Eplontersen May Soon Provide Another Safe, Effective Treatment for People Diagnosed with ATTR

People who have been diagnosed with hereditary transthyretin amyloidosis (ATTRv) may soon have the option of choosing another safe, effective therapy, one that significantly improves quality of life, according to patients who received it in the clinical trial.

ATTRv is a progressive, debilitating, fatal disease in which amyloids form when abnormal transthyretin proteins are produced and misfold. The amyloid fibrils are deposited on various organs, causing tissue damage and interfering with their function. Certain mutations cause amyloid deposits that result in polyneuropathy (ATTRv-PN), while others result in cardiomyopathy (ATTR-CM) or a mixed phenotype (1). Once diagnosed, a person's life expectancy is greatly shortened, and their quality of life swiftly decreases.

While other treatments have been approved, any given drug will not reach maximum possible efficacy on every single patient who receives the treatment, and none provide a cure that completely heals the person. Thus, as you can imagine, any potential new treatment is a beacon of hope to those who are burdened with this disease.

Ionis and AstraZeneca recently presented positive results from a 35-week interim analysis of the phase 3 NEURO-TTRansform study of eplontersen to treat ATTRv-PN. In the press release, Eugene Schneider, M.D., Ionis' executive vice president and chief clinical development officer, summed up the exciting news: "The promising results from NEURO-TTRansform show that eplontersen had a positive impact on disease progression and improved quality of life in a substantial number of patients. We are excited about the potential for delivering a new treatment option to patients living with this relentless and devastating disease."

Eplontersen (AKCEA-TTR-LRx, ION-682884) is an investigational antisense medicine created by Ionis and developed in partnership with AstraZeneca. It reduces the production of TTR protein (transthyretin), allowing all types of ATTR to be treated. Eplontersen shares the same nucleotide sequence as inotersen, Ionis' first antisense medication to treat ATTR that was approved by the FDA and EU in 2018.

However, eplontersen uses ligand-conjugated (LICA) technology (read about advances in ligand conjugation here) to deliver ASOs to target cells while also utilizing a triantennary N-acetylgalactosamine moiety (GalNAc3) which increases the drug's potency, allowing patients to receive lower doses, less frequently than patients who are treated with inotersen.

168 patients are enrolled in the 66 week long global clinical trial. Patients are receiving subcutaneous (SC) injections of either eplontersen once every 4 weeks throughout the duration of the trial or inotersen once a week for the first 34 weeks, after which they will convert to subcutaneously administered eplontersen for the remainder of the study.

At 35 weeks, not only did eplontersen provide an 81.2% reduction in transthyretin serum levels compared to baseline in the NEURO-TTRansform study, but patients also displayed better scores on the modified Neuropathy Impairment Score +7 (mNIS+7) scale (which measures the level of neurological impairment), as well as reporting significantly improved quality of life as measured by the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN).

As the co-primary endpoints and a key secondary endpoint were met, and eplontersen was also safe and well tolerated, Ionis and AstraZeneca plan to seek regulatory approval this year.

In addition to the NEURO-TTRansform study to treat ATTRv patients with neuropathy, Ionis and AstraZeneca are also evaluating eplontersen's efficacy and safety in patients with amyloid transthyretin cardiomyopathy in the CARDIO-TTRansform study which is recruiting approximately 1000 participants.

A Swift Overview of Other Therapies Approved or in Clinical Trials to Treat ATTR

Tegsedi (inotersen), as mentioned previously, is Ionis' first antisense drug to gain approval to treat ATTR. It binds both wild-type and mutant TTR messenger ribonucleic acid (mRNA), inhibiting the expression of TTR protein. It is administered subcutaneously every week. After 15 months, it provided a 74% mean change in serum TTR. Patients also benefit from improved disease course and quality of life as reported by the mNIS+7 (Pbo-adj change -20) and Norfolk QoL-DN (Pbo-adj change -12). However, it can cause low platelet counts and kidney inflammation.

Onpattro (patisiran) was both the first siRNA drug to ever receive FDA approval and the first drug approved to treat polyneuropathy due to hereditary transthyretin amyloidosis, as it was approved two months before inotersen. Alnylam developed Onpattro, which is a double-stranded siRNA and employs a lipid nanoparticle delivery system. The siRNA cleaves to and breaks down mutant and wild-type transthyretin (TTR) mRNA, inhibiting synthesis of TTR protein. Patients receive Onpattro through an IV every three weeks. After 18 months, it provided an 84% mean change in serum TTR, and patients also benefit from improved disease course and quality of life as reported by the mNIS+7 (Pbo-adj change -34) and Norfolk QoL-DN (Pbo-adj change -21).

Amvuttra (vutrisiran) is Alnylam's second drug to receive approval to treat polyneuropathy due to ATTR. Amvuttra is also a siRNA, but it uses Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform. After 9 months, it provided an 83% mean change in serum TTR, and patients also benefit from improved disease course and quality of life as reported by the mNIS+7 (Pbo-adj change -17) and Norfolk QoL-DN (Pbo-adj change -16). It has the advantage of being administered subcutaneously only once every three months, a significant improvement over Onpattro and Tegsedi.

NTLA-2001 takes a different approach, systemically administering a CRISPR-Cas9 candidate to edit the *TTR* gene in hepatocytes inside the human body to knock out wild-type and mutant TTR. In an extremely simplified explanation: NTLA-2001 uses a lipid nanoparticle platform to deliver the guide RNA and messenger RNA that encodes the Cas9 protein. Once in the cell, the CRISPR-Cas9 complex is created, enters the nucleus, cleaves the target DNA sequence, then the DNA repair mechanisms join the ends of the cut, creating a knockout mutation that ultimately prevents misfolded TTR protein from being produced.

In June 2021, Intellia Therapeutics and Regeneron Pharmaceuticals reported that interim results of the Phase 1 study showed that this groundbreaking new method was safe, precisely edited the desired gene in the target cells, and reduced serum TTR by 93% after a single dose in patients who received .3mg/kg of body weight. At this point, only patients were included who had polyneuropathy that did not yet display motor symptoms and a New York Heart Association (NYHA) heart failure class of 1. (Read more details about NTLA-2001 and the interim results here.)

In September 2022, new interim results were announced. Twelve patients with ATTR-CM with NYHA Class I – III heart failure received .7mg/kg or 1.0mg/kg of body weight and displayed between 90-97% serum TTR reduction after 28 days.

It is anticipated that results will last a lifetime, but patients will need to be monitored long-term to determine whether this is true and to ascertain the long-term safety of the drug.

These encouraging results from the interim analysis are yet another incredible milestone in our field. The news that regulatory approval will be sought for eplontersen shows just how far our field has progressed; that patients with a devastating rare disease may soon be able to choose from not just one but four safe, effective medications to enhance their quality of life and improve the debilitating symptoms they must endure.

1. Adams D, Ando Y, Beirão JM, Coelho T, Gertz MA, Gillmore JD, Hawkins PN, Lousada I, Suhr OB, Merlini G. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. J Neurol. 2021 Jun;268(6):2109-2122. doi: 10.1007/s00415-019-09688-0. Epub 2020 Jan 6. PMID: 31907599; PMCID: PMC8179912.