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EPLONTERSEN: A NEW HOPE FOR CARDIAC COMPLICATIONS IN ATTR POLYNEUROPATHY

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ABSTRACT: Transthyretin is essential for transporting retinol and thyroxine, produced mainly in the liver. TTR amyloidosis occurs when misfolded TTR aggregates form amyloid fibrils, leading to organ dysfunction. FAP (Familial amyloid polyneuropathy linked to mutations like the V30M variant, causes progressive sensory and autonomic neuropathy with a poor prognosis if untreated. TTR-related cardiomyopathy involves amyloid deposition in the heart, resulting in heart failure. The NEURO-TTRansform trial methodology provides a robust framework for evaluating the efficacy and safety of Eplontersen in patients with ATTRv-PN and ATTR-CM. The detailed assessment of both clinical outcomes and pharmacokinetics contributes to understanding Eplontersen's potential as a transformative therapy for this patient population. Recent treatment advancements include eplontersen that reduces TTR production by targeting TTR mRNA, effectively preventing amyloid fibril formation. Clinical trials, such as the NEURO-TTRansform study, demonstrated significant efficacy: eplontersen led to an adjusted mean reduction in serum TTR levels of -81.7% compared to placebo, along with improvements in neuropathy impairment (mNIS+7 score change of -24.8, $P < 0.001$) and quality of life (Norfolk QoL-DN score change of -19.7, $P < 0.001$). Eplontersen also showed a 4.3% improvement in left ventricular ejection fraction among hATTR-CM patients. Adverse events were manageable, with two deaths linked to disease complications. Ongoing research is focused on eplontersen's long-term effects and its potential in treating ATTR-CM. These findings highlight eplontersen's promise as a transformative therapy for hATTR, improving both neuropathy and cardiac outcomes while enhancing patient quality of life.

INTRODUCTION:

Transthyretin (TTR): Vitamin A-binding protein, or transthyretin (TTR), is a broadly dispersed protein found in a variety of tissue fluids, cells and plasma [1]. TTR is produced as the carrier protein and is mostly expressed in the liver and brain's choroid plexus. It secretes into the blood and cerebrospinal fluid and is involved in the movement of retinol, or vitamin A, and thyroxine (primarily T4) tovarious bodily tissues and cells [2]. Maintaining human growth and development requires thyroid function [3].

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TTR Amyloidosis: Let us first define amyloidosis. A rare condition known as amyloidosis develops when an aberrant protein known as amyloid accumulates in the organs and impairs their ability to function normally. What is TTR amyloidosis, then? In short, TTR amyloid fibrils deposited in different organs cause TTR amyloidosis [4].

An Overview of Polyneuropathy: The autosomal dominant neurodegenerative disease called FAP (familial amyloid polyneuropathy) [5], commonly referred to as transthyretin-related hereditary amyloidosis or Corino de Andrade's disease [6]. Portuguese neurologist MárioCorino da Costa Andrade was the first to identify and describe it as

a form of amyloidosis in 1952 [7]. It is due to mutations in the transthyretin gene on 18th chromosome, the most prevalent of which is TTR V30M, in which valine is replaced at position 30 by methionine. Transthyretin, a tetrameric protein, misfolds as a result of this mutation, breaking down into monomers to generate amyloid fibrils that harm organs and peripheral nerves. The non-inherited senile systemic amyloidosis (SSA), which mainly affects the elderly, is not the same as FAP. Heterozygous people, who normally deposit both mutant and wild-type TTR subunits, are affected by the autosomal dominant inheritance pattern, which indicates that only one copy of the faulty TTR gene is required for the condition to develop. This genetic foundation emphasises how family the illness is [8, 9].

Pathophysiology: The TTR gene has more than 100 mutations, mostly single amino acid alterations [10], since Andrade first described transthyretin (TTR) amyloidosis in 1952. By replacing valine with the most prevalent mutation, methionine at position 30 [11], p.Val30Met, breaks the tetrameric structure of TTR and causes amyloidogenic monomers to develop, which misfold and build up in different organs [12, 13]. Heterozygosity, or the presence of both normal and mutant TTR proteins, is commonly observed in hereditary ATTR amyloidosis [14, 15]. The type of mutation and age of start influence the clinical appearance [16]. Foot numbness and discomfort are the first symptoms of increasing sensory and autonomic neuropathy in patients with ATTR-FAP, which frequently results in death 11 years after onset [17-20]. People with ATTR-FAC have peripheral neuropathy and heart problems such arrhythmias and heart failure [21, 22]. Seldom, OLMA patients may exhibit ataxia, convulsions, and eye issues [23, 24] **Fig. 1.**

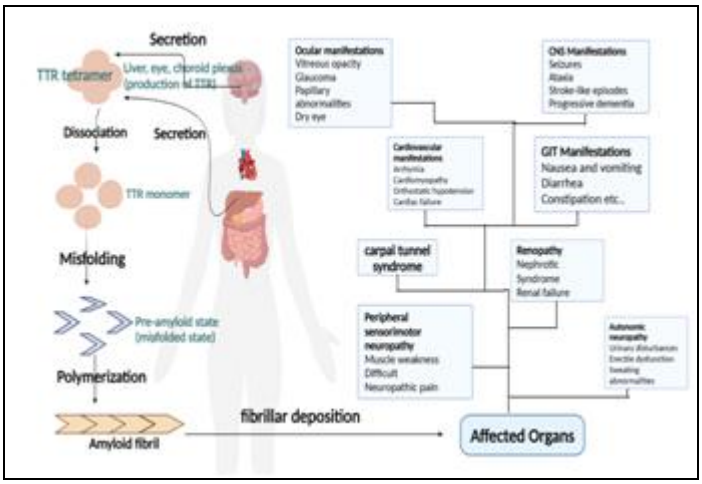

FIG. 1: PATHOPHYSIOLOGY OF ATTR POLYNEUROPATHY. Pathophysiology and the clinical manifestations of ATTR amyloidosis. The tetrameric proteins known as wild-type and mutant transthyretin are produced and discharged into the cerebrospinal fluid (CSF) or blood. When the TTR gene is altered, the TTR protein, which is tetrameric splits into aggregate-prone monomers. Amyloid fibrils are created when these monomers misfold and group together, and they build up in the peripheral nerves, the heart, and other organs. The main factor influencing clinical symptoms is the location of TTR amyloid accumulation.

Background of Crdiomyopathy: Cardiomyopathy is a illness affecting the cardiac muscle, or myocardium. Cardiomyopathy can cause your heart to thicken, harden, or enlarge, which can leave scar tissue behind. This makes it difficult for your heart to circulate blood throughout your body. Over time, your heart may weaken, and cardiomyopathy may cause cardiac failure. Therapy may be beneficial. A cardiac transplant may eventually be necessary for certain cardiomyopathy patients [25]. Parental genes are one of the causes of cardiomyopathy. Thousands of genetic mutations that cause cardiomyopathies have been discovered by researchers. Other autoimmune illnesses that damage the cardiac muscle, coronary artery disease, thyroid disease, heart inflammation, muscular dystrophy, high cholesterol disorders, sarcoidosis, amyloidosis, and hemochromatosis are among the other causes of cardiomyopathy [25].

Pathophysiology: Insoluble fibres are created when TTR protein is misfolded. These fibres build

up in the interstitial spaces of the myocardium, causing cardiac stiffness and fibrosis, which hinders mechanical function [26]. TTR deposition causes thicker myocardium on cardiac imaging, which raises the risk of atrial arrhythmias by causing diastolic dysfunction and elevated left atrial pressures. Frequently, myocardial infiltration also impacts the electrical conduction system [27]. Although documented in ATTR-CM, ventricular arrhythmias are far less prevalent than AL (amyloid light chain) cardiomyopathy [28, 29]. The peripheral and autonomic nerve systems usually exhibit eposition of misfolded TTR protein; hereditary ATTR (hATTR) more commonly affects neurological systems, whereas wild-type ATTR (wATTR) mostly results in cardiomyopathy [30, 31] **Fig. 2.**

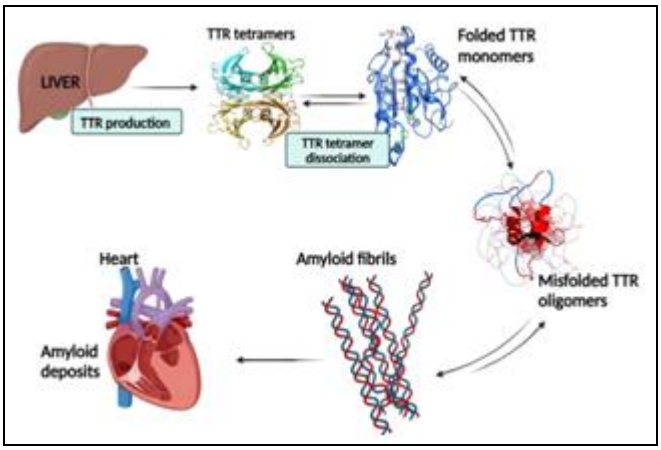

FIG. 2: PATHOPHYSIOLOGY OF ATTR CARDIOMYOPATHY. The liver produces a mutant version of the transthyretin (TTR) protein in hereditary transthyretin-related amyloidosis (ATTR). The TTR tetramer becomes destabilized and undergoes proteolytic remodeling as a result of these alterations, which raises the synthesis of misfolded, amyloidogenic proteins. This comprises full-length monomers and C-terminal fragments, both of them rapidly combine to form amyloid fibrils. Both patients with wild-type (WT) ATTR amyloidosis and those with different TTR mutations have the aggregation-prone C-terminal fragment, which results from the enzymatic degradation of the transthyretin protein. Nonfibrillar substances like sulfonated glycosaminoglycans, serum amyloid P component, and calcium are also present in extracellular amyloid deposits.

Eplontersen an Antisense Oligonucleotide (ASO): Similar in design to inotersen, eplontersen is a second-generation ASO conjugated to a triantennary GalNAc moiety that promotes receptor-mediated absorption into target hepatocytes [32, 33]. Eplontersen is a transthyretin-directed antisense oligonucleotide (ASO) that may be delivered to hepatocytes by covalently attaching it to a ligand that contains three N-acetyl galactosamine (GalNAc) residues [34].

The Eplontersen pharmacological class comprises ligand-conjugated antisense oligonucleotides, or LICAs. Because of its better delivery mechanism, eplontersen can reduce TTR expression up to 50 times more potently than inotersen. This means that it can be delivered every four weeks as opposed to inotersen's weekly subcutaneous injection [35].

Hereditary transthyretin-mediated amyloidosis polyneuropathy (hATTR-PN or ATTRv-PN) is an uncommon, progressive condition that can be fatal if neglected. Eplontersen is used to treat this condition. Additionally, eplontersen is being researched as a potential treatment for ATTR cardiomyopathy (ATTR-CM) [34]. Eplontersen slows the progression of the disease, reduces neuropathy, and enhances the patient's quality of life by reducing the quantity of TTR protein that is produced. Wainua is the brand name of Eplontersen.

DISSCUSSION:

Eplontersen: Mechanism of Action in Treating Polyneuropathy: Eplontersen belongs to the class of antisense oligonucleotides (ASOs), which are short, artificial strands of nucleic acid that are made especially to attach to messenger RNA (mRNA) molecules. An ASO's main job is to suppress a target gene's expression by attaching to the mRNA's complementary sequence and preventing the translation of that mRNA into a protein. When it comes to eplontersen, the target mRNA is transthyretin (TTR), a protein that is mostly made in the liver and is essential for the movement of

retinol and thyroid hormones. On the other hand, toxic amyloid deposits, which mostly impact neural tissues, can result from TTR mutations or misfolding [36, 37].

Eplontersen functions by attaching itself to TTR mRNA and encouraging RNase H-mediated degradation, which breaks down the mRNA. When RNA is hybridized to a DNA strand, the enzyme RNase H breaks down the RNA. Because of this binding, there is less TTR mRNA accessible for translation, which in turn results in less TTR protein being produced. As a result, the bloodstream's TTR content is reduced, which is crucial because elevated TTR is a prerequisite for the development of amyloid fibrils [38].

Amyloid fibrils, which can accumulate in a variety of tissues and particularly impact the peripheral nervous system, causing neuropathy and other severe consequences, can arise from the misfolding and aggregation of TTR[39]. These amyloid buildups interfere with the way tissues normally operate and can cause inflammation, which aggravates nerve injury. Epoentersen works by reducing TTR production, which lessens the formation of these harmful aggregates. This helps shield nerve cells from harm and may even alleviate some polyneuropathy symptoms. The ultimate objective is to improve patients' quality of life and clinical outcomes by stopping or slowing the advancement of TTR amyloidosis-related conditions [40, 41] **Fig. 3**.

Gene Modification Therapy: For patients with ATTR amyloidosis, gene silencing-based therapies that induce TTR knockdown using siRNA and ASO technologies are therapeutically effective; nevertheless, these treatments need to be administered repeatedly in order to sustain a therapeutic impact [42]. One possible single-dose treatment for ATTR amyloidosis is gene-editing therapy [42]. NTLA-2001 has modified the TTR gene in hepatocytes by utilizing the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-Cas9 technology [42]. Small RNA that can direct the system to complementary DNA sequences is produced when CRISPR sequences are transcribed [43, 44]. The target gene is then deleted when the Cas9 endonuclease attaches to and cleaves the DNA [45]. Because only the liver can produce the circulating TTR protein, which is encoded by a single gene, ATTR amyloidosis serves as the standard disease model for targeted in vivo genome-editing therapy [46]. After NTLA-2001 was administered successfully in multiple animal models, a small cohort of patients with ATTR amyloidosis underwent testing of the drug, which consistently produced a durable TTR knockdown [47] **Fig. 3**.

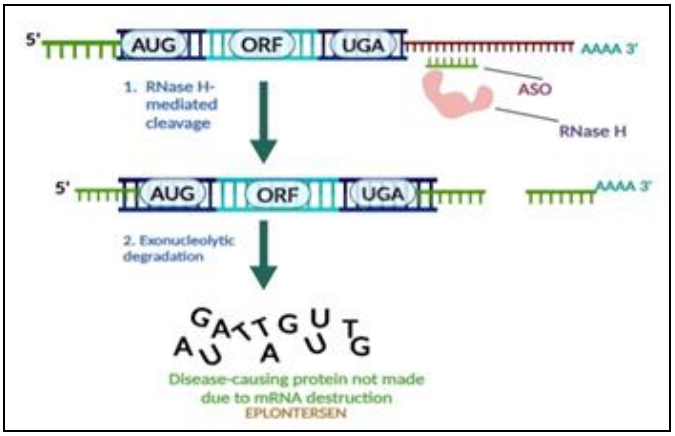

FIG. 3: EPLONSEN'S MODE OF ACTION IN ATTR POLYNEUROPATHY. The major modes of action (MOAS) of the FDA-approved ASOs that are now on the market include the binding of the ASO to its target sequence inside an mRNA, which attracts RNase H activity and causes the destruction of a disease-causing mRNA.

Eplontersen: Mechanism of Action in treating Cardiomyopathy: With Eplontersen, transthyretin amyloidosis (ATTR) treatment has advanced significantly. This is because ligand-conjugated antisense oligonucleotides have special features that improve therapy's efficacy and specificity. Epontersen's focused approach makes this novel design very successful; it binds exclusively to the messenger RNA (mRNA) that codes for the transthyretin (TTR) protein. Epontersen ensures

appropriate targeting of the mRNA within liver cells, the primary site of TTR synthesis, by facilitating efficient hybridization with a sequence that is complementary to a particular area of the TTR mRNA [36, 37]. Emplontersen enlists RNase H, an enzyme essential for breaking down RNA molecules that have hybridized to DNA, as soon as it binds to its target mRNA. This recruitment significantly reduces the amount of mRNA available for translation by starting the breakdown of TTR mRNA [38]. The liver's ability to synthesize TTR protein is consequently greatly diminished. This decrease is essential for lowering the total amount of TTR in the bloodstream because the liver is the main location where TTR is produced. Because too much TTR can misfold and collect into amyloid fibrils, which significantly endanger cardiovascular health, lowering TTR levels is very crucial. These deposits of amyloid fibrils in different organs might result in cardiomyopathy and heart failure. Epolantersen directly targets the root cause of amyloid-related illnesses by lowering the quantity of TTR accessible for misfolding, which lowers the substrate required for fibril production. This treatment approach improves overall cardiovascular health in addition to preventing the buildup of amyloid in cardiac tissues. Improved exercise tolerance and a decrease in cardiovascular problems can lead to improved quality of life for patients. People with less ATTR symptoms are able to participate more completely in their everyday activities, demonstrating the game-changing potential of eplontersen in the management of this difficult condition. In the end, eplontersen is a focused therapeutic strategy that targets the underlying causes of illness and gives patients with ATTR hope for better results [48] **Fig. 4**.

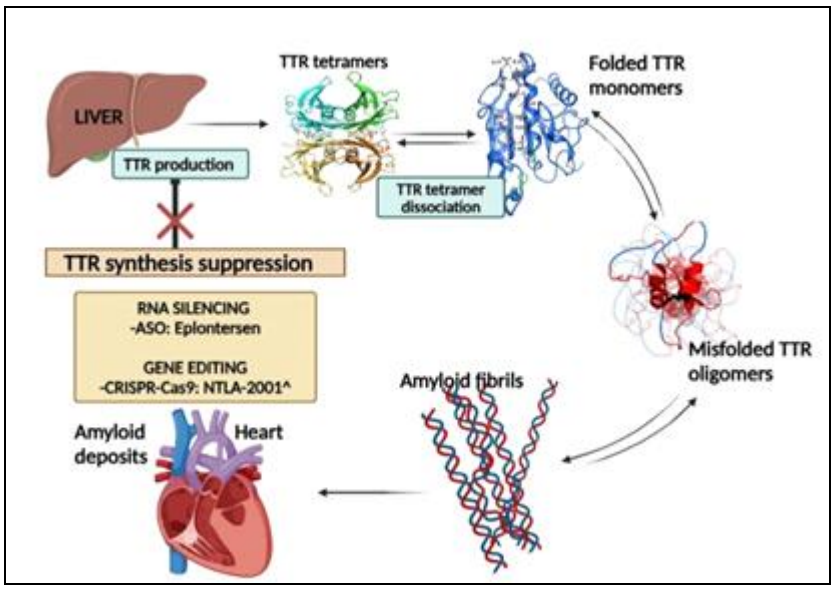

FIG. 4: EPLONTERSEN'S MODE OF ACTION IN ATTR CARDIOMYOPATHY. The development of new pharmacotherapies and therapeutic targets for the treatment of ATTR-CM is guided by the pathophysiology of ATTR amyloidosis. The liver primarily synthesises transthyretin as a homotetramer (PDB 3P3T crystal structure), It splits into various folded monomers, which then self-assemble to form amyloid fibrils.Transthyretin amyloid fibrils of the wild type primarily accumulate in the heart, leading to organ failure. TTR tetramer stabilisers, RNA-targeted gene silencing, gene editing and substances that block amyloid seeds or promote amyloid clearance are some of the current and developing treatment strategies for ATTR-CM.

Clinical Research Advancements: Muhammad Saeed Qazi *et al.* led the NEURO-TTRANSform trial, which looked at Eplontersen's effectiveness in treating ATTRv amyloidosis with polyneuropathy. Important findings showed that serum transthyretin (TTR) levels were significantly lowered with Eplontersen, with a -81.7% adjusted mean percentage decrease in comparison to the placebo. Furthermore, there were notable improvements in neuropathy impairment among patients receiving Eplontersen, as evidenced by a decreased mean change from baseline in the mNIS + 7 composite score (−24.8, 95% CI −31.0 to −18.6, $P < 0.001$). A more favorable improvement in the Norfolk QoL-DN score (−19.7, 95% CI −25.6 to −13.8, $P < 0.001$) suggests that quality of life also improved.

These findings demonstrate the possibility of eplontersen as a successful ATTRv amyloidosis treatment, providing notable therapeutic advantages and improving patients' general quality of life. When transthyretin amyloidosis is inherited, Eplontersen and Inotersen, two antisense oligonucleotides (ASOs), work by breaking down TTR mRNA to lessen the generation of TTR protein. Despite having comparable sequences, their designs and methods of distribution are different. While epflontersen is combined with GalNAc3 (triantennary N-acetyl galactosamine), inotersen mainly targets endothelial or Kupffer cells, which enhances its absorption by hepatocytes through ASGPR-mediated pathways. Eplontersen appears to have increased potency based on preclinical tests, which reveal reductions in EC50 and ED50 of about 50 and 28 fold, respectively [49].

Eplontersen differs from other polyneuropathy medications that aim to stabilize TTR tetramers or prevent TTR synthesis, like diflunisal, tafamidisand patisiran [50]. Eplontersen's innovative treatment method of directly targeting TTR mRNA within hepatocytes is expected to result in more substantial decreases in the TTR levels in serum and better clinical results.Larger, longer-term trials are required to validate Eplontersen's potential as a revolutionary treatment, even if ongoing research into the drug for hereditary ATTR polyneuropathy (hATTR-PN) shows promise. These investigations will offer more thorough understandings of Eplontersen's effectiveness and safety, as well as any possible negative effects and long-term advantages. Moreover, expanding Eplontersen's patient access is essential to guaranteeing fair care and optimizing its effects on hATTR-PN patients worldwide. 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 showed that body weight had an impact on intercompartmental clearance and distribution volumes, whereas lean body mass had a substantial influence on drug clearance. According to population PK modeling, injecting the injection into the abdomen as opposed to the arm resulted in 29.6% greater absorption rates. It was discovered that the population's average terminal elimination half-life was 25.5 days. The association between serum TTR (transthyretin) levels and Eplontersen was well-explained by an indirect response model, which demonstrated that the medication reduced TTR synthesis. The inhibitory half-maximum concentration (IC50) was determined to be 0.0283 ng/ml (13.3% RSE), whereas the Imax (maximum fractional inhibition) was computed to be 0.970 (0.549% RSE). According to the simulation results, people who were lighter had higher exposure levels (AUC and Cmax), and when injection sites were compared (abdomen vs. arm, with a ratio of 1.18), a larger Cmax was seen. The drug's response at the tested doses was not substantially impacted by these 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.while a historical placebo (n = 60) had a change of 25.The adjusted mean difference from baseline resulted in a between-group difference of −24.8 ($p < 0.001$) (95% CI -31.0 to -18.6), indicating that it should be considered a co-primary endpoint **[53]**. At week 66, Eplontersen caused an adjusted mean change in the Norfolk QoL-DN (Norfolk Quality of Life Questionnaire for diabetic neuropathy) total score of −5.5, while the historical placebo caused a change of 14.2 (BGD −19.7, 95% CI −25.6 to −13.8; $p < 0.001$).

The U.S. approval of Eplontersen was supported by 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 −13.5 to −4.5; $p < 0.001$) [54, 55]. The Norfolk QoL-DN scores, on the other hand, were -3.1 and 8.7, respectively (BGD -11.8, 95% CI -16.8 to -5.7; $p < 0.001$). The global, open-label NEURO-TTRansform investigation comprised Patients older than 18 with Coutinho stage 1 or 2 ATTRv-PN, a neuropathic impairment score ranging from 10 to 130, and studied TTR gene variants. Patients were randomised in a 6:1

ratio to receive Inotersen or Eplontersen (reference group; n = 24) based on historical placebo data from the NEURO-TTR study, which had similar eligibility criteria and outcomes [56, 57]. Eplontersen recipients got 45 mg subcutaneously till week 81, every four weeks, In contrast, the individuals in the reference group of Inotersen received 300 mg of inotersen weekly until 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 administered subcutaneously every four weeks to patients receiving standard care medicine, which might include tafamidis, as part of a global, randomised, double-blind, placebo-controlled study known as the phase III trial of CARDIO-TTRansform [58]. 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 investigation, 49 (34%) developed cardiomyopathy, according to Ahmad Masri *et al.* After these patients received Eplontersen, the effectiveness of the treatment was evaluated at week 65 in comparison to a previous placebo group of 60 volunteers (30 patients, or 50% with cardiomyopathy). The therapeutic effects of Eplontersen vs placebo were compared by computing the mean differences (with 95% CIs) and adjusting for factors like sex, baseline values, age, region, ATTRv (Hereditary Transthyretin Amyloidosis) disease stage, previous hereditary transthyretin amyloidosis, treatments, and the V30M transthyretin variant. At baseline, there were notable differences between the group of historical placebo and the Eplontersen group. The cardiomyopathy subgroup showed improvements in its Stroke volume (95% CI 3.99–17.29; P =.002) and fraction of left ventricular ejection (95% CI 1.40–21.01; P =.049) following Eplontersen treatment of 65 weeks is when compared to a placebo [60]. Every other echocardiographic metric remained constant.

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 comparison, 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 decrease in serum transthyretin at week 65 was −70.4% (P < 0.001; 95% CI, -75.2% to -65.7%) for the Eplontersen group and −11.2% for the placebo group.

From the baseline to the week 66, Adjusted mean change was significantly lower (indicating better outcomes) for the Eplontersen group compared to the placebo group in both the Norfolk QoL-DN score, The difference in mNIS+7 composite score was −19.7, 95% CI: −25.6 to −13.8 (−5.5 vs. 14.2; P <.001) and −24.8, 95% CI, −31.0 to −18.6; P <.001.In the Eplontersen group, six patients (4%) had adverse events that led to the trial medication being stopped, compared to placebo group, 2 patients (3%). There were no death recorded among the group that received a placebo during the trial, but two deaths was recorded among the group that received the Eplontersen, which were linked to known consequences of the condition (intracerebral haemorrhage and cardiac arrhythmia) [61].

A study lead by Conceição *et al.* was carried out as part of the NEURO-TTRansform trial, which included ATTRv-PN patients. For the first 34 weeks, a subgroup of these patients was randomly assigned to receive 300 mg of inotersen subcutaneously every week. From weeks 37 to 81, next, they began using subcutaneous eplontersen, 45 milligrams every four weeks. The impact on quality of life, neuropathy impairment, and dietary condition were assessed until week 85 of the research, together with changes in blood TTR levels and TEAEs (treatment-emergent adverse events). Twenty (83%) of the 24 patients. At week 37, those who had been assigned to inotersen at random switched to eplontersen, while four individuals stopped because of adverse events or

decisions made by the investigators. Following the transition to eplontersen (-80.6% at week 85) from inotersen (-74.3% at week 35), there was a greater absolute decrease in serum TTR. There was no reduction in dietary status during the eplontersen treatment, and the neuropathy impairment quality of life and remained steady (showing no progression). Furthermore, with eplontersen (19 out of 20 patients, or 95%) TEAEs were less common than with inotersen (all 24 patients, or 100% up to week 35). With a mean nadir reduction of −40.7% during inotersen treatment, mean platelet counts declined; however, with a mean nadir reduction of −3.2%) during eplontersen treatment, they restored to baseline levels [62].

In the NEURO-TTRANSform experiment, individuals with hereditary ATTR cardiomyopathy (hATTR-CM) who were administered Eplontersen at a dose of 45 mg every four weeks were the subject of a retrospective analysis carried out by Yu AL *et al.* Patients with hereditary transthyretin amyloid cardiomyopathy (hATTR-CM)who hadn't gotten treatment of partisan, tafamidis, inotersen, or eplontersen made comprised the control group. 99mTc-PYP SPECT/CT (Technetium-99m-pyrophosphate single-photon emission computed tomography) scans were performed at baseline and during follow-up. Thirteen hATTR-CM individuals took part, six of whom received Eplontersen and seven of whom were in the control group. 544 days was the median follow-up time. The volumetric heart and lung ratio decreased significantly in the Eplontersen group (P = 0.028 between 3.774 and 2.979), but not significantly in the control group (from 4.079 to 3.915, P = 0.237). 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].

CONCLUSION: The NEURO-TTRANSform trial led by Muhammad Saeed Qazi *et al.* provides compelling evidence for the efficacy of Eplontersenin treating hereditary transthyretin amyloidosis with polyneuropathy. The trial demonstrated a significant decreases in serum the TTR levels, with the adjusted mean decrease of -81.7% when compared with placebo, and marked improvements in both neuropathy impairment and QoL (quality of life) as measured by the mNIS + 7 and Norfolk QoL-DN scores, respectively. This suggests that Eplontersen not only lowers TTR levels effectively but also enhances patient wellbeing. The innovative mechanism of action, targeting TTR mRNA, differentiating the Eplontersen from other treatments that focus on stabilizing transthyretin (TTR) or inhibiting its synthesis. Pharmacokinetic studies have revealed that body weight and lean body mass significantly influence the drug's clearance and distribution, with abdominal injections yielding better absorption rates. The safety profile of Eplontersen remains favorable, with low rates of treatment discontinuation due to adverse events. Furthermore, the treatment has shown potential benefits for patients with hereditary ATTR cardiomyopathy, enhancing cardiac function metrics in those receiving Eplontersen compared to historical controls. These findings underscore the need for larger, longer-term studies to fully ascertain the long-term safety and efficacy of Eplontersen, as well as its potential role in the broader treatment landscape for ATTRv-PN and ATTR cardiomyopathy. Continued research and expanded access to Eplontersen could pave the way for improved outcomes in patients affected by this challenging condition, reinforcing a positive outlook for future therapeutic strategies in managing hereditary transthyretin amyloidosis.

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