many factors, including the properties of particular TTR variants, nutritional status and age, as well as the severity of neuropathy and

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*a Company comments.
*b Expert personal communication.
cardiac amyloid involvement. Liver transplantation in later stages may be complicated by progressive amyloid cardiomyopathy or neuropathy\(^3\). The continued progression of cardiac and peripheral amyloidosis may result from the continued deposition of wild-type TTR and mutant TTR secreted by the choroid plexus, respectively\(^1\).

Tafamidis is a potentially disease-modifying agent that kinetically stabilises TTR and may limit dissociation of the native TTR tetramer into monomers, inhibiting TTR amyloid fibril formation\(^3\). It is licensed in the EU for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy in order to delay peripheral neurologic impairment\(^1\).\(^3\)

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02510261, ALN-TTR02-006, 2014-003877-40; patisiran; phase III extension.</th>
<th>APOLLO, NCT01960348, ALN-TTR02-004, 2013-002987-17; patisiran vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Alnylam Pharmaceuticals.</td>
<td>Alnylam Pharmaceuticals.</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), manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU, USA, Canada and other countries.</td>
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</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=225 (planned); aged 18 to 85 yrs; completed a patisiran study and tolerated the study drug.</td>
<td>n=225; aged 18 to 85 yrs; familial amyloidotic polyneuropathy; neuropathy impairment score of 5-130; no prior liver transplant.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Participants receive patisiran 0.3mg/kg IV every 3 wks.</td>
<td>Randomised to patisiran 0.3mg/kg IV every 3 wks; or placebo IV every 3 wks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for up to 5 yrs.</td>
<td>Active treatment for 18 mths.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Safety and tolerability.</td>
<td>Modified Neuropathy Impairment Score+7 (mNIS+7).</td>
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<tr>
<td>Secondary outcomes</td>
<td>Serum TTR, neurological impairment (mNIS+7 and NIS), quality of life (Norfolk Quality of Life – Diabetic Neuropathy), autonomic function (Composite Autonomic Symptom Score, COMPASS 31), modified body mass index (mBMI), disability (Rasch-built Overall Disability Scare, R-ODS), motor function (NIS Weakness, timed 10m walk and grip strength test).</td>
<td>Quality of life (Norfolk Quality of Life – Diabetic Neuropathy, EuroQol-5D), serum TTR, autonomic function (COMPASS 31), mBMI, disability (R-ODS), motor function (NIS Weakness, timed 10m walk and grip strength test).</td>
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<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as 2020.</td>
<td>Study completion date reported as Aug 2017.</td>
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<tr>
<th>Trial</th>
<th>NCT01961921, ALN-TTR02-003, 2013-001644-65; patisiran; phase II extension.</th>
<th>NCT01617967, ALN-TTR02-002, 2012-000467-24; patisiran; phase II.</th>
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<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
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<td>Participants</td>
<td>n=27; aged 18 to 85 yrs; previously received patisiran in study ALN-TTR02-002.</td>
<td>n=29; aged 18 to 85 yrs; diagnosis of TTR amyloidosis; no prior liver transplant.</td>
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Participants received patisiran 0.3mg/kg IV every 3 wks. Participants received patisiran 0.3mg/kg IV either once every 4 wks or once every 3 wks; or patisiran 0.15mg/kg IV once every 4 wks; or patisiran 0.05mg/kg IV once every 4 wks; or patisiran 0.01mg/kg IV once every 4 wks.

Follow-up
Active treatment for 2 yrs, follow-up 21-56 days post last dose. Active treatment for 2 doses, follow-up 56 days post last dose.

Primary outcomes
Safety and tolerability. Safety and tolerability.

Secondary outcomes
Serum TTR, neurological impairment (mNIS+7 and NIS), quality of life (Norfolk Quality of Life – Diabetic Neuropathy), autonomic function (COMPASS 31), mBMI, disability (R-ODS), motor function (NIS Weakness, timed 10m walk and grip strength test). Pharmacokinetics; serum TTR.

Key results
Mean sustained serum TTR reduction, 80% over 24 mths. Mean change in mNIS+7, -7.0 points at 24 mths. Participants receiving 0.3mg/kg IV dose administered once every 3 wks achieved sustained mean serum TTR reduction of 85%.

Adverse effects (AEs)
7 patients (25.9%) reported serious AEs and two patients died (gastroesophageal cancer, and myocardial infarction); all were unrelated to study drug. Flushing and infusion-related reactions were observed in 6 patients (22.2%) and all events were mild in severity. There were no clinically significant changes in liver function tests, renal function or haematologic parameters. 2 patients reported serious AEs. The most commonly reported adverse event was a mild or moderate infusion-related reaction (10.3%). There were no clinically significant changes in liver function tests, renal function or haematologic parameters.

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<td>Participants received patisiran 0.3mg/kg IV every 3 wks.</td>
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<td>Safety and tolerability.</td>
<td>Serum TTR, neurological impairment (mNIS+7 and NIS), quality of life (Norfolk Quality of Life – Diabetic Neuropathy), autonomic function (COMPASS 31), mBMI, disability (R-ODS), motor function (NIS Weakness, timed 10m walk and grip strength test).</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of patisiran is not yet known.

**IMPACT - SPECULATIVE**

Impact on Patients and Carers

☑ Reduced mortality/increased length of survival: **expert opinion states that evidence suggests patisiran ought to be expected to increase survival as well as reduce symptoms or disability**.

☑ Reduced symptoms or disability: **expert opinion suggests that if patisiran is an effective treatment of early disease and substantially slows progression this may decrease dependence of patients on carers. TRR FAP is a devastating disease for patients**.

☑ Other: **expert opinion notes that families incur substantial costs in terms of caring for eventually very immobile patients with continence issues and poor nutrition**.

☐ No impact identified

☑ Expert personal communication.

☑ Expert personal communication.
Impact on Health and Social Care Services

- Increased use of existing services: *requirement of regular IV treatment.*
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- 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
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES

14. ClinicalTrials.gov. A multicentre, open-label, extension study to evaluate the long-term safety and efficacy of patisiran in patients with familial amyloidotic polyneuropathy who have completed a


16 ClinicalTrials.gov. A phase 2, multicentre, open-label, extension study to evaluate the long-term safety, clinical activity, and pharmacokinetics of ALN-TTR02 in patients with familial amyloidotic polynuropathy who have previously received ALN-TTR02. www.clinicaltrials.gov/show/NCT01961921 Accessed 17 November 2016.
