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About ATTR Amyloidosis

ATTR amyloidosis is a systemic, progressive and fatal disease in which patients experience multiple overlapping clinical manifestations caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow.[1,2] The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death.[2] Depending on the presence or absence of a destabilizing mutation in the TTR gene, the disease can be classified as **hereditary ATTR** (hATTR) or **wild-type** (wtATTR), respectively.[2]

ATTR cardiomyopathy (ATTR-CM) is caused by **the accumulation of misfolded TTR protein in the cardiac muscle.**[3] ATTR-CM is a fatal, under-recognized condition, leading to heart failure (HF) and ultimately death. Deposition of amyloid into the myocardium causes restrictive cardiomyopathy with late decline of systolic function, arrhythmias, and HF.[2] Patients experience ongoing debilitating heart damage resulting in progressive HF, which **can result in death within 3 to 5 years from disease onset.** ATTR cardiomyopathy includes both the genetic and wild-type form of the disease.[2]

Polyneuropathy due to hATTR is caused by the **accumulation of misfolded, mutated TTR protein in the peripheral nerves.**[3] Patients with polyneuropathy due to hATTR experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking.[4] These patients also accumulate TTR in other major organs, which progressively compromises their function and **on average leads to death within five to fifteen years** of disease onset.[5]

Recognizing Cardiomyopathy and Treatment for ATTR

Recent studies have found the path to diagnosis can be difficult as it has been suggested that up to 10% to 15% of older adults with HF may have unrecognized wtATTR cardiac involvement.[6] Additionally, patients with the polyneuropathy form of TTR amyloidosis will also have TTR build-up in the heart and experience cardiomyopathy symptoms. Similarly, patients with the cardiomyopathy form of TTR amyloidosis may often have TTR build-up in their peripheral nerves and can experience nerve damage and progressive difficulty with motor functions.

Even after overcoming the hurdle to diagnosis, **treatment options are lacking.**[6] Despite treatment with a TTR stabilizer, ATTR-CM, disease progression occurs.[7]

But there is hope. Eplontersen (previously known as IONIS TTR-LRx, AKCEA-TTR-LRx or ION-682884) is an investigational antisense oligonucleotide that inhibits the production of TTR. LICA is a technology that involves attaching a ligand molecule to an antisense therapy to specifically target disease causing proteins where produced. LICA improves the benefit-risk profile of antisense therapies This delivery approach aims to increase potency (up to 30-fold) and improve the safety and tolerability of ASOs in human clinical trials.[12-16] Conjugation of this ligand allows the use of a lower dose to achieve

Eplontersen has been studied in early phase studies.
In a phase I, randomized, placebo-controlled study, eplontersen given at a 45 mg, 60 mg or 90 mg dose, by subcutaneous injection every four weeks in 36 healthy volunteers achieved a mean reduction in serum TTR of 86%, 91% and 94%, respectively, compared to baseline.[17] The dosage regimen of 45 mg SC every four weeks was chosen for the pivotal phase III study.[18]

Currently, the **Phase III CARDIO-TTRansform study is enrolling patients** to help determine the safety and efficacy of this treatment in reducing cardiomyopathy symptoms, improving quality of life, and decreasing the level of the disease-causing protein TTR.

For more information on the Phase III CARDIO-TTRansform study, please visit **www.cardio-ttransform.com**

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Select Publications for Additional Information

1. **Lovley, A. et al.** (2021) Patient-reported burden of hereditary transthyretin amyloidosis on functioning and well-being. J. of Patient-Reported Outcomes. 5:3.
2. **Nativi-Nicolau, J.N. et al.** (2021) Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. Heart Fail Rev.
3. **Ackermann, E.J. et al.** (2012) Clinical development of an antisense therapy for the treatment of transthyretin-associated polyneuropathy. Amyloid. 19, 43-44.
4. **Benson, M.D. et al.** (2011) Rate of Progression of Transthyretin Amyloidosis. Am J Cardiol.108, 285-289.
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15. Alexander V, et al. N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. Eur Heart J. 2019 Apr 24.
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