First-in-class ‘gene-silencing’ therapy approved for NHS use in England to treat hereditary form of amyloidosis

July 9, 2019

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- In 2018, patisiran became the first RNAi therapeutic to be licensed for use in the UK

MAIDENHEAD, UK, 8 JULY 2019 – Alnylam UK Limited, the leading RNA interference (RNAi) therapeutics company, today welcomed a decision from the National Institute for Health and Care Excellence (NICE) recommending the use of ONPATTRO®▼ (patisiran) on the NHS in England for the treatment of a progressive, life-threatening disease called hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).i Prior to this decision, there have been few treatment options available to patients with hATTR amyloidosis in England. Patisiran provides eligible patients suffering from this disease with a treatment option that addresses its underlying cause by reducing the production of an abnormal protein that damages nerves and organs across the body.ii

Professor Philip Hawkins, Head of the National Amyloidosis Centre at the Royal Free Hospital, London. said: “Today’s decision marks an important step forward in the treatment of a disease that is both life-threatening to patients and devastating to families. Patisiran has shown in its main clinical study that it can halt or even improve potentially debilitating symptoms of this disease in the majority of patients. This means we now have a real possibility of preserving quality of life for eligible patients for longer than has so far been possible. Gene-silencing is a promising area of medicine and it is heartening to see this science translating into treatments that can potentially help those suffering from serious illnesses like hATTR amyloidosis.”

hATTR amyloidosis is caused by abnormal deposition and accumulation of a protein called transthyretin (TTR). Patisiran works by using RNAi to block the production of the majority of TTR protein before it is made. In 2006, the discovery of RNAi was awarded the Nobel Prize in Physiology or Medicine. In hATTR amyloidosis, the build-up of TTR protein and the damage it causes to tissues and organs, such as the peripheral nerves and heart, results in patients experiencing neuropathy (disease of the nerves) and cardiomyopathy (disease of the heart muscle).iii

In the pivotal clinical trial for patisiran, APOLLO, 56 percent of the study’s 225 patients with hATTR amyloidosis with polyneuropathy who were treated with patisiran saw an improvement in their neuropathy symptoms, compared with four percent of patients treated with placebo. In addition, interim follow-up data presented at the Peripheral Nerve Society Annual Meeting in June 2019 from patients on patisiran treatment for a total of 30 to 36 months provided evidence that the improvements in neuropathy impairment and quality of life seen with patisiran were sustained over this period (relative to corresponding parent study baselines).
Carlos Heras-Palou, spokesperson for the UK ATTR Amyloidosis Patients’ Association said: “Today’s announcement has the potential to change the lives of families across the UK who are affected by this cruel disease, offering them an option that could reduce the burden of symptoms that can be crippling to many. This condition also carries a huge psychological toll, with many patients anxious that they may have passed on the faulty gene to children or grandchildren. The availability of patisiran is welcome news and will help provide important reassurance for patients today, as well as for those who may need treatment in the future. We are grateful to everyone who has played a role in achieving this positive outcome and delighted that many patients may now have the chance to live a fuller life.”

Brendan Martin, UK & Ireland General Manager at Alnylam Pharmaceuticals said: “Over the last year, Alnylam and NICE have worked closely together to ensure access to patisiran on the NHS in England. We are delighted with today’s outcome, which we hope will now help many people affected by this devastating disease to gain greater control of their daily lives. At Alnylam, our aim continues to be taking ground-breaking science in RNAi and transforming this into novel medicines that can improve the lives of patients affected by serious diseases. Today is another important step in that journey.”
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Notes to editors

Supporting Dataii,v
The appraisal for patisiran was based on positive results from the randomised, double-blind, placebo-controlled, global Phase III APOLLO study of 225 patients, the largest-ever interventional study in hATTR amyloidosis patients with polyneuropathy. Results from APOLLO were published in the July 5, 2018, issue of The New England Journal of Medicine and were further included within the journal’s Notable Articles of 2018, a selection of studies highlighted as “being the most meaningful in improving medical practice and patient care.”
In APOLLO, the safety and efficacy of patisiran were evaluated in a diverse, global population of hATTR amyloidosis patients in 19 countries, with a total of 39 TTR mutations. The study showed that, after 18 months of treatment:

- Patients treated with patisiran had a mean 6.0-point decrease (improvement) in modified Neuropathy Impairment Score +7 (mNIS+7) score from baseline compared to a mean 28.0-point increase (worsening) for patients in the placebo group, resulting in a mean 34.0-point difference relative to placebo.
- 56 percent of patisiran-treated patients experienced some improvement of neuropathy impairment (as assessed by mNIS+7 score) relative to their own baseline, compared to four percent of patients who received placebo.
- Patients treated with patisiran had a mean 6.7-point decrease (improvement) in Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) score from baseline compared to a mean 14.4-point increase (worsening) for patients in the placebo group, resulting in a mean 21.1-point difference relative to placebo.
- As measured by Norfolk QoL-DN, 51 percent of patients treated with patisiran experienced improvement in quality of life relative to their own

baseline, compared to 10 percent of the placebo-treated patients.
- Patients treated with patisiran experienced statistically significant benefit vs. placebo for all other secondary efficacy endpoints, including measures of activities of daily living, walking ability, nutritional status, and autonomic symptoms.
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The European Medicines Agency website contains full details of patisiran's product information.

Adverse Reactions
The overall incidence and severity of adverse events were similar in patients receiving patisiran and placebo. The most common adverse events that occurred in patients treated with patisiran were peripheral oedema (30 percent) and infusion-related reactions (19 percent).ii

To reduce the risk of infusion-related reactions, patients received premedications prior to infusion.

About Patisiran
Patisiran is an intravenously administered RNAi therapeutic targeting transthyretin (TTR) for the treatment of hereditary ATTR amyloidosis. It is designed to target and silence specific messenger RNA, potentially blocking the production of TTR protein before it is made. Patisiran reduces the production of TTR in the liver, reducing its accumulation in the body's tissues in order to halt or slow down the progression of the disease.ii,v In August 2018, patisiran received U.S. Food and Drug Administration (FDA) approval and European marketing authorisation for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

About hATTR Amyloidosis
Hereditary transthyretin-mediated (hATTR) amyloidosis is an inherited, progressively debilitating, and often fatal disease caused by mutations in the TTR gene. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. Mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissue, such as the peripheral nerves and heart, resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations.

hATTR amyloidosis is passed down when one parent carries the mutation, giving children a 50 percent chance of inheriting that mutation (although not all people with the mutation will develop symptoms of the disease).

About RNAi
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About Alnylam
Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system/ocular diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. ONPATTRO® (patisiran) is the first-ever RNAi therapeutic approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults and by the European Medicines Agency (EMA) for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including five product candidates in Phase 3 studies and one in registration. Looking forward, Alnylam will continue to execute on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Headquartered in Cambridge, MA, Alnylam employs over 1,200 people worldwide.

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[i] National Institute for Health and Care Excellence. Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]. https://www.nice.org.uk/guidance/indevelopment/gid-hst10014/documents

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