Summary Report of Benefit-Risk Assessment

WAINUA SOLUTION FOR INJECTION IN AUTOINJECTOR 45MG/0.8ML

NEW DRUG APPLICATION

Active Ingredient(s)	Eplontersen
Product Registrant	ASTRAZENECA SINGAPORE PTE LTD
Product Registration Number	SIN17311P
Application Route	Abridged evaluation
Date of Approval	15 August 2025

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A INTRODUCTION

Wainua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or 2 polyneuropathy.

The active substance, eplontersen, is an N-acetylgalactosamine (GalNAc)-conjugated 2′-O-2-methoxyethyl-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate and phosphate diester internucleotide linkages. The GalNAc conjugate enables targeted delivery of the ASO to hepatocytes. The selective binding of eplontersen to the transthyretin (TTR) messenger RNA (mRNA) within the hepatocytes causes the degradation of both mutant and wild type (normal) TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.

Wainua is available as a solution for injection in an autoinjector and contains eplontersen sodium equivalent to 45mg/0.8mL of eplontersen. Other ingredients in the injection solution are sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, eplontersen sodium, is manufactured at Nitto Denko Avecia, Inc., Massachusetts, United States. The drug product, Wainua Solution for Injection in Autoinjector 45mg/0.8mL, is manufactured at Vetter Pharma-Fertigung GmbH & Co KG, Ravensburg, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP) standard.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at -15 to -25ºC with a re-test period of 24 months. The packaging is high-density polyethylene (HDPE) bottle with polypropylene closure, placed in a multi-layered, heat-sealed, secondary pouch.

Drug product:

The manufacturing process involves pooling and homogenisation of the drug substance and formulation of the drug product, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at 2 to 8ºC. The container closure system is a 1mL borosilicate Type I clear glass prefilled syringe, with 27G ½ inch stainless steel needle, rigid needle shield, and chlorobutyl elastomer stopper in an autoinjector.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of eplontersen in the treatment of hATTR amyloidosis with polyneuropathy (hATTR-PN) was based primarily on one pivotal Phase III study (ION-682884-CS3), referred to as the NEURO-TTRansform study. This was a multicentre, open-label, randomised study of eplontersen compared with an external placebo group from the inotersen Phase II/III study (ISIS-420915-CS2, referred to as the NEURO-TTR study) in patients with Stage 1 or 2 hATTR-PN with documented genetic mutation in the TTR gene. Inotersen was also included as an active reference arm in Study NEURO-TTRansform.

Patients in the study were randomised in a 6:1 ratio to receive subcutaneous eplontersen 45 mg every 4 weeks or subcutaneous inotersen 300 mg once weekly till Week 34, then switched to eplontersen at Week 37. All subjects were to continue dosing with eplontersen until week 81, with end of treatment assessments at Week 85. The external placebo control was employed only for 66 weeks.

Since hATTR amyloidosis with polyneuropathy is a rare disease, active comparator designs were considered unfeasible due to the large sample size requirements. Given the life-threatening nature of hATTR amyloidosis with polyneuropathy and the availability of other oligonucleotide therapeutics, a concurrent placebo control group may not be ethical. Hence, the use of an external placebo group was considered reasonable. The concurrent inotersen reference group was included in the study to provide a descriptive comparison with the external inotersen group of Study NEURO-TTR to demonstrate similarity between the populations or treatment responses between the studies.

The co-primary efficacy endpoints were the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and the percent change from baseline in serum TTR protein concentration at Week 35 (interim analysis) and Week 66. The mNIS+7 is a composite measure of motor, sensory, and autonomic polyneuropathy. The mNIS+7 total score ranged from -22.3 to 346.3 points, with higher scores indicating greater impairment. Similar to the NEURO-TTR study, the mNIS+7 central reader was blinded to treatment and mNIS+7 assessors were trained and certified by the Peripheral Nerve Research Laboratory that

developed the composite score. The key secondary efficacy endpoint was the change from baseline in the Norfolk Quality of Life – Diabetic Neuropathy (QOL-DN) questionnaire total score at Week 35 and Week 66. The Norfolk QOL-DN is a comprehensive, patient-reported, health-related quality of life questionnaire that consists of 5 domains including physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy. The total score ranged from -4 to 136, with higher scores indicating a worse quality of life.

The other secondary efficacy endpoints were the change from baseline in Neuropathy Symptom and Change (NCS) at Weeks 35 and 66, as well as change from baseline in the Physical Component Summary (PCS) score of 36-Item Short Form Survey (SF-36), change from baseline in Polyneuropathy disability (PND) score and the change from baseline in modified body mass index (mBMI) at Week 65.

To mitigate potential bias with the use of an external comparator, a placebo group in the same disease population, similar eligibility criteria, sites, study team and objective co-primary endpoint of change from baseline in serum TTR protein concentration were used. Disease stage, previous treatment, and V30M mutation were also used in the propensity score for baseline factor adjustment in the primary analyses to address potential confounding and selection bias. In addition, the Analysis of Covariance (ANCOVA) model employed in the primary analysis of mNIS+7/Norfolk QOL-DN included the effect of the respective baseline value of the endpoint as a covariate.

A total of 168 patients were randomised in Study NEURO-TTRansform. Of these, 160 patients who received at least one dose of study drug and had a baseline and at least one post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score were included in the full analysis set (FAS): 140 patients in the eplontersen arm and 20 patients in the inotersen arm. The FAS was the primary analysis population. In Study NEURO-TTR, 60 subjects were randomised and 59 were included in the FAS in the placebo control arm.

Most subjects were male (eplontersen arm of NEURO-TTRansform vs placebo arm of NEURO-TTR: 69.3% vs 69.5%) and White (77.7% vs 88.1%), and 15.8% vs 5.1% were Asian. The majority of subjects (80.0% vs 71.2%) had Stage 1 disease and 58.6% vs 55.9% had V30M TTR mutation. Overall, some differences in demographics and baseline characteristics were observed between the eplontersen arm of NEURO-TTRansform and the placebo arm of NEURO-TTR. The median age was lower at 51 years (range 24-82) in the eplontersen arm compared to 63 years (range 28-81) in the placebo arm, and a higher proportion of patients were from the region of South America/Australasia/Asia in the eplontersen arm compared to the external placebo arm (48.6% vs 18.6%). A higher proportion of subjects in the eplontersen arm received previous treatment with tafamidis or diflunisal compared to the external placebo arm (70.0% vs 59.3%). Compared to the external placebo arm, the eplontersen arm had higher disease severity as measured by the mNIS+7 scores (mean 79.59 vs 74.12) but better Norfolk QOL-DN total score (mean 43.48 vs 48.60). Nonetheless, the effect sizes of the co-primary endpoints were similar across subgroups based on age (< vs ≥ 65 years), region (North America vs Europe vs South America/Australasia/Asia), and previous treatment with tafamidis or diflunisal. In addition, the imbalances in proportion of subjects who were previously treated with stabilizer therapy and had higher baseline disease severity based on mNIS+7 score did not favour the eplontersen arm and were unlikely to impact the observed treatment effect.

The primary analyses demonstrated statistically significantly greater mean reduction in both co-primary endpoints of change from baseline to Week 35 in mNIS+7 score and serum TTR compared with placebo. At Week 35, the difference in least squares mean (LSM) change in

mNIS+7 score and percent change in serum TTR were -9.01 and -66.43% for eplontersen versus placebo, respectively (both p<0.0001). The results of the primary analyses from this study were supported by the statistically significant positive results in the key secondary efficacy endpoint of change from baseline to Week 35 in the Norfolk QOL-DN score, with a difference in LSM of -11.79 for eplontersen versus placebo (p<0.0001). As the three key efficacy endpoints (mNIS+7, TTR and Norfolk) were statistically significant at Week 35, the interim analyses were considered the final analyses according to the pre-specified testing procedure, and the Week 66 analyses were not formally tested. Nevertheless, the Week 66 results of the co-primary endpoints were consistent with the interim analyses, with sustained effects of eplontersen maintained to Week 66. The results showed differences in LSM change in mNIS+7 score and percent change in serum TTR of -24.8 and -70.4% for eplontersen versus placebo, respectively (both p<0.0001). The difference in LSM change from baseline to Week 66 in the Norfolk QOL-DN score was -19.7 for eplontersen versus placebo (p<0.0001).

Sensitivity propensity analysis using 6 covariates which additionally included gender, mBMI and region demonstrated consistent results for the co-primary and key secondary endpoints. The subgroup analyses for both mNIS+7 and Norfolk assessments also showed a favourable treatment effect across all prespecified subgroups including V30M mutation status, age, gender, race, region, previous treatment with tafamidis or diflunisal and disease stage. This suggested that the efficacy of eplontersen is not significantly influenced by these patient baseline characteristics.

Summary of efficacy results

	Eplontersen (N=140)	**Placebo (N=59)**	**Inotersen-eplontersen (N=21)**
Primary efficacy endpoints			
Change from baseline at Week 35 in mNIS+7 score [a] Mean baseline (SD) Mean change from baseline (SD) LSM (95% CI) Difference in LSM (95% CI) p-value	 79.59 (42.318) -0.03 (16.281) 0.215 (-3.459, 3.889)	 74.12 (39.029) 9.76 (14.199) 9.225 (5.538, 12.912) -9.010 (-13.483, -4.537) **<0.0001**	 65.41 (35.855) 4.06 (13.392)
[Sensitivity Propensity Analysis using 6 Covariates] * LSM (95% CI) Difference in LSM (95% CI) p-value	 -0.154 (-3.797, 3.489)	 7.466 (3.865, 11.067) -7.620 (-12.078, -3.162) 0.0009	
Change from baseline at Week 66 in mNIS+7 score [a] LSM (95% CI) Difference in LSM (95% CI) p-value	 0.3 (-4.46, 5.06)	 25.1 (20.23, 29.88) -24.8 (-30.96, -18.56) <0.0001	 -
Percent change from baseline at Week 35 in Serum TTR [b] Mean baseline in mg/L (SD) Mean % change from baseline (SD) LSM (95% CI) Difference in LSM (95% CI) p-value	 226.9 (75.5) -81.98 (11.702) -81.20 (-84.55, -77.84)	 154.1 (37.5) -11.13 (19.604) -14.76 (-18.73, -10.80) -66.43 (-71.39, -61.47) **<0.0001**	 231.9 (71.8) -74.26 (23.281)
[Sensitivity Propensity Analysis using 6 Covariates] * LSM (95% CI) Difference in LSM (95% CI) p-value	 -81.77 (-85.04, -78.51)	 -12.54 (-16.84, -8.25) -69.23 (-74.36, -64.10) <0.0001	
Percent change from baseline at Week 66 in Serum TTR			

LSM (95% CI) Difference in LSM (95% CI) p-value	-81.7 (-84.82, -78.48)	-11.2 (-15.06, -7.41) -70.4 (-75.17, -65.66) <0.0001	-
Secondary efficacy endpoints			
Change from baseline at Week 35 in Norfolk QOL-DN [a] Mean baseline (SD) Mean change from baseline (SD) LSM (95% CI) Difference in LSM (95% CI) p-value	 43.48 (26.251) -4.79 (16.514) -3.117 (-7.1900, 0.9554)	 48.60 (26.974) 5.51 (20.178) 8.673 (4.531, 12.814) -11.790 (-16.817, -6.763) **<0.0001**	 37.97 (21.512) -2.97 (12.094)
[Sensitivity Propensity Analysis using 6 Covariates] * LSM (95% CI) Difference in LSM (95% CI) p-value	 -3.053 (-6.762, 0.6576)	 8.216 (4.360, 12.072) -11.269 (-15.964, -6.573) <0.0001	
Change from baseline at Week 66 in Norfolk QOL-DN [a] LSM (95% CI) Difference in LSM (95% CI) p-value	 -5.5 (-10.03, -0.96)	 14.2 (9.51, 18.97) -19.7 (-25.63, -13.84) <0.0001	 -
Change in NSC from baseline to Week 35 [b] LSM (95% CI) Difference in LSM (95% CI) p-value	 0.8 [-0.92, 2.50]	 4.7 [2.98, 6.48] -3.9 (-6.08, -1.80) 0.0005	
Change in NSC from baseline to Week 66 [b] LSM (95% CI) Difference in LSM (95% CI) p-value	 0.0 [-1.92, 1.86]	 8.2 [6.24, 10.12] -8.2 (-10.65, -5.76) <0.0001	
Change in SF-36 PCS from baseline to Week 65 [b] LSM (95% CI) Difference in LSM (95% CI) p-value	 0.85 [-0.711, 2.412]	 -4.46 [-6.139, -2.770] 5.31 (3.195, 7.416) <0.0001	
Change in PND score from baseline to Week 65 [b] LSM (95% CI) Difference in LSM (95% CI) p-value	 0.1 [0.0, 0.2]	 0.3 [0.2, 0.4] -0.2 (-0.4, 0.0) 0.0241	
Change in mBMI from baseline to Week 65 [b] LSM (95% CI) Difference in LSM (95% CI) p-value	 -8.1 [-28.55, 12.42]	 -90.8 [-112.84, -68.69] 82.7 (54.64, 110.76) <0.0001	

a. Based on an ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, V30M mutation, previous treatment, and the baseline value.

b. Based on an MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, V30M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction.

* In addition to 3 factors (disease stage, V30M mutation, previous treatment) used in the logistic model for propensity score in the primary analysis, this sensitivity analysis included additional 3 covariates (gender, modified BMI, region).

The similar efficacy results in the inotersen arms of NEURO-TTR and NEURO-TTRansform provided a reference in the interpretation of the effect size of eplontersen and provided assurance on the robustness of the external placebo study design. Although the inherent biases with the use of external placebo could not be completely excluded with the mitigation measures and additional analyses, the observed effect sizes of clinical and pharmacodynamic endpoints were comparable to available therapies based on TTR-lowering mechanisms. These provided reasonable assurance supporting the efficacy of eplontersen in the treatment of

hereditary transthyretin-mediated amyloidosis in adult patients with Stage 1 or 2 polyneuropathy.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of eplontersen was based on safety data derived primarily from the pivotal Phase III NEURO-TTRansform study and the placebo arm of Study NEURO-TTR, comprising a total of 228 patients: 144 subjects in the eplontersen arm, 24 subjects in the inotersen arm, and 60 subjects in the placebo arm. The median duration of exposure was similar in the eplontersen arm (456.0 days) and the placebo arm (449.0 days), but shorter in the concurrent inotersen arm (227.5 days).

The safety of eplontersen was also supported by Study ION-682884-CS13, which included 108 subjects. ION-682884-CS13 was a Phase III, open-label, long-term extension study to evaluate the safety and tolerability of long-term eplontersen, enrolling patients with hATTR-PN from the NEURO-TTRansform study of eplontersen and the Investigator Sponsored Inotersen Study ISIS 420915-CS101. The median duration of exposure to eplontersen in the study was 112 days.

Overview of treatment-emergent adverse events (AEs)

AE	NEURO-TTRansform		NEURO-TTR	ION-682884-CS13 (long-term)
	Eplontersen (N=144) Up to Week 66	**Inotersen (N=24) Weeks 1 to 37**	**Placebo (N=60) Up to Week 66**	**Eplontersen (N=108)**
Any AE	140 (97.2%)	24 (100%)	60 (100%)	47 (43.5%)
Treatment-related AE	53 (36.8%)	17 (70.8%)	23 (38.3%)	4 (3.7%)
Serious AEs	21 (14.6%)	3 (12.5%)	12 (20.0%)	8 (7.4%)
Treatment-related SAE	0	0	1 (1.7%)	0
Discontinuations due to AE	6 (4.2%)	3 (12.5%)	2 (3.3%)	3 (2.8%)
Deaths	2 (1.4%)	0	0	3 (2.8%)

The most frequently reported adverse events (AEs) included diarrhoea (eplontersen arm vs placebo arm: 16.7% vs 18.3%), urinary tract infection (16.7% vs 16.7%), nausea (11.1% vs 11.7%) and vomiting (8.3% vs 5.0%). Other AEs which occurred more frequently in the eplontersen arm compared to placebo arm included vitamin A deficiency (11.8% vs 0), proteinuria (8.3% vs 3.3%), vision blurred (5.6% vs 1.7%), and cataract (4.2% vs 1.7%). The majority of the AEs were mild or moderate in severity and generally consistent with those expected with hATTR amyloidosis.

The most frequent serious AEs (SAEs) in the eplontersen arm included gastrointestinal disorders (4.9% vs 1.7%; including vomiting: 3.5% vs 1.7%; and nausea: 1.4% vs 0%), cardiac disorders (2.8% vs 3.3%), and infections (6.9% vs 8.3%). A total of two fatal AEs (arrhythmia and cerebral haemorrhage) occurred in the eplontersen group in NEURO-TTRansform, three fatal AEs in ION-682884-CS13 (cardiac arrest, gastrointestinal haemorrhage and cardiogenic shock) and no deaths occurred in the external placebo group. All three cardiac deaths occurred in subjects with a history of hATTR related cardiomyopathy. None of the deaths or SAEs in the eplontersen group were considered related to treatment by study investigators.

The AEs of special interest (AESIs) identified based on inotersen safety profile were thrombocytopenia (2.1% vs 1.7%), glomerulonephritis (0 vs 3.3%) and ocular AEs potentially related to vitamin A deficiency (27.1% vs 15.0%). From the limited available data, there was no clear signal of increased risk of thrombocytopenia or glomerulonephritis with eplontersen. The imbalance in ocular AEs potentially related to vitamin A deficiency was driven mainly by AEs of vitamin A deficiency and vitamin A decreased in the eplontersen group. Excluding AEs of vitamin A deficiency and vitamin A decreased, the incidence of other ocular AEs potentially related to vitamin A deficiency was 16.7% in the eplontersen group vs 15.0% in the external placebo, the most frequent of which was blurred vision (5.6% vs 1.7%). Overall, the interpretation of AEs related to Vitamin A deficiency was limited by the lack of vitamin A laboratory values for the external placebo arm in NEURO-TTR. Based on the mechanism of action of eplontersen, serum vitamin A levels are expected to be reduced with treatment and were observed to be decreased in individuals receiving eplontersen in the clinical studies. The risks of vitamin A deficiency have been adequately described as warnings and precautions in the package insert with recommendations for monitoring and vitamin A supplementation.

Other AEs of interest (OAEIs) included coagulation abnormalities, renal impairment, abnormal liver function, injection site reactions, flu-like symptoms, central nervous system (CNS) disorders, haemorrhages, cardiac disorders, and reduced thyroxine. The majority of OAEIs occurred more frequently in the placebo group compared to the eplontersen group. The AESIs and OAEIs generally occurred less frequently compared to the inotersen groups from Studies NEURO-TTRansform and NEURO-TTR.

Overall, there were no new or unexpected safety signals detected in the eplontersen group compared to other currently available antisense oligonucleotide therapies and the safety profile of eplontersen was consistent with that of other available therapies based on TTR-lowering mechanisms.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Hereditary transthyretin amyloidosis with polyneuropathy is a serious disease that can result in significant morbidity. Currently, only one therapeutic product belonging to the therapeutic class of small interfering ribonucleic acid (siRNA) is approved for the treatment of hATTR-PN locally and there remains a clinical need for safe and effective treatments for hATTR polyneuropathy.

The efficacy of eplontersen in adult patients with hATTR amyloidosis with polyneuropathy was primarily assessed in Study NEURO-TTRansform, in comparison with the external placebo group from Study NEURO-TTR. Potential biases were mitigated through employing an external placebo comparator in the same disease population, similar eligibility criteria, sites, study team and inclusion of objective co-primary endpoint. Adjustment by propensity score weights based on 3 baseline factors were employed in the primary analyses to address potential confounding and selection bias. Compared to the external placebo group, the eplontersen group from Study NEURO-TTRansform demonstrated significantly greater mean reduction from baseline to Week 35 in the primary endpoint of mNIS+7 score (difference -9.01; $p<0.0001$) as well as the key secondary endpoint of Norfolk QOL-DN score (difference -11.79; $p<0.0001$). The clinical endpoints were also supported by the pharmacodynamic co-primary endpoint of percent reduction in serum TTR from baseline to Week 35 (difference -66.43; $p<0.0001$). Subgroup analyses of the key clinical endpoints demonstrated a favourable treatment effect across all

prespecified subgroups. The similar efficacy outcomes observed in both inotersen arms of NEURO-TTRansform and NEURO-TTR provided a reference in the assessment of eplontersen's effect size. While some inherent bias associated with the use of an external placebo remains, the substantial effect sizes of the efficacy endpoints comparable to current therapies utilising TTR-lowering mechanisms lend further support for the efficacy of eplontersen.

The majority of the AEs reported with eplontersen were mild or moderate in severity and generally consistent with those expected in patients with hATTR amyloidosis. Among AESIs, ocular AEs potentially related to vitamin A deficiency occurred more commonly in the eplontersen group; while the incidences of thrombocytopenia, glomerulonephritis, as well as other AEs of interest were comparable to the external placebo group and generally lower compared to the inotersen groups from Studies NEURO-TTRansform and NEURO-TTR. There were no new or unexpected safety signals detected in the eplontersen group as compared with other available antisense oligonucleotide therapies. The safety findings have been adequately addressed in the local package insert via the provision of relevant warnings and precautions.

Overall, the benefits of eplontersen in hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or 2 polyneuropathy outweighed the potential risks and the benefit-risk assessment of eplontersen was positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Wainua for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or 2 polyneuropathy was deemed favourable and approval of the product registration was granted on 15 August 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

WAINUA®

(eplontersen)

1. NAME OF THE MEDICINAL PRODUCT

WAINUA 45 mg solution for injection in a single-dose autoinjector.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 56 mg eplontersen, equivalent to 59 mg eplontersen sodium.

Each single-dose autoinjector contains 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) in 0.8 mL solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a single-dose autoinjector (injection).
Sterile, clear, preservative-free, colourless to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

WAINUA is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or 2 polyneuropathy.

4.2 Posology and method of administration

Treatment should be prescribed and supervised by a treating physician knowledgeable in the management of patients with amyloidosis.

Posology

The recommended dose of WAINUA is 45 mg administered by subcutaneous injection. Doses should be administered monthly.

Vitamin A supplementation at approximately, but not exceeding, 2 500 IU to 3 000 IU vitamin A per day is advised for patients treated with WAINUA (see section 4.4)

The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.

Missed dose

If a dose of eplontersen is missed, then the next dose should be administered as soon as possible. Resume dosing at monthly intervals from the date of the last dose.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥45 to <90 mL/min/1.73 m^2) (see section 5.2). WAINUA has not been studied in patients with eGFR<45 mL/min/1.73 m^2 or end-stage renal disease.

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (see section 5.2). WAINUA has not been studied in patients with moderate or severe hepatic impairment.

Elderly population

No dose adjustment is required in elderly patients (≥65 years of age) (see section 5.2).

Paediatric population

The safety and efficacy of WAINUA in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

Subcutaneous use only.

The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the subcutaneous administration of WAINUA.

The autoinjector should be removed from refrigerated storage at least 30 minutes before use and allowed to reach room temperature prior to injection. Other warming methods should not be used.

Inspect solution visually before use. The solution should appear colourless to yellow. **Do not** use if cloudiness, particulate matter or discolouration is observed prior to administration.

If self-administered, inject WAINUA in the abdomen or upper thigh region. If a caregiver administers the injection, the back of the upper arm can also be used.

Comprehensive instructions for administration are provided in the 'Instructions for Use'.

4.3 Contraindications

None.

4.4 Special warnings and special precautions for use

Reduced Serum Vitamin A Levels and Recommended Supplementation

Based on the mechanism of action, WAINUA is expected to reduce serum vitamin A (retinol) below normal levels (see section 5.1).

Any symptoms or signs related to vitamin A deficiency should be evaluated prior to initiation of treatment with WAINUA.

Patients receiving WAINUA should take oral supplementation of approximately, but not exceeding, 2 500 IU (female) to 3 000 IU (male) of vitamin A per day to reduce the potential risk of ocular symptoms due to vitamin A deficiency. Referral for ophthalmological assessment is recommended if patients develop ocular symptoms consistent with vitamin A deficiency, including reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening or corneal perforation.

It is not known whether vitamin A supplementation in pregnancy will be sufficient to prevent vitamin A deficiency if the pregnant female continues to receive WAINUA (see section 4.6). However, increasing vitamin A supplementation to above the daily recommended dose during pregnancy is unlikely to correct serum retinol levels due to the mechanism of action of eplontersen and may be harmful to the mother and foetus.

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug-drug interaction studies have been performed (see section 5.2).

4.6 Pregnancy and lactation

Women of child-bearing potential

WAINUA will reduce the plasma levels of vitamin A, which is crucial for normal foetal development. It is not known whether vitamin A supplementation will be sufficient to reduce the risk to the foetus. For this reason, pregnancy should be excluded before initiation of WAINUA therapy and women of child-bearing potential should practise effective contraception.

If a woman intends to become pregnant, WAINUA and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and have returned to normal before conception is attempted. Due to the long half-life of eplontersen (see section 5.2), a vitamin A deficit may develop even after cessation of treatment.

Contraception in males and females

Women of child-bearing potential should practise effective contraception.

Pregnancy

There are no data regarding the use of WAINUA in pregnant women.

Administration of eplontersen or a pharmacologically-active rodent-specific surrogate at doses up to 38-fold higher than the recommended human dose in a combined fertility and embryo-foetal development toxicity study in mice did not result in effects on male and female fertility or embryo-foetal development (see section 5.3).

Due to the potential teratogenic risk arising from unbalanced vitamin A levels, WAINUA should not be used during pregnancy. In the event of an unplanned pregnancy, WAINUA should be discontinued and close monitoring of the foetus and Vitamin A status should be carried out, especially during the first trimester.

Breast-feeding

Human or animal lactation studies have not been conducted to assess the presence of eplontersen or it's metabolites in breast milk, the effects on the breastfed infant, or the effects on milk production for the mother. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from WAINUA therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There is no information available on the effects of eplontersen on human fertility.

Administration of eplontersen or a pharmacologically-active rodent-specific surrogate in doses up to 38-fold higher than the recommended human exposure in mice did not indicate any impact of eplontersen on male or female fertility.

4.7 Effects on ability to drive and use machines

WAINUA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Overall summary of the safety profile

The safety data described below reflects exposure to WAINUA in 144 patients with polyneuropathy caused by ATTRv (ATTRv-PN) randomised to WAINUA and who received at least one dose of WAINUA. Of these, 141 patients received at least 6 months of treatment and 137 patients received at least 12 months of treatment. The mean duration of treatment was 541 days (range: 57 to 582 days).

The most frequent adverse reactions during treatment with WAINUA observed in ≥5% of patients were vomiting and vitamin A decreased.

Adverse Drug Reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Summary of Adverse Reactions per Frequency Category

System Organ Class	Adverse Reaction	Frequency
Gastrointestinal disorders	Vomiting	Common
General disorders and administration site conditions	Injection site erythema	Common
	Injection site pain	Common
	Injection site pruritus	Common
Investigations	Vitamin A decreased	Very Common

System Organ Class	Adverse Reaction	Frequency
Renal and urinary disorders	Proteinuria	Common
Eye disorders	Cataracts	Common

Description of selected adverse reaction

Vitamin A decreased

In the clinical study in patients with ATTRv-PN, all patients were instructed to take the recommended daily allowance of vitamin A. All patients treated with WAINUA had normal vitamin A levels at baseline, 96.5% of those developed vitamin A levels below the lower limit of normal (LLN) during the study (see section 5.1).

Injection site reactions

In patients with ATTRv-PN treated with WAINUA, injection site erythema, injection site pain and injection site pruritus were reported in 3.5%, 3.5%, and 2.1% respectively.

4.9 Overdose

There is no specific treatment for an overdose with eplontersen. In the event of an overdose, supportive medical care should be provided including consulting with a healthcare professional.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Nervous System Drugs, ATC code: N07XX21.

Mechanism of action

Eplontersen is a N-acetylgalactosamine (GalNAc) conjugated 2′-*O*-2-methoxyethyl (2′-MOE)-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate (PS) and phosphate diester (PO) internucleotide linkages. The GalNAc conjugate enables targeted delivery of the ASO to hepatocytes. The selective binding of eplontersen to the TTR messenger RNA (mRNA) within the hepatocytes causes the degradation of both mutant and wild type (normal) TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.

TTR is a carrier protein for retinol binding protein 4 (RBP4), which is the principal carrier of vitamin A (retinol). Therefore, a reduction in plasma TTR is expected to result in the reduction of plasma retinol levels to below the lower limit of normal.

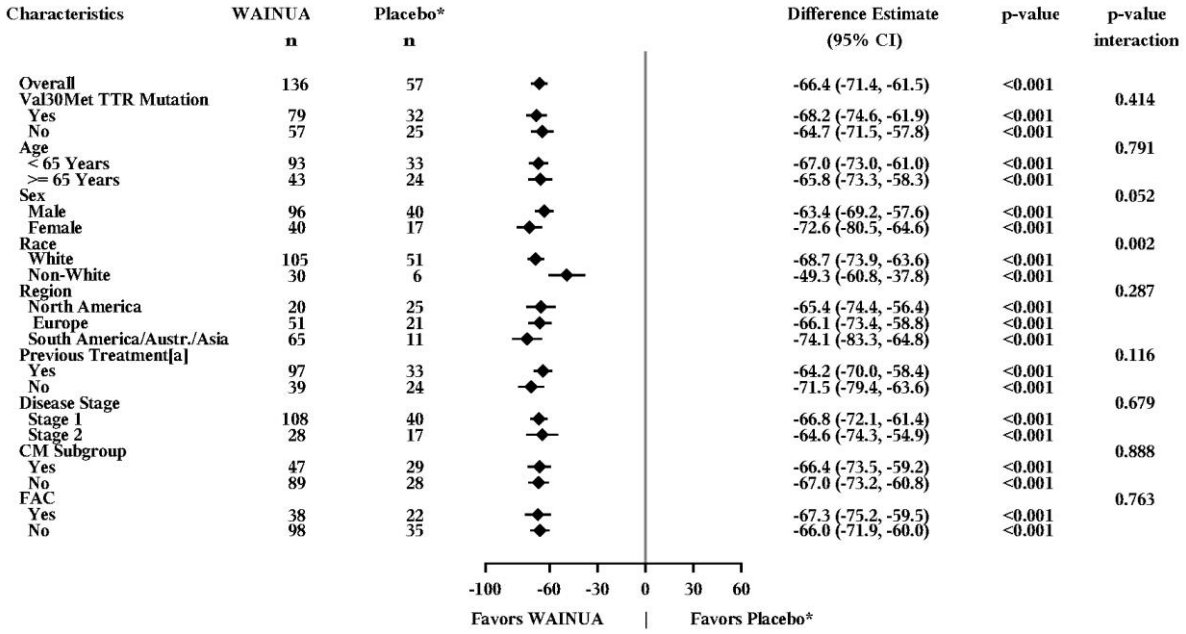
Pharmacodynamics

In the clinical study in patients with ATTRv-PN receiving eplontersen, a decrease in serum TTR concentrations was observed at the first assessment (Week 5), and TTR concentrations continued to decrease through Week 35. A sustained reduction of TTR concentration was observed throughout the duration of the treatment (85 weeks). Mean (SD) for serum TTR percent reduction from baseline was 82.1% (11.7) at Week 35, 83.0% (10.4) at Week 65 and

81.8% (13.4) at Week 85 when treated with eplontersen. Similar reduction from baseline in serum TTR concentrations compared to placebo was observed regardless of sex, race, age, region, body weight, cardiomyopathy status, previous treatment, Val30Met mutation status, disease stage, and familial amyloid cardiomyopathy (FAC) clinical diagnosis at baseline (Figures 1a and b).

Figure 1 Forest Plot of Treatment Difference in LSM for Percent Change from Baseline in TTR (g/L) for Key Subgroups (NEURO-TTRansform Study) (full analysis set)

a) at Week 35



* External placebo group from another randomised controlled trial (NEURO-TTR).

[a] Previously treated with tafamidis or diflunisal.

Based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time-interaction.

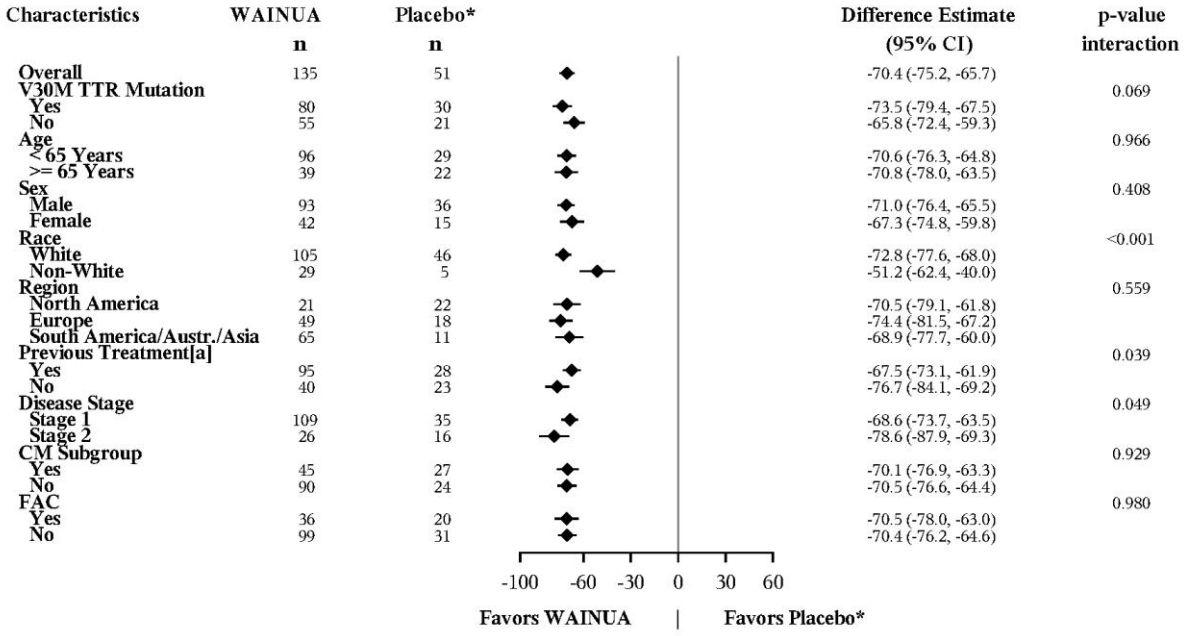
Subgroup models also included treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions. Only data up to Week 35 are included in the Week 35 interim analysis.

CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].

The Week 35 LSM treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.

CI = Confidence interval; LSM = Least squares mean; MMRM = Mixed effects model with repeated measures; TTR = Transthyretin, CM = cardiomyopathy, FAC = familial amyloid cardiomyopathy.

b) at Week 65



* External placebo group from another randomised controlled trial (NEURO-TTR).
[a] Previously treated with tafamidis or diflunisal.
Based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time-interaction.
Subgroup models also included treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions.
CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].
The Week 65 LSM treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.
CI = Confidence interval; LSM = Least squares mean; MMRM = Mixed effects model with repeated measures; TTR = Transthyretin, CM = cardiomyopathy, FAC = familial amyloid cardiomyopathy

Cardiac Electrophysiology

Formal QTc studies have not been conducted with WAINUA. The potential for QTc prolongation with eplontersen was evaluated in a randomised, placebo-controlled trial in healthy volunteers. At a dose 2.7 times the recommended dose of 45 mg eplontersen, no clinically relevant effect on the QT interval was observed.

Immunogenicity

In the clinical study in patients with ATTRv-PN, after an 84-week treatment period (median treatment duration 561 days (80 weeks), range 57 to 582 days), 58 patients (40.3%) developed treatment-emergent anti-drug antibodies (ADAs).

In the patients who tested positive for anti-eplontersen antibodies, there was no clinically meaningful impact on the efficacy, safety, pharmacokinetics, or pharmacodynamics of WAINUA.

The presence of ADAs did not affect eplontersen plasma C_{max} or AUC, but increased C_{trough}.

Clinical efficacy

The efficacy and safety of WAINUA was evaluated in a randomised, multicentre, open-label, externally-controlled trial (NEURO-TTRansform) that included a total of 168 patients with ATTRv-PN. Patients were randomised in a 6:1 ratio to receive subcutaneous injection every 4 weeks with WAINUA 45 mg (N=144) or weekly inotersen 284 mg (N=24) as a reference group. Of the 144 patients randomised to eplontersen, 140 (97.2 %) patients completed treatment through Week 35, 135 (93.8%) completed treatment through Week 65 and 130 (90.3%) completed treatment through Week 85.

An external placebo control consisted of a placebo cohort of patients from the inotersen pivotal study: randomised, double-blind, placebo-controlled, multicentre clinical trial in adult patients with ATTRv-PN (NEURO-TTR). That cohort received subcutaneous injections of placebo once weekly. Both studies employed identical eligibility criteria.

The characteristics of the eplontersen and external placebo groups were generally similar, and potential imbalances in key baseline characteristics (Val30Met mutation status, disease stage and previous treatment) were accounted in the prespecified statistical analysis. Baseline demographic and disease characteristics are shown in Table 2.

Table 2 Baseline Demographics and Disease Characteristics in NEURO-TTRansform Study (safety set)

	Placebo* (N=60)	WAINUA (N=144)
Age, years Mean (SD) Median (min, max) <65, n (%) 65-74, n (%) ≥75, n (%)	 59.5 (14.1) 63 (28, 81) 34 (56.7) 17 (28.3) 9 (15.0)	 53.0 (15.0) 51.5 (24, 82) 100 (69.4) 36 (25.0) 8 (5.6)
Male, n (%)	41 (68.3)	100 (69.4)
Race, n (%) Asian Black or African American White Other Multiple	 3 (5.0) 1 (1.7) 53 (88.3) 2 (3.3) 1 (1.7)	 22 (15.4) 5 (3.5) 112 (78.3) 3 (2.1) 1 (0.7)
Ethnicity, n (%) m Hispanic or Latino	 60 7 (11.7)	 142 22 (15.5)
Previous treatment with tafamidis or diflunisal, n (%) Yes	 36 (60.0)	 100 (69.4)
ATTRv-PN Disease stage[1], n (%) Stage 1 Stage 2	 42 (70.0) 18 (30.0)	 115 (79.9) 29 (20.1)
mNIS+7 composite score, mean (SD)	74.8 (39.0)	81.3 (43.4)

	Placebo* (N=60)	WAINUA (N=144)
Norfolk QoL-DN total score, m mean (SD)	 59 48.7 (26.8)	 137 44.1 (26.6)
Val30Met TTR mutation, n (%) Yes[2] No[3] Glu89Gln, Glu109Gln Leu58His, Leu78His Phe64Leu, Phe84Leu Ser50Arg, Ser70Arg Ser77Tyr, Ser97Tyr, S97Y Thr49Ala, Thr69Ala Thr60Ala, Thr80Ala Val122Ile, Val142Ile Other[3]	 33 (55.0) 27 (45.0) 0 3 (5.0) 3 (5.0) 1 (1.7) 5 (8.3) 0 8 (13.3) 1 (1.7) 6 (10.0)	 85 (59.0) 59 (41.0) 1 (0.7) 4 (2.8) 5 (3.5) 2 (1.4) 3 (2.1) 1 (0.7) 4 (2.8) 4 (2.8) 35 (24.3)
NYHA classification, n (%) I II	 40 (66.7) 20 (33.3)	 105 (72.9) 39 (27.1)
Duration of disease from ATTRv-PN diagnosis (months), mean (SD)	39.3 (40.3)	46.8 (58.1)
Duration from onset of ATTRv-PN symptoms (months), mean (SD)	64.0 (52.3)	67.7 (50.9)
Diagnosed with familial amyloid cardiomyopathy (FAC)[4], n (%) Criteria Used to Document the Clinical Diagnosis of FAC[4], n (%)[5] Cardiac biopsy Echo result Other	22 (36.7) 5 (22.7) 17 (77.3) 0	39 (27.1) 1 (2.6) 24 (61.5) 24 (61.5)
Duration of Disease from FAC[4] Clinical Diagnosis from CRF (months), mean (SD)	21.0 (22.5)	18.5 (21.4)
Duration from onset of FAC[4] symptoms (months), mean (SD)	34.1 (29.3)	36.3 (63.8)
NT-proBNP (pmol/L), mean (SD)	82.0 (159.2)	54.0 (122.6)
Short form 36 item health survey (SF-36) Physical component summary score), mean (SD)	37.2 (9.8)	39.7 (9.3)
Neuropathy symptoms and change (NSC) total score, mean (SD)	23.0 (12.6)	23.1 (12.4)
Polyneuropathy disability (PND) score, n (%) I II IIIa IIIb	 23 (38.3) 19 (31.7) 15 (25.0) 3 (5.0)	 56 (39.2) 61 (42.7) 16 (11.2) 10 (7.0)
Body Mass Index (kg/m^2)		

	Placebo* (N=60)	WAINUA (N=144)
m mean (SD) Median (Min, Max)	60 24.2 (4.9) 23.8 (14.5, 39.8)	138 24.4 (4.9) 24.1 (15.4, 35.4)
Modified Body Mass Index (kg/m^2 x g/L), m mean (SD) Median (Min, Max)	 60 1049.89 (228.43) 1027.55 (668.7, 1710.0)	 138 1025.78 (235.12) 1003.14 (615.7, 1714.0)

* External placebo group from another randomised controlled trial (NEURO-TTR).
[1] Disease stage is defined as stage 1 = does not require assistance with ambulation and stage 2 = requires assistance with ambulation.
[2] Includes the genotypes V30M, V50M, V50M MUTATION, VAL50MET, and P.VAL50MET.
[3] Based on clinical database. Non Val30Met mutations included: GLU89GLN, LEU58HIS, PHE64LEU, SER50ARG, SER77TYR, THR49ALA, THR60ALA, VAL122ILE and other (including ALA97SER).
[4] Familial amyloid cardiomyopathy = Hereditary transthyretin-mediated amyloidosis with cardiomyopathy (ATTRv-CM).
[5] Denominator for the percentage calculation is the number of patients diagnosed with FAC.
Only year and months were collected from the informed consent date to calculate disease duration from diagnosis and from onset of symptoms of ATTRv-PN, FAC.
N=number of patients in the safety set; n=number of patients in a subgroup, m=number of patients with non-missing data if different from N, CRF=case report form; NT-proBNP= N-terminal proB-type natriuretic peptide; SD=standard deviation.

Of the 39 patients (27.1%) in the eplontersen group who had diagnosis of TTR cardiomyopathy at study entry, 41.0% of patients were classified as New York Heart Association (NYHA) class I and 59.0% were NYHA class II.

Week 35 analyses (interim analysis)

The primary efficacy endpoints were the change from baseline to Week 35 in serum transthyretin (TTR) concentration (see Figure 2) and in the modified Neuropathy Impairment Score + 7 (mNIS+7) composite score. The mNIS+7 composite score is an objective assessment of neuropathy and comprises the NIS and Modified +7 composite scores. In the version of the mNIS+7 composite score used in the trial, the NIS objectively measures deficits in cranial nerve function, muscle strength, reflexes, and sensations, and the Modified +7 assesses heart rate response to deep breathing, quantitative sensory testing (touch-pressure and heat-pain), and peripheral nerve electrophysiology. The validated version of the mNIS+7 composite score used in the trial had a range of -22.3 to 346.3 points, with higher scores representing a greater severity of disease.

The secondary endpoint was the change from baseline in the Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) questionnaire total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN total

score that was used in the trial had a range from -4 to 136 points, with higher scores representing greater impairment.

WAINUA showed statistically significant improvement compared to external placebo control at Week 35 in reducing serum TTR with percent change of -66.43% (95%CI: -71.39%, -61.47%; p<0.0001) (see Figure 2). WAINUA showed statistically significant improvement compared to external placebo control at Week 35 for mNIS+7 composite score with LSM difference of -9.0 (95%CI: -13.5, -4.5; p<0.0001) (see Figures 3, 4a, 7a). WAINUA showed statistically significant improvement compared to external placebo control at Week 35 for Norfolk QoL-DN total score with LSM difference of -11.8 (95%CI: -16.8, -6.8; p<0.0001) (Table 3 and Figures 5, 6a, 8a).

Week 65/66 (final analysis)

The co-primary endpoints for the primary objective at the final analysis at Week 66 included percent change from baseline in serum TTR concentration at Week 65, change from baseline in mNIS+7 composite score at Week 66 and change from baseline in Norfolk QoL-DN total score at Week 66. At Week 65, the serum TTR concentration reduction was sustained. In addition, the results at Week 66 for the mNIS+7 composite and Norfolk total scores were all consistent with Week 35 results (see Table 3 and Figures 3, 4b, 5, 6b).

The secondary endpoints were change from baseline in neuropathy symptoms and change (NSC) at Weeks 66 and 35, change from baseline in the physical component score (PCS) score of short form 36 item health survey (version 2) (SF-36) at Week 65, change from baseline in polyneuropathy disability (PND) score at Week 65, and change from baseline in modified body mass index (mBMI) at Week 65.

The NSC was a patient-answered questionnaire to quantify the type, distribution, and severity of muscle weakness, sensory symptoms, pain symptoms, and autonomic symptoms. Higher scores represent worse symptoms.

The SF-36 PCS included 4 scales assessing physical function, role limitations caused by physical problems, bodily pain, and general health. Higher scores represent better physical health.

The PND categorises disability by mobility (e.g., need for stick, crutch, wheelchair, or bed). Higher PND score represents worse disability.

Modified BMI (BMI × serum albumin) is an assessment method of nutritional status in ATTR. Higher scores represent better nutritional status.

All secondary endpoints showed statistically significant superiority to external placebo (see Table 4).

Table 3 Treatment Effect for the Primary and Key Secondary Endpoints (NEURO-TTRansform Study) (full analysis set)

Analysis/Endpoint	Baseline, Mean (SD)		LSM Change/Percent Change from Baseline, (SE) [95% CI]		WAINUA – External Placebo* Difference in LSM (95% CI)	p-value
	External Placebo*	WAINUA	External Placebo*	WAINUA		
Week 35	**N = 59**	**N = 140**	**N = 59**	**N = 140**		
Serum TTR, g/L [1], Percent change from baseline	0.15 (0.04)	0.23 (0.08)	-14.8% (2.0) [-18.73, -10.80]	-81.2% (1.7) [-84.55, -77.84]	-66.4% (-71.39, -61.47)	p < 0.0001
mNIS+7 composite score [2,3] Change from baseline	74.1 (39.0)	79.6 (42.3)	9.2 (1.9) [5.54, 12.91]	0.2 (1.9) [-3.46, 3.89]	-9.0 (-13.48, -4.54)	p < 0.0001
Norfolk QoL-DN total score [2,3] Change from baseline	48.6 (27.0)	43.5 (26.3)	8.7 (2.1) [4.53, 12.81]	-3.1 (2.1) [-7.19, 0.96]	-11.8 (-16.82, -6.76)	p < 0.0001
Week 65/66	**N = 59**	**N = 141**	**N = 59**	**N = 141**		
Serum TTR, g/L [1] Percent change from baseline	0.15 (0.04)	0.23 (0.08)	-11.2% (1.9) [-15.06, -7.41]	-81.7% (1.6) [-84.82, -78.48]	-70.4% (-75.17, -65.66)	p < 0.0001[4]
mNIS+7 composite score [1] Change from baseline	74.1 (39.0)	79.8 (42.3)	25.1 (2.4) [20.23, 29.88]	0.3 (2.4) [-4.46, 5.06]	-24.8 (-30.96, -18.56)	p < 0.0001[4]
Norfolk QoL-DN total score [1] Change from baseline	48.6 (27.0)	43.3 (26.2)	14.2 (2.4) [9.51, 18.97]	-5.5 (2.3) [-10.03, -0.96]	-19.7 (-25.63, -13.84)	p < 0.0001[4]

* External placebo group from another randomised controlled trial (NEURO-TTR).

[1] Based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. Only data up to Week 66 are included in the Week 66 analysis.

[2] Based on an ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, Val30M mutation, previous treatment, and the baseline value. Only data up to Week 35 are included in the interim analysis.

[3] Participants with a missing mNIS+7 or Norfolk QoL-DN at Week 35 had value multiply imputed using an imputation model. Each of 500 imputed data sets was analyzed using simple ANCOVA model and the 500 ANCOVA model results were combined using Rubin's rules.

[4] Not formally tested due to statistically significant results at Week 35.

Analysis based on data collected up to 52 days after last dose of study drug. Week 35 data from interim analysis and Week 65/66 data from Week 66 analysis. In the Full Analysis Set, the eplontersen group included 140 participants at Week 35 and 141 participants at Week 66. One participant did not have a mNIS+7 or Norfolk QoL-DN assessment at Week 35 but did have an assessment for at least one of these at Week 66.
ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MMRM = mixed effects model with repeated measures; mNIS+7 = modified Neuropathy Impairment Score +7; N = number of participants in group; Norfolk QoL-DN = Norfolk Quality of Life – Diabetic Neuropathy questionnaire; SD = standard deviation; SE = standard error; TTR = transthyretin.

Table 4 Hierarchical Testing of Secondary Endpoints (NEURO-TTRansform Study)

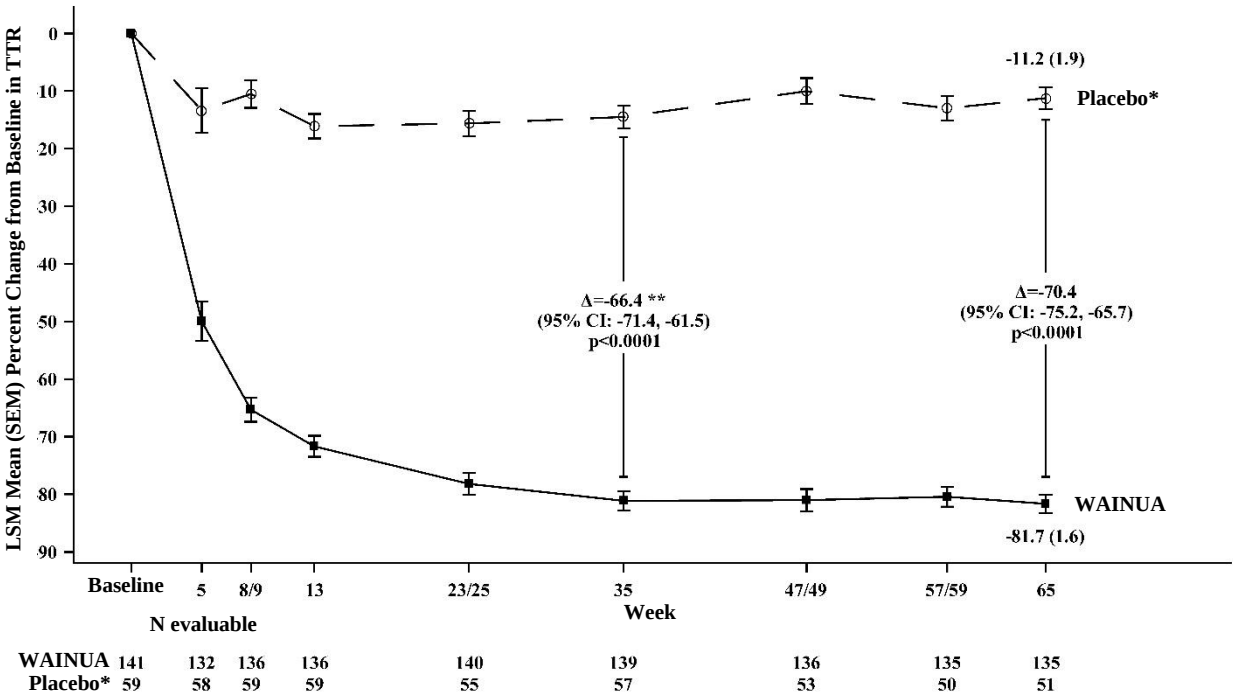
Secondary Endpoint/ Treatment group (N)	n	Change from baseline LSM (95% CI)	Comparison WAINUA versus external placebo*		
			Estimate	95% CI	p value
LSM change in NSC from baseline at Week 66					
WAINUA (N = 141)	132	0.0 (-1.92, 1.86)	-8.2	-10.65, -5.76	<0.0001
External placebo* (N = 59)	52	8.2 (6.24, 10.12)			
LSM change in NSC from baseline at Week 35					
WAINUA (N = 141)	141	0.8 (-0.92, 2.50)	-3.9	-6.08, -1.80	0.0005
External placebo* (N = 59)	56	4.7 (2.98, 6.48)			
LSM change in SF-36 PCS from baseline at Week 65					
WAINUA (N = 141)	136	0.85 (-0.711, 2.412)	5.31	3.195, 7.416	<0.0001
External placebo* (N = 59)	50	-4.46 (-6.139, -2.770)			
LSM change in PND score from baseline at Week 65					
WAINUA (N = 141)	134	0.1 (0.0, 0.2)	-0.2	-0.4, 0.0	0.0241
External placebo* (N = 59)	51	0.3 (0.2, 0.4)			
LSM change in mBMI from baseline at Week 65					
WAINUA (N = 141)	130	-8.1 (-28.55, 12.42)	82.7	54.64, 110.76	<0.0001
External placebo* (N = 59)	49	-90.8 (-112.84, -68.69)			

* External placebo group from another randomised controlled trial (NEURO-TTR).

N=Number of patients in Full Analysis Set at Week 66.

n=Number of patients with non-missing data on baseline covariates and change from baseline at the time point.
Analysis based on data collected up to 28 days after last dose of study drug. Analysis visit window of Week 65 is from Day 419 to Day 479.
Based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30M mutation, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. Only data up to Week 65 are included in the Week 66 final analysis.
CI = confidence interval; LSM = least squares mean; mBMI = modified body mass index; NSC = neuropathy symptoms and change; PND = polyneuropathy disability; PCS = physical component score; SF-36 PCS= short form-36 health survey questionnaire Physical Component Score.

Figure 2 LSM Percent Change in Serum TTR Concentration from Baseline to Week 65, WAINUA vs. External Placebo* through Week 65 (NEURO-TTRansform Study) (full analysis set)



* External placebo group from another randomised controlled trial (NEURO-TTR).

** Treatment difference presents results from formal Week 35 interim analysis. Only data up to Week 35 are included in the Week 35 interim analysis.

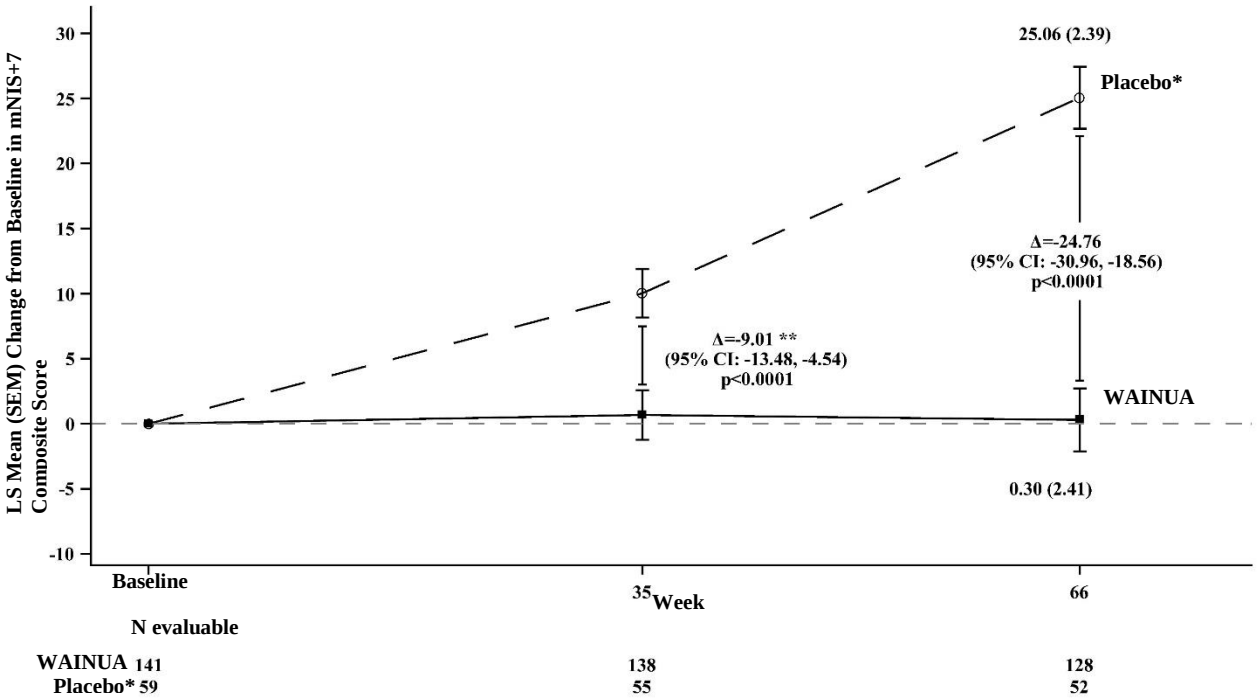
Based on MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the base-line-by-time interaction.

Analysis based on data collected up to 28 days after last dose of study treatment. Data up to Week 65 are included. Placebo was assessed at Baseline, Weeks 5, 8, 13 23, 35, 47, 59 and 65, WAINUA assessed at Baseline, Weeks 5, 9, 13, 25, 35, 49, 57 and 65.

The Week 35 and Week 65 LS Mean treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.

CI = Confidence Interval; LSM = Least squares mean; SEM = standard error of mean, MMRM = Mixed effects model with repeated measures; TTR = Transthyretin.

Figure 3 LSM Change in mNIS+7 Composite Score from Baseline (NEURO-TTRansform Study) (full analysis set)



* External placebo group from another randomised controlled trial (NEURO-TTR).

** Treatment difference presents results from formal Week 35 interim analysis. Based on MI ANCOVA adjusted by propensity score weights with fixed categorical effects for treatment, disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline. Only data up to Week 35 are included in the Week 35 interim analysis.

Week 66 analysis based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time interaction.

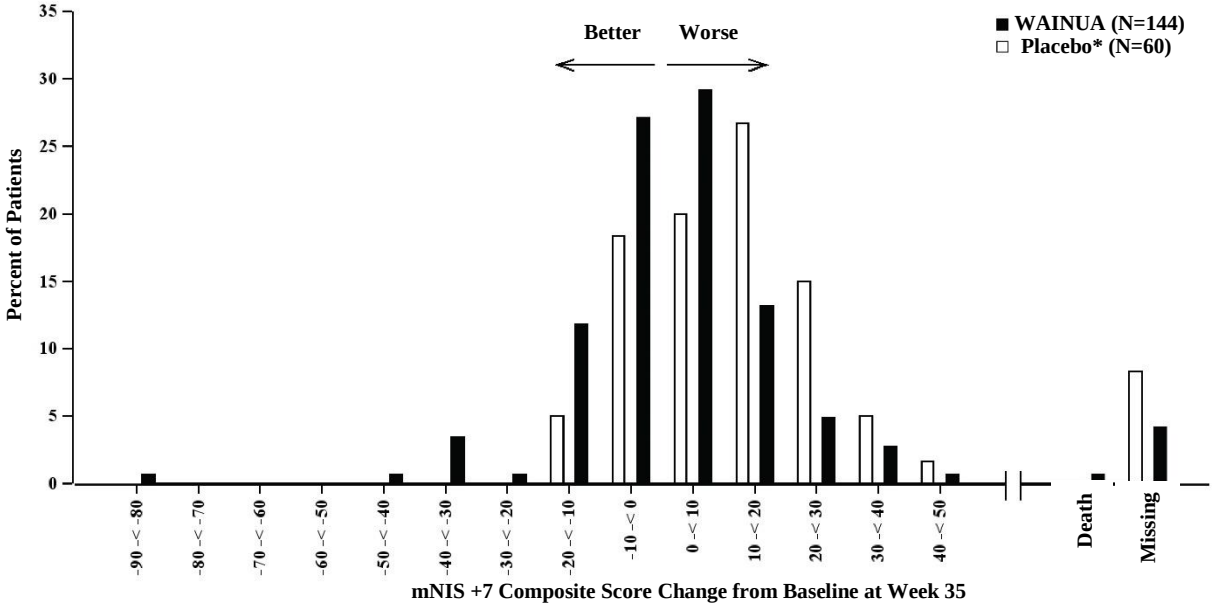
Analysis based on data collected up to 52 days after last dose of study treatment. Data up to Week 66 are included.

The Week 35 and Week 66 LS Mean treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.

CI = Confidence interval; LS Mean = Least squares mean; SEM = standard error of mean, MI ANCOVA = Multiple imputation Analysis of covariance; MMRM = Mixed effects model with repeated measures.

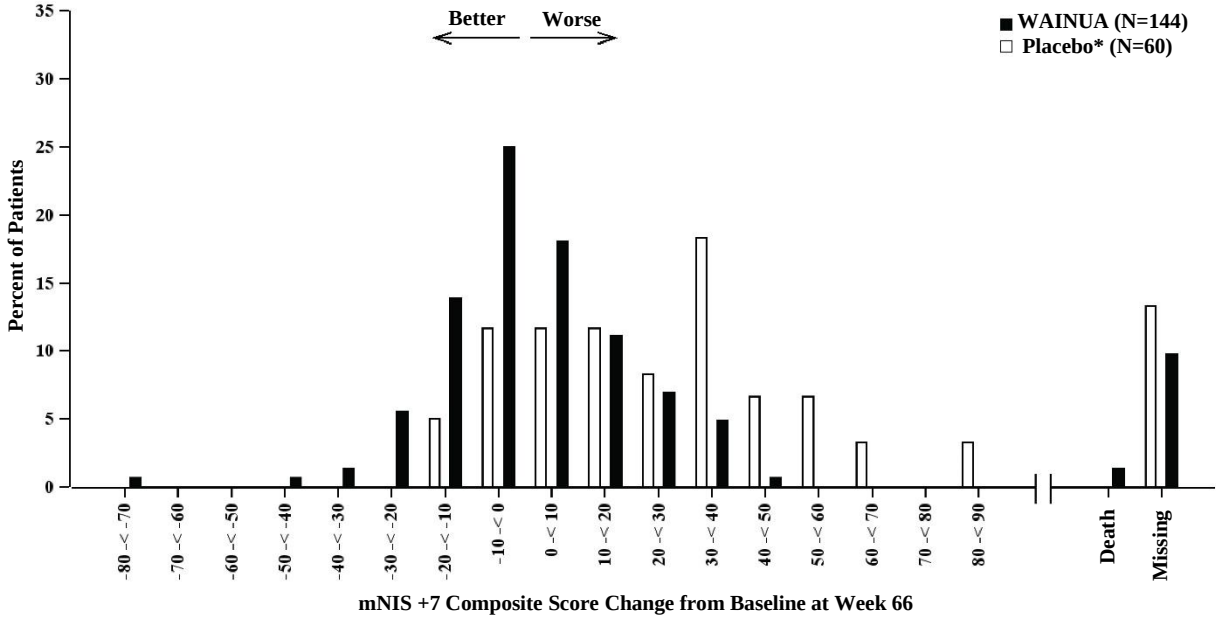
Figure 4 Histogram of mNIS+7 Composite Score Change from Baseline (NEURO-TTRansform Study) (safety analysis set)

a) at Week 35



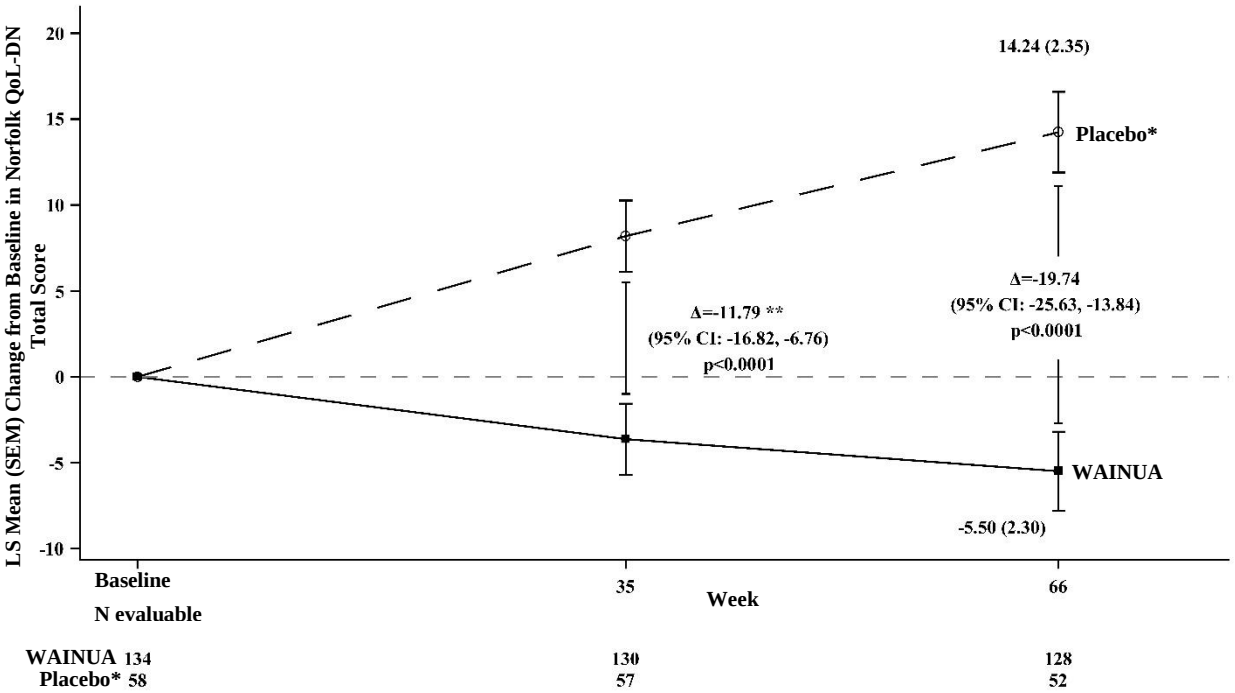
* External placebo group from another randomised controlled trial (NEURO-TTR).

b) at Week 66



* External placebo group from another randomised controlled trial (NEURO-TTR).

Figure 5 LSM Change in Norfolk QoL-DN Total Score from Baseline (NEURO-TTRansform Study)



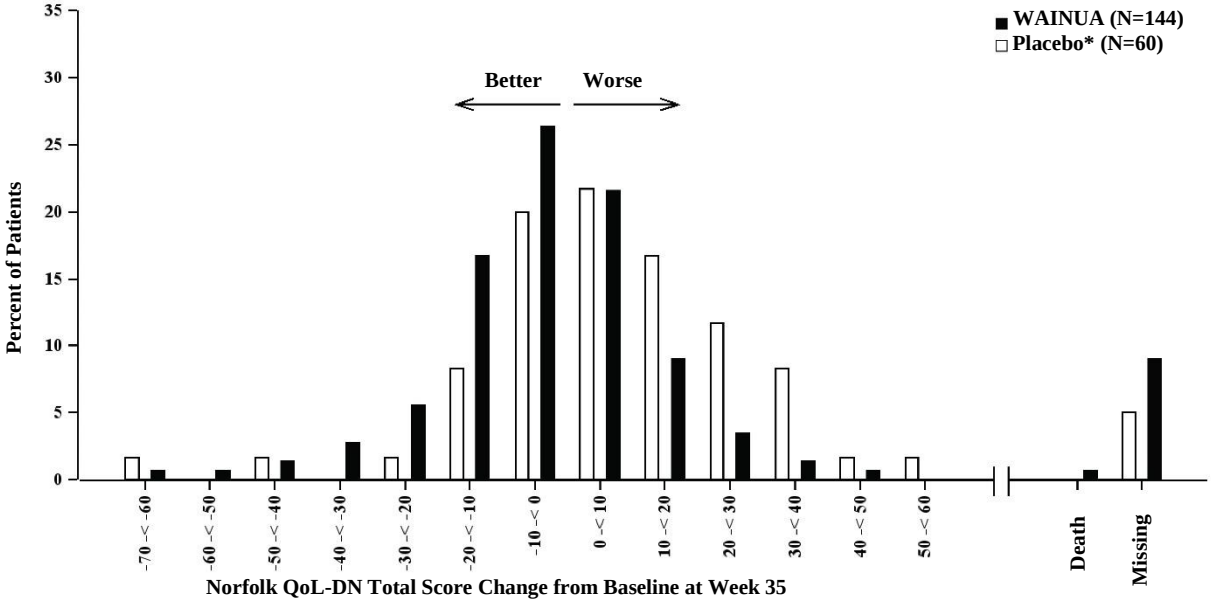
* External placebo group from another randomised controlled trial (NEURO-TTR).

** Treatment difference presents results from formal Week 35 interim analysis. Based on MI ANCOVA adjusted by propensity score weights with fixed categorical effects for treatment, disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline. Only data up to Week 35 are included in the Week 35 interim analysis.

Week 66 analysis based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time interaction.
Analysis based on data collected up to 52 days after last dose of study treatment. Data up to Week 66 are included.
The Week 35 and Week 66 LS Mean treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.
CI = Confidence interval; LS Mean = Least squares mean; SEM = standard error of mean, MI ANCOVA = Multiple imputation Analysis of covariance; MMRM = Mixed effects model with repeated measures.

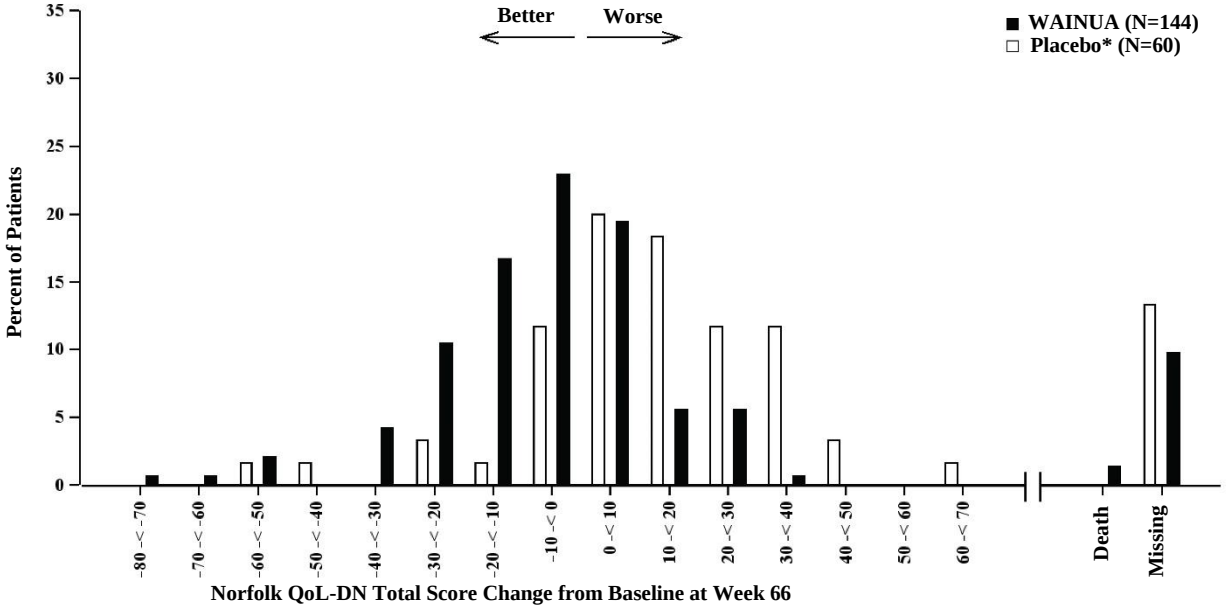
Figure 6 Histogram of Norfolk QoL-DN Total Score Change from Baseline (NEURO-TTRansform Study) (safety analysis set)

a) at Week 35



* External placebo group from another randomised controlled trial (NEURO-TTR).

b) at Week 66

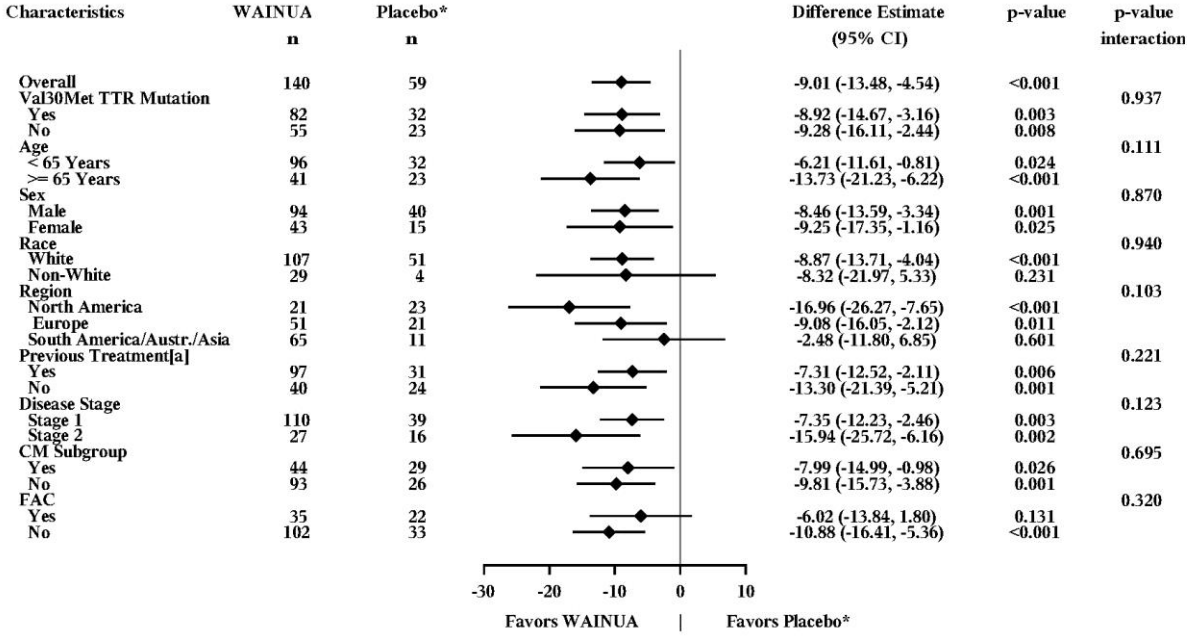


* External placebo group from another randomised controlled trial (NEURO-TTR).

At both Week 35 and Week 65/66, patients receiving WAINUA experienced similar improvements relative to placebo in the reduction of serum TTR concentration, mNIS+7 composite and Norfolk QoL-DN total scores across all subgroups including age, sex, race, region, Val30Met mutation status, cardiomyopathy status, FAC diagnosis at baseline, and disease stage (Figures 1a and b, 7a and b and 8a and b).

Figure 7 Forest Plot of Treatment Difference in LSM for Change from Baseline in mNIS+7 Composite Score for Key Subgroups (NEURO-TTRansform Study) (full analysis set)

a) at Week 35



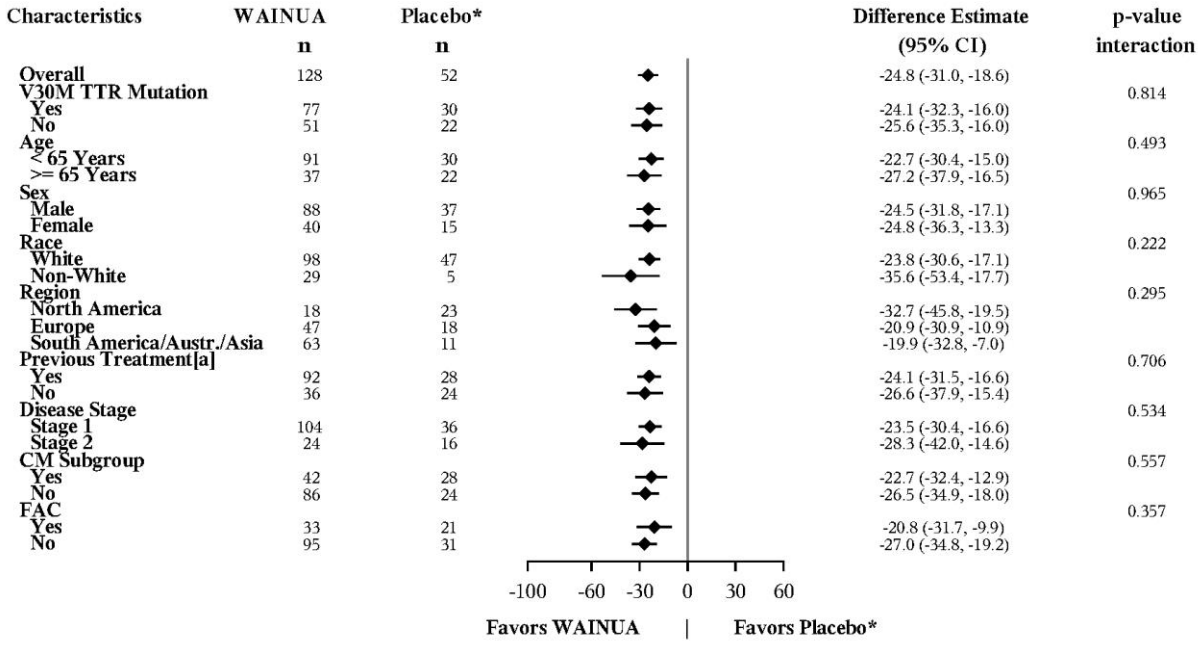
* External placebo group from another randomised controlled trial (NEURO-TTR).

[a] Previously treated with tafamidis or diflunisal.

CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].

Difference in LS means, confidence intervals, and p-values are based on an ANCOVA model adjusted by propensity score with the effects of treatment, subgroup factors, disease stage, Val30Met mutation, previous treatment, treatment-by-subgroup interaction, and the Baseline value. Data up to Week 35 are included in the Week 35 analysis.

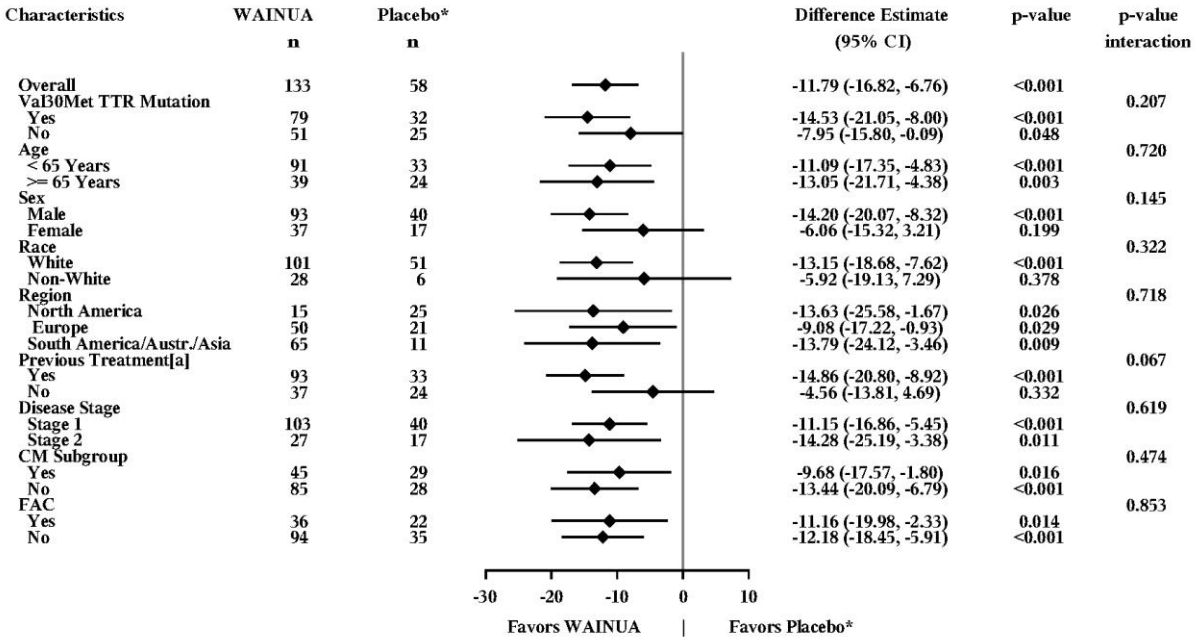
b) at Week 66



* External placebo group from another randomised controlled trial (NEURO-TTR).
[a] Previously treated with tafamidis or diflunisal.
Based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time-interaction.
Subgroup models also included treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions. Data up to Week 66 are included.
CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].
The Week 66 LSM treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.
CI = Confidence interval; LSM = Least squares mean; MMRM = Mixed effects model with repeated measures, CM = cardiomyopathy, FAC = familial amyloid cardiomyopathy.

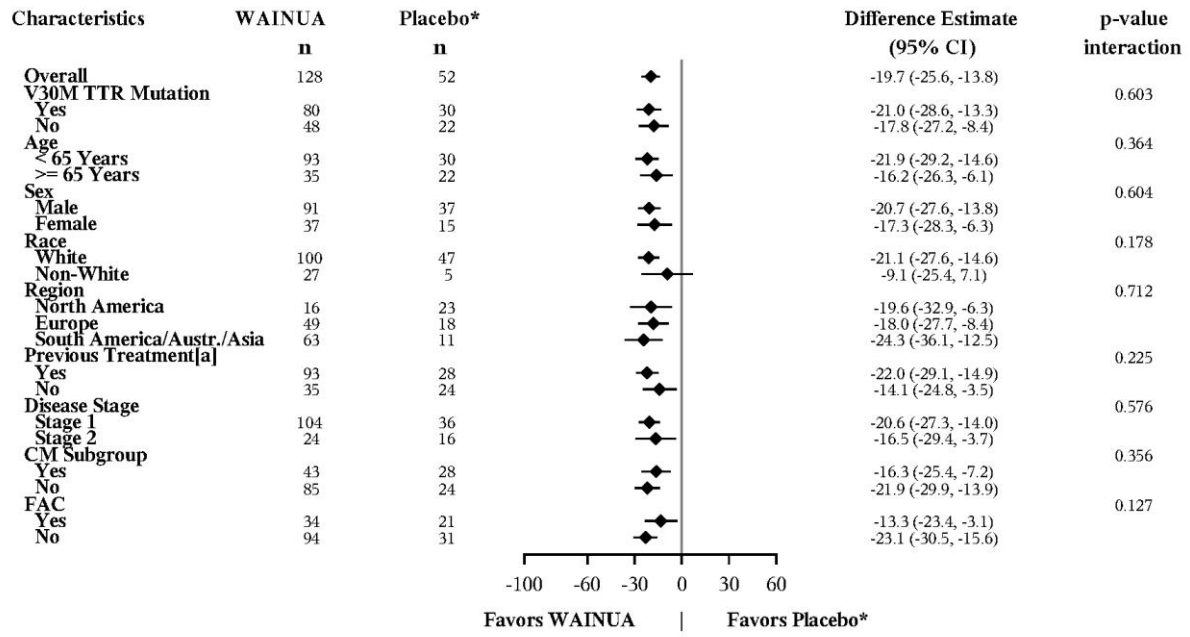
Figure 8 Forest Plot of Treatment Difference in LSM for Change from Baseline in Norfolk QoL-DN Total Score for Key Subgroups (NEURO-TTRansform Study) (full analysis set)

a) at Week 35



* External placebo group from another randomised controlled trial (NEURO-TTR).
[a] Previously treated with tafamidis or diflunisal.
CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].
Difference in LS means, confidence intervals, and p-values are based on an ANCOVA model adjusted by propensity score with the effects of treatment, subgroup factors, disease stage, Val30Met mutation, previous treatment, treatment-by-subgroup interaction, and the Baseline value. Only data up to Week 35 are included in the Week 35 interim analysis.

b) at Week 66



* External placebo group from another randomised controlled trial (NEURO-TTR).
[a] Previously treated with tafamidis or diflunisal.
Based on MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time-interaction.
Subgroup models also included treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions. Data up to Week 66 are included.
CM subgroup includes patients with either diagnosis of FAC at study entry or baseline IV septum wall thickness ≥ 13 mm with no hypertension [history or diagnosis during the study].
The Week 66 LSM treatment difference (WAINUA – Placebo) with 95% CI (unadjusted) are presented.
CI = Confidence interval; LSM = Least squares mean; MMRM = Mixed effects model with repeated measures, CM = cardiomyopathy, FAC = familial amyloid cardiomyopathy.

In an exploratory analysis of cardiac assessments with serial echocardiograms, WAINUA demonstrated improvement in E/e' ratio (a measure of left ventricular diastolic function) after 65 weeks of treatment in the cardiomyopathy subgroup (adjusted placebo-controlled LS mean difference: -3.94 [95% CI -6.46, -1.42]). Directional changes toward benefit of WAINUA over placebo at week 66 were also observed for pre-specified exploratory cardiac endpoints of mean LV wall thickness (LSM difference -0.04 cm, [95% CI -0.12, 0.04]), interventricular septal wall thickness (LSM difference -0.05 cm, [95% CI -0.16, 0.06]), and NT-proBNP, a prognostic biomarker of cardiac dysfunction, (geometric LSM 0.88, [95% CI 0.68, 1.14]). Despite these observed values a clinical benefit in cardiomyopathy is yet to be confirmed.

Week 85 (end of treatment analysis)

Week 85 data are not available for the external placebo group as the treatment period in NEURO-TTR study was only 66 weeks.

The observed effect in the WAINUA treated group in mNIS+7 composite score was consistent and sustained through the end of treatment at Week 85. The mean (SD) change from baseline

in mNIS+7 composite score was -0.04 (16.2) at Week 35, -0.21 (17.6) at Week 66 and -2.9 (20.5) at Week 85. The mean Norfolk QoL-DN total score remained stable through Week 85. In the eplontersen group the mean (SD) change from baseline in Norfolk QoL-DN total score was -4.8 (16.5) at Week 35, -7.2 (18.5) at Week 66 and -6.2 (18.0) at Week 85.

NSC, PND and mBMI remained stable through Week 85, while SF-36 continued to show trend towards improvement.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) properties of WAINUA were evaluated following subcutaneous administration of single and multiple doses (once every 4 weeks) in healthy subjects and multiple doses (once every 4 weeks) in patients with ATTRv-PN.

Absorption

Following subcutaneous administration, eplontersen is absorbed rapidly into systemic circulation with the time to maximum plasma concentrations of approximately 2 hours, based on population estimates.

Distribution

Based on animal studies (mouse, rat, and monkey), eplontersen distributes primarily to the liver and kidney cortex after subcutaneous dosing. Eplontersen is highly bound to human plasma proteins (>98%). The population estimates for the apparent central volume of distribution is 12.9 L and the apparent peripheral volume of distribution is 11,100 L.

Biotransformation

Eplontersen is metabolised by endo- and exonucleases to short oligonucleotide fragments of varying sizes within the liver. There were no major circulating metabolites in humans. Oligonucleotide therapeutics, including eplontersen, are not typically metabolised by CYP enzymes.

Elimination

Eplontersen is primarily eliminated by metabolism followed by renal excretion of the short oligonucleotide metabolites. The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose within 24 hours. The terminal elimination half-life is approximately 3 weeks based on population estimates.

Linearity/non-linearity

Eplontersen Cmax and AUC showed a slightly greater than dose-proportional increase following single subcutaneous doses ranging from 45 to 120 mg (i.e., 1 to 2.7 times the recommended dose) in healthy volunteers.

Population estimates of steady state maximum concentrations (Cmax), trough concentrations (Ctrough), and area under the curve (AUCτ) were 0.218 µg/mL, 0.000200 µg/mL, and 1.95 µg h/mL, respectively, following 45 mg once every 4 weeks dosing in patients with ATTRv-PN. No accumulation of eplontersen Cmax and AUC was observed in plasma after repeated dosing (once every 4 weeks). Accumulation was observed in Ctrough, and steady-state is reached after approximately 17 weeks.

Special populations

Based on the population pharmacokinetic and pharmacodynamic analysis, body weight, sex, race, and Val30Met mutation status have no clinically meaningful effect on eplontersen exposure or serum TTR reductions at steady-state. Definitive assessments were limited in some cases as covariates were limited by the overall low numbers.

Elderly population

No overall differences in pharmacokinetics were observed between adult and elderly (≥65 years of age) patients.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on eplontersen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on mild and moderate renal impairment (eGFR≥45 to <90 mL/min). Eplontersen has not been studied in patients with severe renal impairment or in patients with end-stage renal disease.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on eplontersen. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST). Eplontersen has not been studied in patients with moderate or severe hepatic impairment or in patients with prior liver transplant.

Drug-Drug Interaction

No formal clinical drug interaction studies have been conducted. *In vitro* studies indicate that eplontersen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound drugs, and is not an inhibitor or inducer of CYP enzymes. Oligonucleotide therapeutics, including eplontersen, are not typically substrates of CYP enzymes. Therefore, eplontersen is not expected to cause or be affected by drug-drug interactions mediated through drug transporters, plasma protein binding or CYP enzymes.

5.3 Preclinical safety data

Non-clinical/Repeat-dose toxicity

Repeated administration of eplontersen or rodent specific surrogate produced reduction in hepatic TTR mRNA levels (up to ~62% and 82% reductions in monkeys and mice, respectively), with subsequent decreases in TTR plasma protein levels (up to 70% reduction in monkeys). There were no toxicologically relevant findings related to this pharmacologic inhibition of TTR expression.

Most of the findings observed after repeated dosing for up to 6 months in mice and 9 months in monkeys were related to the uptake and accumulation of eplontersen and were not considered adverse. Microscopic findings related to uptake of eplontersen was observed by various cell types in multiple organs of all tested animal species including monocytes/macrophages, kidney

proximal tubular epithelia, Kupffer cells of the liver, and histiocytic cell infiltrates in lymph nodes and injection sites.
Severely decreased platelet counts associated with spontaneous haemorrhage were observed in a sub-chronic toxicity study in one monkey at the highest dose tested (24 mg/kg/week). Similar findings were not observed in monkeys dosed at a mid-dose of 6 mg/kg/week which is 73-fold the human AUC at the recommended therapeutic eplontersen dose.

Mutagenicity and carcinogenicity

Eplontersen did not exhibit genotoxic potential *in vitro* and *in vivo* and was not carcinogenic in ras.H2 transgenic mice.

Eplontersen was negative for genotoxicity in *in vitro* (bacterial mutagenicity, chromosomal aberration in Chinese hamster lung) and *in vivo* (mouse bone marrow micronucleus) assays.

In a subcutaneous carcinogenicity study in ras.H2 transgenic mice, eplontersen was administered for 26 weeks at doses of 250, 500, and 1500 mg/kg/month. There was no evidence of carcinogenicity for eplontersen following 26 weeks of treatment in mice.

Reproductive toxicity

Embryofoetal/Developmental toxicity/Fertility

Eplontersen had no effects on fertility or embryo-foetal development in the mouse up to 38-fold to the recommended human monthly dose of 45 mg. Eplontersen is not pharmacologically active in mice. However, no effect on fertility or embryo-foetal development was noted with a mouse-specific analogue of eplontersen in mice, which was associated with >90% inhibition of TTR mRNA expression.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate anhydrous
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

6.3 Shelf-life

Please refer to expiry date on the outer carton.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

WAINUA may be stored in original carton unrefrigerated for up to 6 weeks below 30°C. If not used within 6 weeks, it should be discarded.

Store in the original package in order to protect from light.

Do not freeze. Do not expose to heat.

6.5 Nature and contents of container

0.8 mL sterile solution in a single-use, type I glass syringe with a staked 27-gauge ½ inch (12.7 mm) stainless steel needle, rigid needle shield, and siliconised chlorobutyl elastomer stopper in an autoinjector.

Pack size of 1 pre-filled autoinjector.

6.6 Instructions for use, handling and disposal

WAINUA should be inspected visually prior to administration. The solution should be clear and colourless to yellow. Do not use WAINUA if the solution is cloudy, contains visible particulate matter or discoloured.

Single-use pre-filled autoinjector should be discarded in a puncture-resistant sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

AstraZeneca AB

SE-151 85 Södertälje

Sweden

Date of revision of text

August 2025

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