Journal of Science and Technology
ISSN: 2456-5660 Volume 8, Issue 10 (Oct -2023)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2023.v8.i10.pp71- 80*

Eplontersen Therapy: Bridging Cardiac Health and Neuropathy Relief in Hereditary ATTR Amyloidosis

K. Srikanth[1], M. Reeni Diana[2], S.Gowthami[3], D. Dhachinamoorthi[4]

1.Assistant Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P

2.Assistant Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P

3.Assistant Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P

4.Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P

To Cite this Article
K. Srikanth, M. Reeni Diana, S.Gowthami, D. Dhachinamoorthi**,** "**Eplontersen Therapy: Bridging Cardiac Health and Neuropathy Relief in Hereditary ATTR Amyloidosis**" *Journal of Science and Technology, Vol. 08, Issue 10-Oct 2023, pp71-80*

Article Info
Received: 30-09-2023 Revised: 07-10-2023 Accepted: 18-10-2023 Published: 29-10-2023

Abstract

Amyloidosis, Transthyretin, Transthyretin is generated mostly in the helix, and it is necessary for transferring retinol and thyroxine. When misfolded TTR polyneuropathy (ATTR-PN) aggregates to create amyloid fibrils, it causes TTRamyloidosis, which results in organ failure. If left untreated, familial transthyretin cardiomyopathy (FAP), an amyloid polyneuropathy connected to mutations like the V30M variant, generates increasing sensory and autonomic neuropathy with a dismal prognosis.

Corresponding Author: K.Srikanth
Mail: Srikanth.k@gmail.com

INTRODUCTION:

Vitamin A-binding protein, also known as transthyretin (TTR), is a widely distributed protein that may be detected in a range of tissue fluids, cells, and plasma. 1. TTR is the carrier protein and is mostly expressed in the choroid plexus of the brain and liver. It is involved in the transfer of retinol, or vitamin A, and thyroxine (mostly T4) to different body tissues and cells. It secretes into the blood and cerebrospinal fluid. 2. Thyroid function is necessary for sustaining human growth and development. 3. TTR Amyloidosis: Let's start by defining this condition. When an abnormal protein called amyloid builds up in the organs and disrupts their normal function, a rare disorder called amyloidosis occurs. So what exactly is TTR amyloidosis? To put it simply, TTR amyloidosis is brought on by TTR amyloid fibrils that are formed in several organs. 4. An Introduction to Polyneuropathy: FAP (familial amyloid polyneuropathy) 5 is an autosomal dominant neurodegenerative illness that is also known as Corino de Andrade's disease or transthyretin-related hereditary amyloidosis. 6. In 1952, Portuguese neurologist Mário Corino da Costa Andrade was the first to recognize and characterize it as a kind of amyloidosis. 7. The most common mutation in the transthyretin gene on the 18th chromosome, TTR V30M, causes valine to be replaced at position 30 by methionine. As a consequence of this mutation, the tetrameric protein transthyretin misfolds, dissolving into monomers to produce amyloid fibrils that damage peripheral nerves and organs. FAP is not the same as non-inherited senile systemic amyloidosis (SSA), which mostly affects the elderly. The autosomal dominant inheritance pattern affects heterozygous individuals, who often deposit both mutant and wild-type TTR subunits. This means that only one copy of the defective TTR gene is needed for the problem to manifest. This genetic basis highlights the illness's familial

nature. 8. 9. Pathophysiology: There are over 100 mutations in the TTR gene, most of which are single amino acid changes. 10, since transthyretin (TTR) amyloidosis was first reported by Andrade in 1952. The tetrameric structure of TTR is broken by substituting the most common mutation, methionine at position 30 11, p.Val30Met, for valine. This results in the formation of amyloidogenic monomers, which misfold and accumulate in various organs. 12, 13. Hereditary ATTR amyloidosis often exhibits heterozygosity, or the coexistence of both normal and mutant TTR proteins 14,15. The clinical presentation is influenced by the age of onset and the kind of mutation. 16. In individuals with ATTR-FAP, foot numbness and pain are the first signs of worsening sensory and autonomic neuropathy, which often leads to mortality 11 years after start 17–20. Peripheral neuropathy and cardiac issues including arrhythmias and heart failure are common in people with ATTR-FAC. 21, 22. Ataxia, convulsions, and visual problems are rare in OLMA patients 23,24Fig. 1.

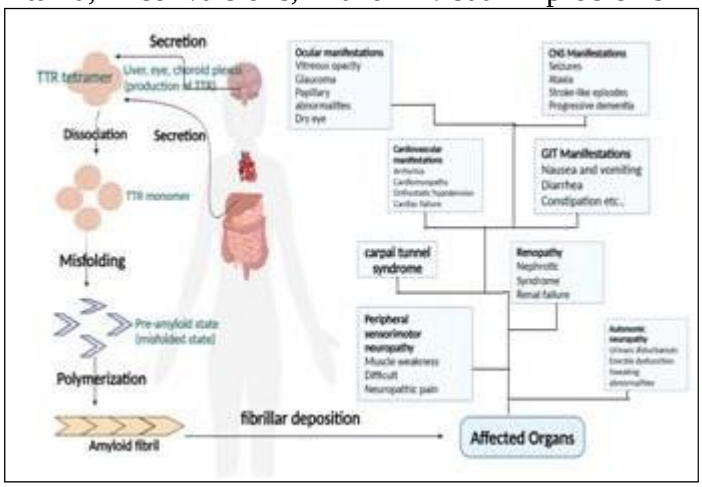

FIG. 1: PATHOPHYSIOLOGY OF ATTR POLYNEUROPATHY. Pathophysiology and the clinical manifestations of Amyloidosis ATTR. Both wild-type and mutant transthyretin are tetrameric proteins that are generated and released into the blood or cerebrospinal fluid (CSF). The tetrameric TTR protein breaks into aggregate-prone monomers when the TTR gene is changed. These monomers misfold and aggregate to form amyloid fibrils, which accumulate in the heart, peripheral nerves, and other organs. The site of TTR amyloid buildup is the primary factor affecting clinical symptoms.

Background of Cardiomyopathy: Cardiomyopathy is a disease that affects the myocardium, or heart muscle. Your heart may thicken, stiffen, or expand as a result of cardiomyopathy, leaving behind scar tissue. Your heart has a harder time pumping blood throughout your body as a result. Your heart may weaken with time, and cardiac failure may result from cardiomyopathy. Therapy might be helpful. Some people with cardiomyopathy may ultimately need a heart transplant. 25. One of the reasons of cardiomyopathy is parental genes. Researchers have found thousands of genetic abnormalities that cause cardiomyopathies. Additional causes of cardiomyopathy include coronary artery disease, thyroid disease, heart inflammation, muscular dystrophy, high cholesterol problems, sarcoidosis, amyloidosis, hemochromatosis, and other autoimmune diseases that harm the heart muscle. Pathophysiology: 25 TTR protein folding results in the formation of insoluble fibers. These fibers accumulate in the myocardium's interstitial spaces, leading to heart fibrosis and stiffness, which impair mechanical function 26. By resulting in diastolic dysfunction and increased left atrial pressures, TTR deposition thickens the myocardium on cardiac imaging, increasing the likelihood of atrial arrhythmias. Myocardial infiltration often affects the electrical conduction system as well (27). Ventricular arrhythmias are far less common than AL (amyloid light chain) cardiomyopathy, although being observed in ATTR-CM 28, 29. Misfolded TTR protein is often deposited in the peripheral and autonomic nervous systems; wild-type ATTR (wATTR) mostly causes cardiomyopathy 30,31Fig. 2, whereas hereditary ATTR (hATTR) more frequently impacts neurological systems.

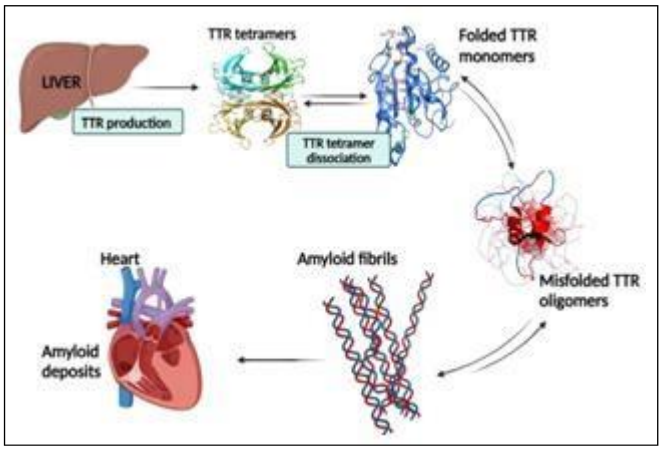

FIG. 2: PATHOPHYSIOLOGYOFATTRCARDIOMYOPATHY. Theliver producesa mutantversionofthetransthyretin (TTR) protein in transthyretin-related amyloidosis (ATTR), a genetic condition. These changes cause the TTR tetramer to become destabilized and undergo proteolytic remodeling, which increases the production of misfolded, amyloidogenic proteins. This includes both C-terminal fragments and full-length monomers, which quickly join to produce amyloid fibrils. The aggregation-prone C-terminal fragment, which is caused by the enzymatic breakdown of the transthyretin protein, is present in individuals with wild-type (WT) ATTR amyloidosis as well as those with various TTR mutations. Extracellular amyloid deposits also include nonfibrillar materials such as calcium, serum amyloid P component, and sulfonated glycosaminoglycans.

Antisense Oligonucleotide (ASO) Eplontersen: Eplontersen, a second-generation ASO conjugated to a triantennary GalNAc moiety, is designed similarly to inotersen and facilitates receptor-mediated absorption into target hepatocytes 32, 33. Eplontersen is a transthyretin-directed antisense oligonucleotide (ASO) that may be covalently attached to a ligand that has three N-acetyl galactosamine (GalNAc) residues 34 in order to transport it to hepatocytes. LICAs, or ligand-conjugated antisense oligonucleotides, are members of the Eplontersen pharmacological family. Eplontersen may decrease TTR expression up to 50 times more potently than inotersen due to its superior delivery mechanism. In contrast to Inotersen's weekly subcutaneous injection, this implies that it may be administered every four weeks. 35.

The rare, progressive disorder known as hereditary transthyretin-mediated amyloidosis polyneuropathy (hATTR-PN or ATTRv-PN) may be lethal if left untreated. This disorder is treated with eplontersen. Eplontersen is also being studied as a possible therapy for ATTR cardiomyopathy (ATTR-CM). 34. Eplontersen lowers the amount of TTR protein generated, which slows the disease's course, lessens neuropathy, and improves the patient's quality of life. Emplentersen's brand is called Wainua.

Discussion:

Eplontersen: Polyneuropathy Treatment Mechanism of Action: Eplontersen is a member of the family of short, synthetic strands of nucleic acid known as antisense oligonucleotides (ASOs), which are specifically designed to bind to messenger RNA (mRNA) molecules. The primary function of an ASO is to inhibit the expression of a target gene by binding to the complementary sequence of the RNA and blocking the translation of the mRNA into a protein. Transthyretin (TTR), a protein mostly found in helverine and crucial for the transport of thyroid hormones and retinol, is the target mRNA for eplontersen. On the other hand, TTR mutations or misfolding may cause toxic amyloid deposits, which mostly affect brain regions. 36, 37.

Eplontersen works by binding to TTR mRNA and promoting the mRNA's breakdown via RNase H-mediated degradation. The enzyme RNase H degrades RNA when it hybridizes to a DNA strand. Less TTR mRNA is available for translation as a consequence of this binding, which lowers the amount of TTRprotein that is made. This leads to a decrease in the amount of TTR in the blood, which is important since high levels of TTR are necessary for the formation of amyloid fibrils 38.

TTR39 misfolding and aggregation may result in amyloid fibrils, which can build up in a number of tissues and specifically affect the peripheral nervous system, causing neuropathy and other serious effects. These amyloid accumulations disrupt normal tissue function and may lead to inflammation, which exacerbates nerve damage. By lowering TTR production, Epoentersen decreases the development of these dangerous aggregates. This may even lessen some of the symptoms of polyneuropathy and protect nerve cells from damage. The ultimate goal is to halt or decrease the progression of disorders linked to TTR amyloidosis in order to enhance clinical outcomes and patients' quality of life. 40,41 Figure 3: Treatment by Gene Modification: Gene silencing-based treatments that use siRNA and

ASO technologies to produce TTR knockdown are therapeutically successful for individuals with ATTR amyloidosis; however, these treatments must be given regularly to maintain their therapeutic effect. 42. NTLA-2001 has altered the TTR gene in hepatocytes using the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-Cas9 technology, which is one potential single-dose treatment for ATTR amyloidosis42. 42. Transcription of CRISPR sequences results in the production of small RNA that can guide the system to complementary DNA sequences 43,44. The Cas9 endonuclease then binds to and cleaves the DNA 45, deleting the target gene. The typical disease model for targeting invivogenome-editing treatment is ATTR amyloidosis because only the liver can manufacture the circulating TTR protein, which is encoded by a single gene. 46. Following effective administration of NTLA-2001 in many animal models, the medication was tested in a limited group of ATTR amyloidosis patients, and it consistently resulted in a long-lasting TTR knockdown 47Fig. 3.

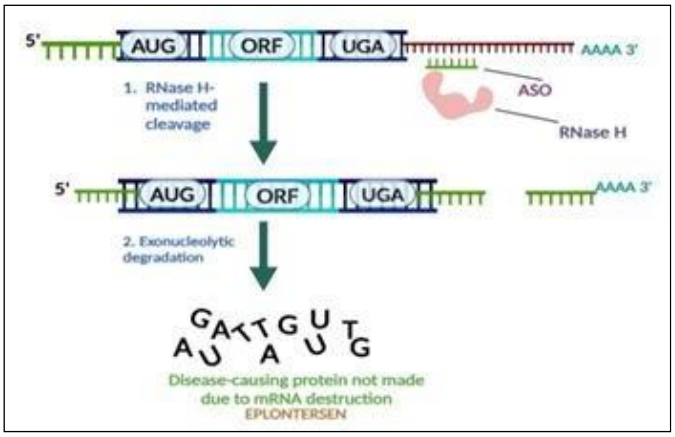

FIG. 3: EPLONSEN'S MODE OF ACTION IN ATTR POLYNEUROPATHY.

The FDA-approved ASOs currently available on the market have several major modes of action (MOAS), one of which is the binding of the ASO to its target sequence inside an mRNA, which draws RNase H activity and destroys the disease-causing mRNA.

Eplontersen: Cardiomyopathy Treatment Mechanism of Action: Treatment for transthyretin amyloidosis (ATTR) has evolved dramatically with Eplontersen. This is due to the unique characteristics of ligand-conjugated antisense oligonucleotides that enhance the effectiveness and specificity of therapy. This innovative design is very effective due to Epontersen's targeted strategy; it only binds to the messenger RNA (mRNA) that codes for the transthyretin (TTR) protein. By enabling effective hybridization with a sequence complementary to a specific region of the TTR mRNA, epontersen ensures proper targeting of the mRNA within liver cells, the main site of TTR synthesis 36,37. As soon as it attaches to its target mRNA, Emplontersen activates RNase H, an enzyme necessary for decomposing RNA molecules that have hybridized to DNA. By initiating the degradation of TTR mRNA 38, this recruitment dramatically lowers the quantity of mRNA accessible for translation. As a result, the liver's capacity to produce TTR protein is significantly reduced. Since the liver is the primary site of TTR production, this reduction is necessary to reduce the overall level of TTR in the circulation. Reducing TTR levels is essential because excessive TTR can misfold and aggregate into amyloid fibrils, which seriously jeopardize cardiovascular health. These amyloid fibril deposits Heart failure and cardiomyopathy may be caused by several organs. By reducing the amount of TTR available for misfolding, epolantersen directly addresses the underlying cause of amyloid-related diseases by lowering the substrate needed for fibril formation. This therapy strategy not only stops amyloid from accumulating in cardiac tissues but also improves cardiovascular health in general. Patients may have a higher quality of life as a result of increased exercise tolerance and a decline in cardiovascular issues. Individuals who have less symptoms of ATTR are able to engage more fully in their daily activities, indicating the revolutionary potential of eplontersen in the treatment of this challenging illness. Ultimately, eplontersen is a targeted treatment approach that addresses the root causes of disease and offers ATTR patients hope for improved outcomes. 48 Fig. 4.

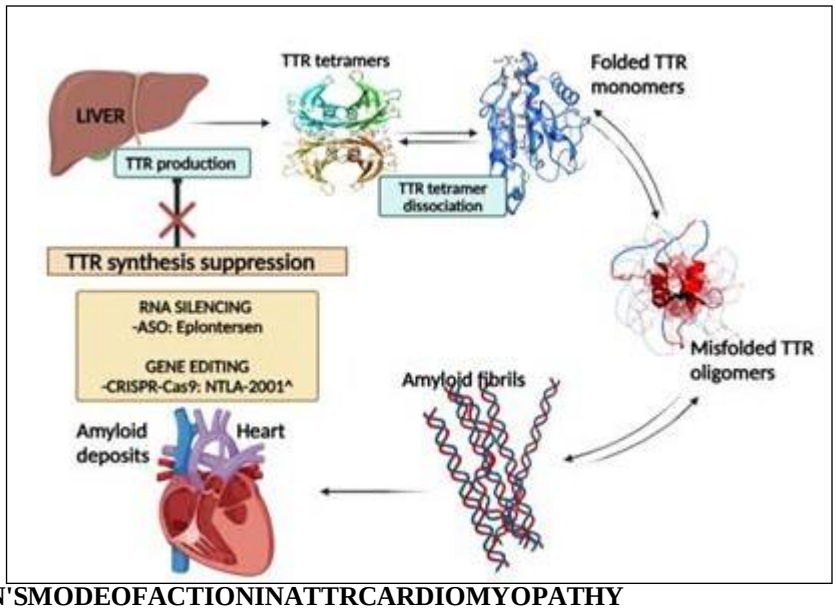

FIG.4:EPLONTERSEN'SMODEOFACTIONINATTRCARDIOMYOPATHY

. The pathophysiology of ATTR amyloidosis serves as a guide for the development of novel pharmacotherapies and therapeutic targets for the treatment of ATTR-CM. Transthyretin is mostly produced by the liver as a homotetramer (PDB 3P3T crystal structure). It then breaks up into different folded monomers, which self-assemble to create amyloid fibrils. Wild-type transthyretin amyloid fibrils mostly build up in the heart, causing organ failure. Among the existing and emerging treatment approaches for ATTR-CM are TTR tetramer stabilisers, RNA-targeted gene silencing, gene editing, and compounds that inhibit amyloid seeds or encourage amyloid clearance.

Clinical Research Advancements: The NEURO-TTRANSform trial, headed by Muhammad Saeed Qazi et al., examined the efficacy of Eplontersen in treating ATTRv amyloidosis with polyneuropathy. Important results revealed that Eplontersen significantly reduced serum transthyretin (TTR) levels, with an adjusted mean percentage decrease of -81.7% when compared to the placebo. Additionally, a lower mean change from baseline in the mNIS + 7 composite score (−24.8,95%CI−31.0to−18.6,P<0.001) indicated significant improvements in neuropathy impairment among patients receiving Eplontersen. The Norfolk QoL-DNscore improved more favorably (−19.7,95%CI−25.6to−13.8,P<0.001), indicating that quality of life also improved. These results show that eplontersen may be an effective treatment for ATTRv amyloidosis, offering notable therapeutic benefits and enhancing patients' overall quality of life. Two antisense oligonucleotides (ASOs), Eplontersen and Inotersen, function by degrading TTR mRNA to reduce the production of TTR protein in hereditary transthyretin amyloidosis. Their designs and distribution strategies differ even though their sequences are similar. Inotersen primarily targets endothelial or Kupffer cells, which improves its absorption by hepatocytes through ASGPR-mediated pathways, whereas epflontersen is combined with GalNAc3 (triantennary N-acetyl galactosamine). Preclinical tests show EC50 and ED50 reductions of approximately 50 and 28 fold, respectively, indicating Eplontersen's increased potency 49. Eplontersen is distinct from other polyneuropathy drugs such as patisiran 50, tafamidis, and diflunisal that work to stabilize TTR tetramers or stop TTR synthesis. Better clinical outcomes and more significant drops in serum TTR levels are anticipated as a result of Eplontersen's novel therapeutic approach, which targets TTR mRNA directly within hepatocytes. Larger, longer-term studies are necessary to evaluate Eplontersen's potential as a breakthrough therapy, even if continuing research into the medicine for hereditary ATTR polyneuropathy (hATTR-PN) shows promise. More comprehensive knowledge of Eplontersen's efficacy and safety, as well as any potential drawbacks and long-term benefits, will be provided by these studies. Furthermore, in order to ensure equitable treatment and maximize Eplontersen's impact on hATTR-PN patients globally, patient access must be increased. With more research and innovation in the works, the prognosis for hATTR-PN therapy is

still positive 51.
John K. Diep et al.' study of Eplontersen's pharmacokinetics (PK) successfully predicted the drug's behavior under two distinct compartments. Demographic data analysis indicated that body weight had an effect on intercompartmental clearance and distribution volumes, but lean body mass had a large influence on drug clearance. According to population PK modeling, injecting the injection into the abdomen as opposed tothearmresultedin 29.6%greaterabsorption

rates. It was observed that the population's average terminal elimination half-life was 25.5 days. The link between blood TTR (transthyretin) levels and Eplontersen was well- described by an indirect response model, which revealed that the medicine lowered TTR production. The inhibitory half-maximum concentration (IC50) was found to be 0.0283 ng/ml (13.3% RSE), whilst the Imax (highest fractional inhibition) was estimated to be 0.970 (0.549% RSE). Accordingto the simulation findings, peoplewho werelighter hadhigher exposurelevels (AUC and Cmax), and when injection locations were compared (abdomen vs. arm, with a ratio of 1.18),a greater Cmax was found. The drug's response at the tested doses was not substantially impacted bythese exposure variations, though 52.
Under Tina Nie's direction, the phase III NEURO- TTRansform investigation (NCT04136184) found that subcutaneous Eplontersen every four weeks dramatically slowed the progression of neuropathy and that patients with ATTRv-PN had improved health-related quality of life. By week 66, Eplontersen (n = 144) had a modified Neuropathy Impairment Score + 7 (mNIS+7) composite score with an adjusted mean change from baseline of 0.3.whileahistoricalplacebo(n=60)had achange of 25. The adjusted mean difference from baseline resultedinabetween-groupdifferenceof−24.8($p < 0.001$) (95% CI -31.0 to -18.6), indicating that it should be considered a co-primary endpoint 53. The NorfolkQoL-DN (NorfolkQuality of Life Questionnaire for Diabetic Neuropathy) total score changed by −5.5 on average at week 66 due to Eplontersen, while the historical placebo produced a decrease of 14.2 (BGD−19.7,95%CI−25.6 to −13.8; $p < 0.001$).
The adjusted mean shift in mNIS+7 at week 35, which was 0.2 for Eplontersen and 9.2 for the placebo (BGD−9.0,95%CI−13.5to−4.5; $p<0.001$), supported the U.S. approval of Eplontersen. 54, 55. In contrast, the Norfolk QoL-DN values were -3.1 and 8.7, respectively (BGD - 11.8,95%CI-16.8to-5.7;$p<0.001$). Patients over the age of 18 with Coutinho stage 1 or 2 ATTRv-PN, a neuropathic impairment score between 10 and 130, and TTR genevariants were included in the worldwide, open-label NEURO-TTRansform study. Inotersen or Eplontersen (reference group; n = 24) were administered to patients in a 6:1 ratio based on previous placebo data from the NEURO-TTR trial, which had comparable eligibility requirements and results. 56,57. Eplontersen recipients got 45 mg subcutaneously until week 81, everyfour weeks, In comparison, the participants in the reference group of Inotersen received 300 mg of inotersen weekly till week 34 and Eplontersen from weeks 37 to 81 53.
There are several active studies assessing Eplontersen in ATTR-CM, including an open-label expansion of NEURO-TTRansform (the NCT05071300). Eplontersen is provided subcutaneously every four weeks to patients taking standard care therapy, which could include tafamidis, as part of a worldwide, randomised, double-blind, placebo-controlled study known as thephaseIIItrialofCARDIO-TTRansform58. This project, which has a 140-week treatment length, is open to adults with ATTR-CM (wild-type or hereditary) with symptoms of NYHA class I–III. Eplontersen's long-term tolerability and safety will also assessed during a 36-month open-label extension (NCT05667493). In addition, patients in the United States who have completed a 24-month inotersen study are slated to take part in the single- center, NCT04843020, an open-label phase II trial, while patients in China are being enrolled in the randomly assigned phase III trial of EPIC-ATTR (the NCT06194825) 59.
Of the 144 ATTRv polyneuropathy patients in the open-label NEURO-TTRansform trial, 49 (34%) developed cardiomyopathy, according to Ahmad Masri et al. At week 65 after Eplontersen administration, the efficacy of the therapy was assessed by comparing it to a prior placebo group of 60 volunteers (30 patients, or 50% with cardiomyopathy). By calculating the mean differences (with 95% CIs) and controlling for variables such as sex, baseline values, age, region, ATTRv (Hereditary Transthyretin Amyloidosis) disease stage, prior hereditary transthyretin amyloidosis, treatments, and the V30Mtransthyretinvariant, the therapeutic effects of

Eplontersen vs. placebo were compared. The Eplontersen group and the historical placebo group differed significantly at baseline. When compared to a placebo, the cardiomyopathy subgroup improved its percentage of left ventricular ejection (95% CI 1.40–21.01; P =.049) and stroke volume (95% CI 3.99–17.29; P=.002) after 65 weeks of Eplontersen therapy. All other echocardiographic measurements did not change.
In an Eplontersen study, Teresa Coelho et al. administered the drug to 144 patients (69% male; mean age 53.0 years); 136 (94.4%) of them completed the week-66 follow-up. In contrast, 52 (86.7%) of the 60 patients in the placebo group (68% male; mean age 59.5 years) completed the follow-up. The adjusted mean percentage reduction in serum transthyretin at week 65 was −70.4% (P < 0.001;95%CI,-75.2%to-65.7%)forthe Eplontersen group and −11.2% for the placebo group.
Between baseline and week 66, the Eplontersen group's adjusted mean change was significantly lower than that of the placebo group, suggesting better results in terms of both the Norfolk QoL-DN score, A difference of −19.7,95%CI:−25.6to−13.8 (−5.5vs.14.2; P<.001) and −24.8,95%CI,−31.0to−18.6; P<.001 was seen in the mNIS+7 composite score. Six patients (4%) in the Eplontersen group had side effects that resulted in the trial drug being discontinued, compared to two patients (3%), in the placebo group. During the trial, no deaths were reported in the group that received a placebo, but two deaths were reported in the group that received Eplontersen, which were associated with known consequences of the condition (cardiac arrhythmia and intracerebral hemorrhage) 61.
Patients with ATTRv-PN were enrolled in a study conducted by Conceição et al. as part of the NEURO-TTRansform experiment. A portion of these individuals was allocated at random to receive 300 mg of inotersen subcutaneously each week for the first 34 weeks. They then started taking subcutaneous eplontersen, 45 milligrams every four weeks, from weeks 37 to 81. Up to week 85 of the study, the effects on nutritional status, neuropathic impairment, and quality of life were evaluated in addition to variations in blood TTR levels and TEAEs (treatment-emergent adverse events). 83 percent of the 24 patients, or 20. Those who had been randomly allocated to inotersen switched to eplontersen at week 37, whereas four people discontinued due to unfavorable circumstances or choices made by the researchers. Serum TTR decreased more absolutely after switching from inotersen (-74.3% at week 35) to eplontersen (-80.6% at week 85). During the eplontersen therapy, there was no decrease in nutritional status, and the neuropathy that impairs quality of life was constant (not progressing). Additionally, TEAEs were less frequent with eplontersen (19 out of 20 patients, or 95%) than with inotersen (all 24 patients, or 100% up to week 35). Mean platelet counts decreased with a mean nadir drop of -40.7% after inotersen therapy; however, they returned to baseline levels of 62 with a mean nadir reduction of -3.2% with eplontersen treatment.
In the NEURO-TTRANSform investigation, Yu AL et al. conducted a retrospective study on participants with hereditary ATTR cardiomyopathy (hATTR-CM) who received Eplontersen at a dosage of 45 mg every four weeks. Patients with hereditary transthyretin amyloid cardiomyopathy (hATTR-CM)who hadn't gottentreatmentofpartisan,tafamidis,inotersen,or eplontersen made constituted the control group. 99mTc-PYP SPECT/CT (Technetium-99m- pyrophosphate single-photon emission computed tomography) images were done at baseline and duringfollow-up. Thirteen hATTR-CM participants participated, seven of whom were in the control group and six of whom were given Eplontersen. The median follow-up period was 544 days. The Eplontersen group saw a significant drop in the volumetric heart to lung ratio (P = 0.028 between 3.774 and 2.979), whereas the control group did not see a significant decrease (P = 0.237 between 4.079 and 3.915). Additionally, When compared to the control group, the volumetric heart to lung ratio was significantly worse in the Eplontersen-treated individuals (P = 0.007) (-20.7% vs. -3.4%) 63. RESULTS: The effectiveness of eplontersenin in treating hereditary transthyretin amyloidosis with polyneuropathy is strongly supported by the NEURO-TTRANSform study, which was headed by Muhammad Saeed Qazi et al. The experiment showed substantial improvements in neuropathy impairment and QoL (quality of life) as evaluated by the NIS+7 and Norfolk QoL-DN scores, respectively, and a significant drop in blood TTR levels, with an adjusted mean decrease of -81.7% when compared with placebo. This shows that Eplontersen not only decreases TTR levels efficiently but also promotes patient wellbeing. Eplontersen's novel mode of action, which targets TTR mRNA, sets it apart from current therapies that concentrate on blocking the manufacture of transthyretin (TTR) or stabilizing it. According to pharmacokinetic studies, lean body mass and body weight have a major impact on

the drug's distribution and clearance, with abdominal injections producing higher rates of absorption. Low rates of treatment termination owing to adverse events indicate that Eplontersen's safety profile is still good. Furthermore, the medication has showed prospective advantages for individuals with inherited ATTR cardiomyopathy, boosting cardiac function measures in those taking Eplontersen compared to historical controls. These results underline the necessity for bigger, longer-term trials to completely assess the long-term safety and effectiveness of Eplontersen, as well as its potential position in the wider therapy landscape for ATTRv-PN and ATTR cardiomyopathy. Future treatment approaches for treating hereditary transthyretin amyloidosis seem to have a bright future as more research and more availability to Eplontersen may lead to better results for people with this difficult illness.

REFERENCES:

1. Rosales and Francisco J: "Determination ofa cut-off value for the molar ratio of retinol-binding protein to transthyretin(RBP:TTR)inBangladeshipatientswithlow hepatic vitamin A stores." The Journal of Nutrition 2002; 132(12): 3687-3692.
2. Wojtczak, Andrzej, Piotr Neumann and Vivian Cody: "Structure of a new polymorphic monoclinic form of human transthyretin at 3 Å resolution reveals a mixed complex between unliganded and T4-bound tetramers of TTR." ActaCrystallographica Section D: Biological Crystallography 2001; 57(7): 957-967.
3. Zhao and Xiaoya: "Screening and Analysis of Thyroid- Disrupting Chemicals Based on Selective Recognition foraThyroxine-BindingPeptide."IntJElectrochemSci2021; 16(2): 211012.
4. Kapoor andMahima: "Clinical presentation,diagnosis and treatment of TTR amyloidosis." Journal of Neuromuscular Diseases 2019; 6(2): 189-199.
5. Jump Ando Y and Ueda M: "Novel methods for detecting amyloidogenic proteins in transthyretin related amyloidosis". Frontiers in Bioscience 2008;13(13): 5548–58.doi:10.2741/3098.PMID18508604.
6. Online Mendelian Inheritance in Man (OMIM): Amyloidosis, hereditary, transthyretin-related - 105210
7. Andrade C: "A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves". Brain 1952; 75(3): 408–27. doi:10.1093/brain/75.3.408. PMID 12978172.
8. Coles LS and Young RD: "Supercentenarians and transthyretin amyloidosis: the next frontier of human life extension".PreventiveMedicine2012;54:9–11. doi:10.1016/j.ypmed.2012.03.003.PMID22579241.
9. Online Mendelian Inheritance in Man (OMIM): Transthyretin (TTR) - 176300
10. Benson MD: Transthyretin amyloidosis: a little history of hereditary amyloidosis. Amyloid 2017; 24: 76–77. doi: 10.1080/13506129.2017.1281116
11. Stewart M, Shaffer S, Murphy B, Loftus J, Alvir J, Cicchetti M: Characterizing the high disease burden of transthyretin amyloidosis for patients and caregivers. Neurol Ther 2018; 7: 349–364.
12. Ando Y, Nakamura M and Araki S: Transthyretin-related familial amyloidotic polyneuropathy. Arch Neurol 2005; 62: 1057–1062. doi: 10.1001/ archneur.62.7.1057
13. Coelho T, Merlini G, Bulawa CE, Fleming JA, Judge DP and Kelly JW: Mechanism of Action and clinical application of tafamidis in hereditary transthyretin amyloidosis. Neurol Ther 2016; 5: 1–25.
14. Hamilton JA and Benson MD: Transthyretin: a review from a structural perspective. Cell Mol Life Sci 2001; 58; 1491–1521. doi: 10.1007/PL00000791
15. Suhr OB, Svendsen IH, Andersson R, Danielsson A, Holmgren G and Ranlo PJ: Hereditary transthyretin amyloidosis from a Scandinavian perspective. J InternMed 2003; 254: 225–235.
16. Ruberg FL and Berk JL: Transthyretin (TTR) cardiac amyloidosis. Circulation 2012; 126: 1286–1300. doi: 10.1161/Circulationaha.111.078915
17. HundE:Familialamyloidoticpolyneuropathy:currentand emerging treatment options for transthyretin-mediated amyloidosis. Appl Clin Genet 2012; 5: 37–41. doi: 10.2147/TACG.S19903
18. Plante-Bordeneuve V and Said G: Familial amyloid polyneuropathy. Lancet Neurol 2011; 10: 1086–1097. doi: 10.1016/S1474-4422(11)70246-0
19. KoikeH,TanakaF,HashimotoR,TomitaM,Kawagashira Y and Iijima M: Natural history oftransthyretin Val30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. J Neurol Neurosurg Psychiatry2012;83:152–158.doi:10.1136/jnnp-2011-301299
20. Adams D: Recent advances in the treatment of familial amyloidpolyneuropathy.TherAdvNeurolDisord2013;6: 129–139. doi: 10.1177/ 1756285612470192
21. Castano A, Drachman BM, Judge D and Maurer MS: Natural history and therapy of TTR-cardiac amyloidosis: emerging

disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. Heart Fail Rev 2015; 20: 163–178. doi: 10.1007/s10741-014-9462-7

22. Haagsma EB, Hawkins PN, Benson MD, Lachmann HJ, Bybee A and Hazenberg BP: Familial amyloidotic polyneuropathy with severe renal involvement in association with transthyretin Gly47Glu in Dutch, British andAmerican-Finnishfamilies.Amyloid 2004;11:44–49. doi:10.1080/ 13506120410001682578
23. McColganP,ViegasS,GandhiS,BullK,TudorR,Sheikh F: Oculoleptomeningeal amyloidosis associated with transthyretin Leu12Pro in an African patient. J Neurol 2015; 262: 228–234. doi: 10.1007/s00415-014-7594-2
24. Mathieu F, Morgan E, So J, Munoz DG, Mason W and Kongkham P: Oculoleptomeningeal amyloidosissecondary to the rare transthyretinc.381TG (p.Ile127Met) mutation. World Neurosurg 2018; 111: 190–193. doi: 10.1016/j.wneu.2017.12.096
25. https://my.clevelandclinic.org/health/diseases/16841- cardiomyopathy
26. Connors LH, Sam F, Skinner M, Salinaro F, Sun F,RubergFL,BerkJLandSeldinDC:Heart failureresulting from age-related cardiac amyloid disease associated with wild-typetransthyretin:aprospective,observationalcohort study. Circulation 2016; 133(3): 282-90. [PMC freearticle] [PubMed]
27. Donnellan E, Wazni OM, Hanna M, Elshazly MB, Puri R, Saliba W, Kanj M, Vakamudi S, Patel DR, Baranowski B, CantillonD,DresingTandJaberWA: Atrialfibrillationin transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. JACC Clin Electrophysiol 2020; 6(9): 1118-1127. [PubMed]
28. Khanna S, Lo P, Cho K and Subbiah R: Ventricular arrhythmias in cardiac amyloidosis: a review of current literature. Clin Med Insights Cardiol 2020; 14: 1179546820963055. [PMC free article] [PubMed]
29. Falk RH, Alexander KM, Liao R and Dorbala S: AL (Light-Chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016; 68(12): 1323-41. [PubMed]
30. Pomerance A: Senile cardiac amyloidosis. Br Heart J. 1965; 27(5): 711-8. [PMC free article] [PubMed]
31. Pinney JH, Whelan CJ, Petrie A, Dungu J, BanypersadSM, Sattianayagam P, Wechalekar A, Gibbs SD, Venner CP, Wassef N, McCarthy CA, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD and Lachmann HJ: Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc 2013; 2(2): 000098. [PMCfree article] [PubMed]
32. Prakash TP, Graham MJ and Yu J: Targeted delivery of antisense oligonucleotides to hepatocytes using triantennary N-acetyl galactosamine improves potency 10- foldinmice.Nucleic AcidsRes2014;42:8796–807.DOI: 10.1093/nar/gku531.
33. Tanowitz M, Hettrick L and Revenko A: Asialoglycoprotein receptor 1 mediates productive uptakeof N-acetylgalactosamine-conjugated and unconjugated phosphorothioate antisense oligonucleotides into liver hepatocytes. Nucleic Acids Res 2017; 45: 12388–400. DOI: 10.1093/nar/gkx960.
34. https://www.clinicaltrialsarena.com/projects/wainua- eplontersen-for-the-treatment-of-polyneuropathy-of- hereditary-transthyretin-mediated-amyloidosis-usa/?cf- view
35. VineyNJ, Guo S and Tai LJ: Ligand conjugated antisense oligonucleotide for the treatment of transthyretin amyloidosis: Preclinical and phase 1 data. ESC Heart Fail 2021; 8: 652–61. DOI: 10.1002/ehf2.13154.
36. Population pharmacokinetic/pharmacodynamic modelling of eplontersen, an antisense oligonucleotide indevelopment for transthyretin amyloidosis - Diep - 2022 - British Journal of Clinical Pharmacology - Wiley Online Library. Accessed 29 April 2024.
37. Adams D, Koike H and Slama M: Hereditarytransthyretin amyloidosis: a model of medical progress for a fatal disease. Nat Rev Neurol 2019; 15: 387–404.
38. Chan JH, Lim S and Wong WS: Antisense oligonucleotides: from design totherapeutic application. Clin Exp Pharmacol Physiol 2006; 33: 533–540.
39. KoleR,Williams TandCohen L:RNAmodulation,repair and remodeling bysplice switching oligonucleotides. Acta Biochim Pol 2004; 51: 373–378.
40. Nasevicius A and Ekker SC: Effective targeted gene “knockdown” in zebrafish. Nat Genet 2000; 26: 216–220.
41. van Deutekom JC, Janson AA, Ginjaar IB, Frankhuizen WS, Aartsma-Rus A and Bremmer-Bout M: Local dystrophin restoration with antisenseoligonucleotide PRO051. N Engl J Med 2007; 357: 2677–2686.
42. Ioannou A, Fontana M and Gillmore JD: RNA targeting and gene editing strategies for transthyretin amyloidosis. BioDrugs 2023; 37: 127–42. Jinek M, Chylinski K and Fonfara I: A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012; 337: 816–21. DOI: 10.1126/science.1225829.
43. WiedenheftB,SternbergSHandDoudnaJA:RNA-guided genetic silencing systems in bacteria and archaea. Nature 2012; 482: 331–8. DOI: 10.1038/nature10886.
44. Finn JD, Smith AR and Patel MC: A single administration of CRISPR/Cas9 lipid nanoparticles achieves robust and persistent *in-vivo* genome editing. Cell Rep 2018; 22: 2227–35. DOI: 10.1016/j.celrep.2018.02.014.
45. Maurer MS: Gene editing – A cure for transthyretin amyloidosis. N Engl J Med 2021; 385: 558–9
46. Gillmore JD, Gane E and Taubel J: CRISPR-Cas9 *in-vivo* gene editing for transthyretin amyloidosis. N Engl J Med 2021; 385: 493–502. DOI: 10.1056/NEJMoa2107454.
47. Nativi-Nicolau J, Judge DP and Hoffman JE: Natural history and progression of transthyretin amyloid cardiomyopathy: insights from ATTR-ACT ESC HeartFail 2021; 8: 3875-3884
48. Population pharmacokinetic/pharmacodynamic modelling of eplontersen, an antisense oligonucleotide indevelopment for

transthyretin amyloidosis - Diep - 2022 - British Journal of Clinical Pharmacology - Wiley Online Library. Accessed 29 April 2024.

49. The treatment of amyloidosis is being refined - PubMed. Accessed 29 April 2024.
50. Qazi, Muhammad Saeeda; Tariq, Muhammad Burhanb; Farhan, Kanzab; Salomon, Izerec,*. Eplontersen: a promisingbreakthrough in treatinghereditarytransthyretin amyloidosis-related polyneuropathy. Annals of Medicine& Surgery 2024; 86(8): 4336-4337. DOI: 10.1097/MS9.0000000000002330
51. Diep JK, Yu RZ, Viney NJ, Schneider E, Guo S, Henry S, Monia B, Geary R and Wang Y: Population pharmacokinetic/pharmacodynamic modelling of eplontersen, an antisense oligonucleotide in development for transthyretin amyloidosis. British Journal of Clinical Pharmacology 2022; 88(12): 5389-98.
52. Coelho T, Marques W and Dasgupta NR: Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. JAMA 2023; 330(15): 1448–58.
53. Ionis Pharmaceuticals Inc. WAINUA™ (eplontersen) grantedregulatoryapprovalintheU.S.forthetreatmentof adults with polyneuropathy of hereditary transthyretin- mediated amyloidosis [media release]. 21 Dec 2023.
54. AstraZeneca Pharmaceuticals LP. WAINUA™ (eplontersen) injection, for subcutaneous use. 2023. https://www.accessdata.fda.gov/. Accessed 09 Feb 2024.
55. Keam SJ. Inotersen: first global approval. Drugs. 2018; 78(13): 1371–6.
56. Benson MD, Waddington-Cruz M and Berk JL: Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018; 379(1): 22–31.
57. FalkRH,GertzMAandBensonMD:Rationaleanddesign of a phase 3 study to evaluate the efficacy and safety of ION-682884 in patients with transthyretin-mediated amyloid cardiomyopathy (ATTR-CM) [abstract]. Blood. 2019; 134(1): 5764.
58. NieT:Eplontersen:FirstApproval.Drugs2024;84:473–478.
59. Masri A, Maurer MS, Claggett BL, Kulac I, Cruz MW, Conceição I, Weiler M, Berk JL, Gertz M, Gillmore JDand Rush S: Effect of eplontersen on cardiac structure and function in patients with hereditary transthyretin amyloidosis. J of Cardiac Failure 2024; 30(8): 973-80.
60. Coelho T, Marques W and Dasgupta NR: Eplontersen for Hereditary Transthyretin Amyloidosis with Polyneuropathy. JAMA 2023; 330(15): 1448–1458. doi:10.1001/jama.2023.18688.
61. Conceição I, Berk JL, Weiler M, Kowacs PA, Dasgupta NR, Khella S, Chao CC, Attarian S, Kwoh TJ, Jung SW and Chen J: Switching from inotersen to eplontersen in patients with hereditary transthyretin-mediatedamyloidosis with polyneuropathy: analysis from NEURO- TTRansform. Journal of Neurology 2024; 1-2.
62. An-Li Yu, Yi-Chieh Chen, Cheng-Hsuan Tsai, Yuan-Kun Aden Wu, Mao-Yuan Su, Chia-Hung Chou, Chia-Tung Shun, Hsueh-Wen Hsueh, Jimmy Jyh-Ming Juang, Ming-Jen Lee, Ping-Huei Tseng, Chia-Hua Hsu, Sung-Tsang Hsieh, Chi-LunKo, Mei-Fang Cheng, Chi-Chao Chao, Yen-Hung Lin Journal of the American Heart Association 2024; 13(2): 030512.