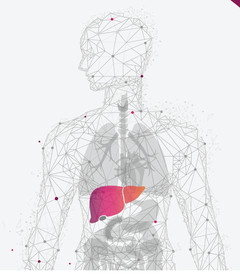


Eplontersen in hereditary ATTR-polyneuropathy: Week 66 final analysis of the phase 3 NEURO-TTRansform study

Sami Khella, Wilson Marques Jr, Noel R. Dasgupta, Chi-Chao Chao, Yeşim Parman, Marcondes Cavalcante França Jr, Yuh-Cherng Guo, Jonas Wixner, Long-Sun Ro, Cristian R. Calandra, Pedro Kowacs, John L. Berk, Laura Obici, Fabio A. Barroso, Markus Weiler, Isabel Conceição, Shiangtung W. Jung, Gustavo Buchele, Michela Brambatti, Steven G. Hughes, Eugene Schneider, Nicholas J. Viney, Ahmad Masri, Morie R. Gertz, Yukio Ando, Julian D. Gillmore, P. James B. Dyck, Márcia Waddington Cruz, Teresa Coelho

neuro TTRansform

Poster #008

Introduction

- Hereditary transthyretin (ATTRv) amyloidosis is a rare, severe, progressive, debilitating, and ultimately fatal disease caused by systemic accumulation of transthyretin (TTR) amyloid fibrils in multiple organ systems[1]
- Eplontersen is an investigational ligand-conjugated antisense (LICA) oligonucleotide designed to degrade hepatic *TTR* mRNA and inhibit TTR protein synthesis[2]
  - Eplontersen is conjugated to a triantennary *N*-acetyl galactosamine ligand to specifically target receptor-mediated hepatocyte uptake
- NEURO-TTRansform (NCT04136184, EudraCT 2019-001698-10) is a global, open-label, phase 3 study designed to evaluate the efficacy and safety of eplontersen in adults with ATTRv amyloidosis with polyneuropathy (ATTRv-PN)

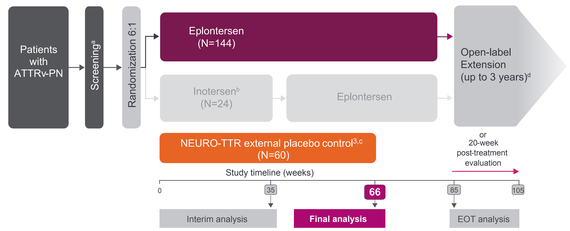
Objective

- To evaluate the effects of eplontersen at the final analysis in patients with ATTRv-PN enrolled in the NEURO-TTRansform study

Methods

- Key inclusion criteria:
  - Adult patients 18–82 years
  - ATTRv-PN defined by:
    - Coutinho Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance)
    - Documented genetic mutation in the *TTR* gene
    - Signs/symptoms consistent with polyneuropathy (Neuropathy Impairment Score ≥ 10 and ≤ 130)
- The primary analysis compared eplontersen with an external placebo control from NEURO-TTR[3] (**Figure 1**)
- The external placebo control from NEURO-TTR[3] was appropriate because of similar eligibility criteria and endpoints

Figure 1. NEURO-TTRansform Study Design



ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; EOT, end of treatment; SC, subcutaneous.
[a]The screening period is ≤ 6 weeks (or ≤ 10 weeks if genetic testing is required). [b]The inotersen reference group was intended to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTR[3] (NCT01737398) and NEURO-TTRansform. [c]Placebo arm of the NEURO-TTR study[3]. [d]Patients not participating in the open-label extension will enter a 20-week post-treatment evaluation after completing EOT assessments.
Figure adapted from Coelho et al, *Neurol Ther*, 10:375-89, 2021.[2]

- All endpoints were compared with the external placebo arm of the earlier NEURO-TTR[3] trial using propensity score weights to adjust for differences between groups
- Data from up to 66 weeks of treatment were analyzed for eplontersen and external placebo
- The inotersen reference group was intended to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTR[3] (NCT01737398) and NEURO-TTRansform

Prespecified co-primary and secondary endpoints

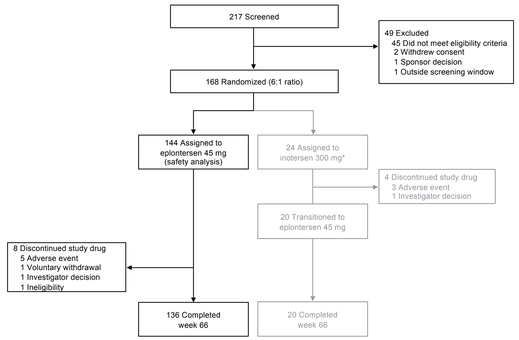
- Co-primary endpoints
  - Percent change from baseline in serum TTR concentration
  - Change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) composite score
  - Change from baseline in Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN) total score
- Secondary endpoints
  - Change from baseline in Neuropathy Symptom and Change (NSC) total score, 36-item Short Form Survey Physical Component Summary (SF-36 PCS) score, Polyneuropathy Disability (PND) score, and modified body mass index (mBMI; BMI [kg/m^2] × serum albumin [g/L])
- Final analysis endpoints were performed at Week 65 or Week 66 to reduce patient burden in data collection

Results

Patient Disposition

- NEURO-TTRansform enrolled 168 patients across 15 countries, with 144 patients in the eplontersen arm and 24 in the inotersen arm
- Study retention through Week 66 was high (**Figure 2**)

Figure 2. NEURO-TTRansform Patient Disposition



*The inotersen reference group was intended to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTRansform and NEURO-TTR,[3] the source of the external placebo control.

Baseline Demographics and Clinical Characteristics

- Baseline demographics and clinical characteristics were generally well balanced between the eplontersen and placebo groups (**Table 1**)
  - Patients in the eplontersen group were slightly younger, had less severe disease, were more likely to have received previous treatment with stabilizers, and were more likely to have the V30M variant than those in the placebo group

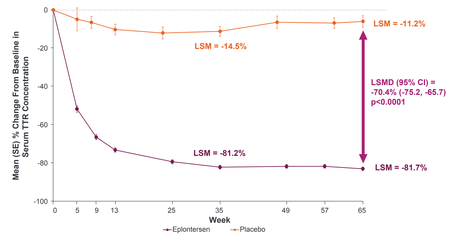
Table 1. Baseline Characteristics

Baseline Characteristics	Placebo	Eplontersen
N	60	144
Age, mean years (SD)	59.5 (14.0)	53.0 (15.0)
Male, n (%)	41 (68.3)	100 (69.4)
Race,[a] n (%)		
White	53 (88.3)	112 (78.3)
Asian	3 (5.0)	22 (15.4)
Black or African American	1 (1.7)	5 (3.5)
Other/Multiple	3 (5.0)	4 (2.8)
Region, n (%)		
Europe	23 (38.3)	54 (37.5)
North America	26 (43.3)	21 (14.6)
So. America/Australasia	11 (18.3)	69 (47.9)
Previous treatment, n (%)		
Tafamidis or Diflunisal	36 (60.0)	100 (69.4)
Disease stage, n (%)		
Stage 1 – mild	42 (70.0)	115 (79.9)
Stage 2 – moderate (use aids)	18 (30.0)	29 (20.1)
PND score,[a] n (%)		
I (sensory, but can walk)	23 (38.3)	56 (39.2)
II (difficulty walking, no aids)	19 (31.7)	61 (42.7)
IIIA (1 walk stick or crutch)	15 (25.0)	16 (11.2)
IIIB (2 walk sticks or crutches)	3 (5.0)	10 (7.0)
***TTR* variant**, n (%)		
V30M	33 (55.0)	85 (59.0)
Non-V30M	27 (45.0)	59 (41.0)
mNIS+7 composite score, mean (SD)	74.8 (39.0)	81.3 (43.4)
Norfolk QoL-DN total score, mean (SD)	48.7 (26.7)	44.1 (26.6)

mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life – Diabetic Neuropathy; PND, Polyneuropathy Disability; *SD*, standard deviation.
mNIS+7 maximum 346 points; Norfolk QoL-DN maximum 136 points.
[a]Data missing for one subject in eplontersen group.

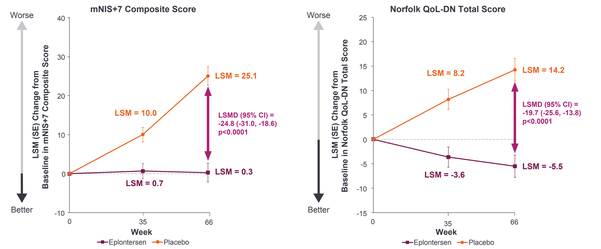
Co-Primary Endpoints

Figure 3. Significant and Sustained Reduction in Serum TTR Concentration From Baseline With Eplontersen Compared With Placebo at Week 65



CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference; SE, standard error; TTR, transthyretin.
The statistical analysis of percent change from baseline is based on a mixed effects model with repeated measures adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.

Figure 4. Eplontersen Halted Progression of Neuropathy Impairment and Significantly Improved Quality of Life Compared With Placebo at Week 66



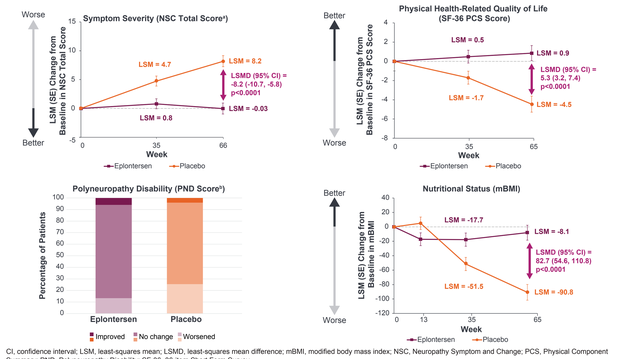
CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life – Diabetic Neuropathy.
mNIS+7 composite scores can range from −22.3 to 346.3, with higher scores indicating poorer function; a decrease in score indicates improvement.
Norfolk QoL-DN total scores can range from −4 to 136, with higher scores indicative of poorer quality of life; a decrease in score indicates improvement.
The statistical analysis of change from baseline is based on a mixed effects model with repeated measures adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.

- Overall, 47.2% and 57.6% of patients treated with eplontersen improved from baseline in mNIS+7 and Norfolk QoL-DN at Week 66; in the placebo group, 16.7% and 20.0% improved
- Among study completers, 53.1% and 64.8% of patients treated with eplontersen improved from baseline in mNIS+7 and Norfolk QoL-DN at Week 66; in the placebo group, 19.2% and 23.1% improved
- Eplontersen treatment effect was consistent across prespecified subgroups as well as for mNIS+7 components and Norfolk QoL-DN domains at Week 66

Secondary Endpoints

- Eplontersen treatment resulted in a statistically significant change from baseline in all secondary endpoints compared with placebo at Week 66 (**Figure 5**)
  - Eplontersen halted progression of symptom severity and improved physical symptoms and nutritional status compared with placebo
  - Polyneuropathy disability improved or remained stable with eplontersen to a greater extent compared with placebo

Figure 5. Consistent Improvement Across All Secondary Endpoints Compared With Placebo at Week 66



CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference; mBMI, modified body mass index; NSC, Neuropathy Symptom and Change; PCS, Physical Component Summary; PND, Polyneuropathy Disability; SF-36, 36-item Short Form Survey.
[a]Change from baseline in NSC total score at Week 35 was also assessed in the final analysis but was not reported due to space.
[b]The analysis of change from baseline in PND score vs placebo at Week 65 was statistically significant (p<0.05).
NSC total scores range from 0 to 114 (men) or 108 (women), with higher scores indicative of worse symptoms.[4] SF-36 PCS scores range from 0 to 100, with higher scores indicative of better physical health.[5] PND categorizes disability according to patient mobility on a scale of I to IV; higher scores are indicative of worse disability.[6] mBMI, calculated as BMI (kg/m^2) × serum albumin (g/L), assesses nutritional status, with higher scores indicative of better nutritional status.[7]

Safety

- Eplontersen and placebo had comparable incidences of TEAEs, including those related to study drug and leading to treatment discontinuation (**Table 2**)
- No TEAEs of special interest led to study drug discontinuation
- No SAEs were related to study drug
- 2 deaths occurred in the eplontersen group prior to the interim analysis, both related to known sequelae of ATTR amyloidosis[7-11] and neither assessed as drug-related

Table 2. Eplontersen Safety Profile

Incidence, n (%)	Placebo	Eplontersen
N	60	144
Any TEAE	60 (100)	140 (97.2)
Related to study drug	23 (38.3)	53 (36.8)
Leading to study drug discontinuation	2 (3.3)	5 (3.5)
TEAE of special interest	12 (20.0)	41 (28.5)
Ocular events potentially related to Vit A deficiency[a]	9 (15.0)	39 (27.1)
Thrombocytopenia[b]	1 (1.7)	3 (2.1)
Glomerulonephritis[c]	2 (3.3)	0
Other TEAE of interest[d]	47 (78.3)	87 (60.4)
Any serious TEAE	12 (20.0)	21 (14.6)
Related to study drug	1 (1.7)	0
Fatal TEAE[e]	0	2 (1.4)
Related to study drug	0	0

HLT, high level term; NEC, not elsewhere classified, PT, preferred terms; SAE, serious adverse event; SMQ, standardized MedDRA query; SOC, System Organ Class; TEAE, treatment-emergent adverse event (an adverse event that first occurred or worsened after the first dose of investigational product).
[a]HLT of Fat soluble vitamin deficiencies and disorders; PT of Vitamin A decreased, Vitamin A abnormal; SMQ of Optic nerve disorders, Corneal disorders, Retinal disorders. Vitamin A levels were blinded in the external placebo group but not in the eplontersen group.
[b]PT of Thrombocytopenia, Platelet count decreased. All events were mild, grade 1, and not associated with bleeding adverse events, did not lead to study drug discontinuation, and resolved without sequelae.
[c]PT of Nephritis, Glomerulonephritis, Glomerulonephritis proliferative, Glomerulonephritis acute, Glomerulonephritis rapidly progressive, C3 Glomerulonephritis, Chronic autoimmune glomerulonephritis, Glomerulonephritis chronic, Fibrillary glomerulonephritis, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Henoch-Schonlein purpura nephritis, Immune mediated nephritis, Immunotactoid glomerulonephritis, Lupus nephritis, Nephritis allergic. Nephrotic syndrome. In the placebo group, there were two cases of potential glomerulonephritis identified (1 glomerulonephritis chronic; 1 nephrotic syndrome).
[d]Other TEAEs of interest include coagulation abnormalities (HLT: Coagulopathies), renal impairment (SMQ: Acute renal failure), abnormal liver function (SMQ: Drug-related hepatic disorders-comprehensive search), adverse events at the injection site (HLT: Injection site reaction; or HLT: Administration site reaction NEC), flu-like symptoms (PT: Influenza like illness; or PT: Pyrexia [or Feeling hot or Body temperature increased] plus at least one of the following symptoms: Chills, Myalgia, Arthralgia, Malaise, Fatigue, Headache, Nausea), central nervous system disorders (SOC: Nervous system disorders), hemorrhages (SMQ: Haemorrhages), cardiac disorders (SOC: Cardiac disorders; or PT under "Investigations" SOC: Cardiac troponin I increased, Cardiac troponin T increased, Ejection fraction decreased, Electrocardiogram QT corrected interval prolonged), reduced thyroxine (SMQ: Hypothyroidism).
[e]One patient with intracerebral hemorrhage in setting of normal platelet counts; one patient with arrhythmia in setting of known transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

Conclusions

- In patients with ATTRv-PN, eplontersen treatment resulted in clinically and statistically significant benefits through Week 66 compared with placebo
  - Sustained reduction in serum TTR concentration
  - Halted progression of neuropathy impairment
  - Improved patient quality of life
- These findings are further supported by statistically significant improvements in all secondary endpoints at Week 66 compared with placebo
- Eplontersen was well tolerated and demonstrated an acceptable safety profile
- Long-term safety and tolerability data are being assessed in the open-label extension study

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Study Drug
Eplontersen is an investigational drug and has not been approved by the FDA, EMA, or any other regulatory agency.

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Supplementary Material

neuro TTRansform

Poster #008

Authors

Sami Khella[1], Wilson Marques Jr[2], Noel R. Dasgupta[3], Chi-Chao Chao[4], Yeşim Parman[5], Marcondes Cavalcante França Jr[6], Yuh-Cherng Guo[7], Jonas Wixner[8], Long-Sun Ro[9], Cristian R. Calandra[10], Pedro Kowacs[11], John L. Berk[12], Laura Obici[13], Fabio A. Barroso[14], Markus Weiler[15], Isabel Conceição[16], Shiangtung W. Jung[17], Gustavo Buchele[17], Michela Brambatti[17], Steven G. Hughes[17], Eugene Schneider[17], Nicholas J. Viney[17], Ahmad Masri[18], Morie R. Gertz[19], Yukio Ando[20], Julian D. Gillmore[21], P. James B. Dyck[19], Márcia Waddington Cruz[22], Teresa Coelho[23]

Affiliations

[1]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [2]Universidade de São Paulo, Ribeirão Preto, Brazil; [3]Indiana University School of Medicine, Indianapolis, Indiana; [4]National Taiwan University Hospital, Taipei, Taiwan; [5]Istanbul Üniversitesi - Istanbul Tıp Fakültesi, Istanbul, Turkey; [6]Universidade Estadual de Campinas, Campinas, SP, Brazil; [7]China Medical University Hospital, Taichung, Taiwan; [8]Umeå University, Umeå, Sweden; [9]Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan; [10]Hospital El Cruce, Buenos Aires, Argentina; [11]Instituto de Neurologia de Curitiba, Curitiba, PR, Brazil; [12]Boston University School of Medicine, Boston, Massachusetts; [13]Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [14]Neurology Department, Fleni, Buenos Aires, Argentina; [15]Amyloidosis Center and Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany; [16]Centro Hospitalar Universitário Lisboa-Norte, Hospital de Santa Maria, Lisbon, Portugal; [17]Ionis Pharmaceuticals, Inc., Carlsbad, California; [18]OHSU Center for Hypertrophic Cardiomyopathy and Amyloidosis, Portland, Oregon; [19]Mayo Clinic, Rochester, Minnesota; [20]Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [21]National Amyloidosis Centre, University College London, London, United Kingdom; [22]Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [23]Centro Hospitalar Universitário do Porto, Porto, Portugal

Disclosures

SK: is a consultant to Alnylam, Ionis, SOBI, Pfizer, and Eidos. **WM:** reports no conflicts of interest. **NRD:** has consulted for Alnylam, Eidos, and Intellia and has lectured for Alnylam. **C-CC:** reports no conflicts of interest. **YP:** has lectured for Alnylam and Pfizer. **MCF:** has lectured and taken part in advisory boards to Pfizer, PTC, and Alnylam. **Y-CG:** reports no conflicts of interest. **JW:** has served as member of advisory boards for Pfizer, Alnylam, Intellia, and AstraZeneca, and lecturer for Pfizer and Alnylam. **L-SR:** reports no conflicts of interest. **CRC:** reports no conflicts of interest. **PK:** is currently participating in the ION trial. **JLB:** has participated in an Ionis ad hoc advisory committee. **LO:** has received speaker honoraria from Pfizer, SOBI, and Alnylam. **FAB:** has received honoraria from Ionis for conducting clinical trials. **MW:** has received advisory board and speaker honoraria and financial support for conference attendance from Akcea, Alnylam, Pfizer, and SOBI. **IC:** has received financial support as primary investigator and consultant from Pfizer Inc., Alnylam Pharmaceuticals, and Ionis. **SWJ, ES,** and **NJV:** are employed by Ionis. **GB** and **MB:** were employed by Ionis at the time of this study. **SGH:** is a consultant to Ionis. **AM:** has received research Grants from Pfizer, Ionis, Attralus, Cytokinetics, Ultromics, and the Wheeler Foundation, and personal fees from Cytokinetics, BMS, Eidos, Pfizer, Ionis, Alnylam, Attralus, Haya, and Tenaya. **MRG:** has received personal fees from Ionis/Akcea, Prothena, Sanofi, Janssen, Aptitude Health, Juno, Physicians Education Resource, AbbVie, Johnson & Johnson, Celgene, Research to Practice, and Sorrento; grants and personal fees from Ashfield; and development of educational materials from i3 Health. **YA:** reports no conflicts of interest. **JDG:** has served as an expert advisor for Alnylam, Ionis, Intellia, Eidos, Pfizer, and ATTRalus. **PJBD:** reports no conflicts of interest. **MWC:** is a principal investigator for the NEURO-TTRansform trial and is a consultant for Ionis. **TC:** is a principal investigator for the NEURO-TTRansform trial (paid to institution) and has received financial support from Ionis and Akcea to attend scientific meetings.

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