SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Wainzua 45 mg solution for injection in pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 56 mg eplontersen (as eplontersen sodium).
Each pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 ml solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless to yellow solution (pH 6.9 to 7.9, osmolality 250 to 330 mOsm/kg).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv amyloidosis) in adult patients with Stage 1 and 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 Wainzua is 45 mg administered by subcutaneous injection. Doses should be administered monthly.

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

Missed dose

If a dose of Wainzua 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

Elderly population

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

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). Eplontersen has not been studied in patients with eGFR <45 ml/min/1.73 m^2 or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment. Eplontersen has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Patients undergoing liver transplant

Wainzua has not been studied in patients undergoing liver transplant.

Paediatric population

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

Method of administration

Wainzua is for subcutaneous use only. Wainzua is a pre-filled pen for self-administration, ready to use and for single-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 Wainzua.

The pre-filled pen 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 Wainzua in the abdomen or upper thigh region. If a caregiver administers the injection, the back of the upper arm can also be used.

Wainzua should not be injected into skin that is bruised, tender, red, or hard, into scars or damaged skin, the area around the navel should be avoided.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Vitamin A deficiency

Based on the mechanism of action, Wainzua is expected to reduce serum vitamin A (retinol) below normal levels (see section 5.1). Serum vitamin A levels below the lower limit of normal should be corrected and any symptoms or signs related to vitamin A deficiency should be evaluated prior to initiation of treatment with Wainzua.

Patients receiving Wainzua 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.

During the first 60 days of pregnancy, both too high and too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should be excluded before treatment initiation and women of childbearing potential should practise effective contraception (see section 4.6). If a woman intends to become pregnant, Wainzua and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored. Before conception is attempted, vitamin A should have returned to normal levels.

In the event of an unplanned pregnancy, Wainzua should be discontinued. Due to the long half-life of eplontersen (see section 5.2), a vitamin A deficit may even develop after cessation of treatment. No recommendation can be given whether to continue or discontinue vitamin A supplementation during the first trimester of an unplanned pregnancy. If vitamin A supplementation is continued, the daily dose should not exceed 3 000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 2 500 IU to 3 000 IU per day should be resumed in the second and third trimester if serum vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

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 Wainzua. However, increasing vitamin A supplementation to above 3 000 IU per day 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.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose of 0.8 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug-drug interaction studies have been performed. *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.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Wainzua 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 Wainzua therapy and women of child-bearing potential should practice effective contraception.

If a woman intends to become pregnant, Wainzua and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and have returned to normal before conception is attempted (see section 4.4). Due to the long half-life of eplontersen (see section 5.2), a vitamin A deficit may develop even after cessation of treatment.

Pregnancy

There are no data regarding the use of Wainzua in pregnant women. Animal studies did not indicate reproductive toxicity (see section 5.3). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Wainzua should not be used during pregnancy. In case of pregnancy, 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 its 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 Wainzua 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. No impact on male or female fertility was detected in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety data described below reflects exposure to Wainzua in 144 patients with polyneuropathy caused by ATTRv (ATTRv-PN) randomised to eplontersen and who received at least one dose of eplontersen. 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 eplontersen observed in ≥5% of patients were vitamin A decreased, injection site reactions, vomiting and proteinuria.

Tabulated list of adverse reactions

Adverse reactions 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 reported for Wainzua

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Vomiting	Common
General disorders and administration site conditions	Injection site reactions [a]	Common
Investigations	Vitamin A decreased	Very Common
Renal and urinary disorders	Proteinuria	Common
Eye disorders	Cataracts	Common

a. Injection site erythema, injection site pain, injection site pruritus

Description of selected adverse reaction

Vitamin A decreased

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

Injection site reactions

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

Immunogenicity

In the clinical study in patients with ATTRv-PN, after an 84-week treatment period (median treatment duration of 561 days (80 weeks), range: 57 to 582 days), 58 patients (40.3%) developed treatment-emergent anti-drug antibodies (ADAs). The presence of ADAs did not affect eplontersen plasma Cmax or AUC, but increased Ctrough. In the patients who tested positive for anti-eplontersen antibodies, there was no clinically meaningful impact on the efficacy, safety, pharmacokinetics, or pharmacodynamics of eplontersen.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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 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.

Pharmacodynamic effects

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 was observed regardless of sex, race, age, region, body weight, cardiomyopathy status, previous treatment, Val30Met mutation status, disease stage, and familial amyloid cardiomyopathy clinical diagnosis at baseline.

TTR is a carrier protein for retinol binding protein 4, 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.

Clinical efficacy and safety

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

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

The characteristics of the Wainzua and external placebo groups were generally similar, and potential imbalances in key baseline characteristics (Val30Met mutation status, disease stage, and previous treatment) were accounted for in the prespecified statistical analysis.

Of the 144 patients randomised to Wainzua, the median patient age at baseline was 51.5 years (range 24 to 82), 44 (30.6%) were ≥65 years old (36 patients were 65 to 74 years old and 8 patients were ≥75 years), and 69.4% of patients were male. Twenty (20) different TTR variants were represented: Val30Met (59.0%), Glu89Gln (0.7%), Leu58His (2.8%), Phe64Leu (3.5%), Ser50Arg (1.4%), Ser77Tyr (2.1%), Thr49Ala (0.7%), Thr60Ala (2.8%), Val122Ile (2.8%), and Other (24.3%, includes Ala97Ser). At baseline, 79.9% of patients had stage 1 disease (unimpaired ambulation; mild sensory, motor, and autonomic neuropathy in the lower limbs), and 20.1% had stage 2 disease (assistance with ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk), and there were no patients with stage 3 disease. 69.4% of patients had prior treatment with either tafamidis or diflunisal. Of 39 (27.1%) of patients who had diagnosis of TTR cardiomyopathy at study entry, 41% of patients were classified as the New York Heart Association (NYHA) class I and 59% were NYHA class II.

At Week 35 interim analysis the primary efficacy endpoints were the change from baseline in serum transthyretin (TTR) concentration and in the modified Neuropathy Impairment Score + 7 (mNIS+7) composite score, and the key secondary endpoint was the change from baseline in the Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) questionnaire total score. In Week 66 analysis the co-primary endpoints included percent change from baseline in serum TTR concentration at Week 65, change from baseline in mNIS+7 score and change from baseline in Norfolk QoL-DN total score at Week 66, all when eplontersen was compared to placebo.

The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified +7 composite scores. In the version of the mNIS+7 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 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 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 that was used in the trial had a range from -4 to 136 points, with higher scores representing greater impairment.

Other secondary endpoints were formally tested hierarchically at Week 66 analysis and included change from baseline in neuropathy symptoms and change score, in the physical component summary score of short form 36-item health survey (version 2), in polyneuropathy disability score and in nutritional status (modified body mass index).

Treatment with Wainzua in NEURO-TTRansform study demonstrated statistically significant improvements in all endpoints at both Week 35 and Week 66 (see Table 2 and Figures 1-3) compared to the external placebo group (all $p < 0.0001$).

Table 2: Summary of clinical efficacy results from NEURO-TTRansform Study (full analysis set)

Analysis/Endpoint	Baseline, Mean (SD)		LSM Change/Percent Change from Baseline, (SE) [95% CI]		Wainzua - Placebo* Difference in LSM [95% CI]	p-value
	External Placebo*	Wainzua	Placebo*	Wainzua		
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 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
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
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
Neuropathy symptom and change score change from baseline at Week 66			8.2 [6.24, 10.12]	-0.0 [-1.92, 1.86]	-8.2 [-10.65, -5.76]	p < 0.0001
Physical component score of short form 36 item health survey change from baseline at Week 65			-4.46 [-6.139, -2.770]	0.85 [-0.711, 2.412]	5.31 [3.195, 7.416]	p < 0.0001
Modified body mass index change from baseline at Week 65			-90.8 [-112.84, -68.69]	-8.1 [-28.55, 12.42]	82.7 [54.64, 110.76]	p < 0.0001

* 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.

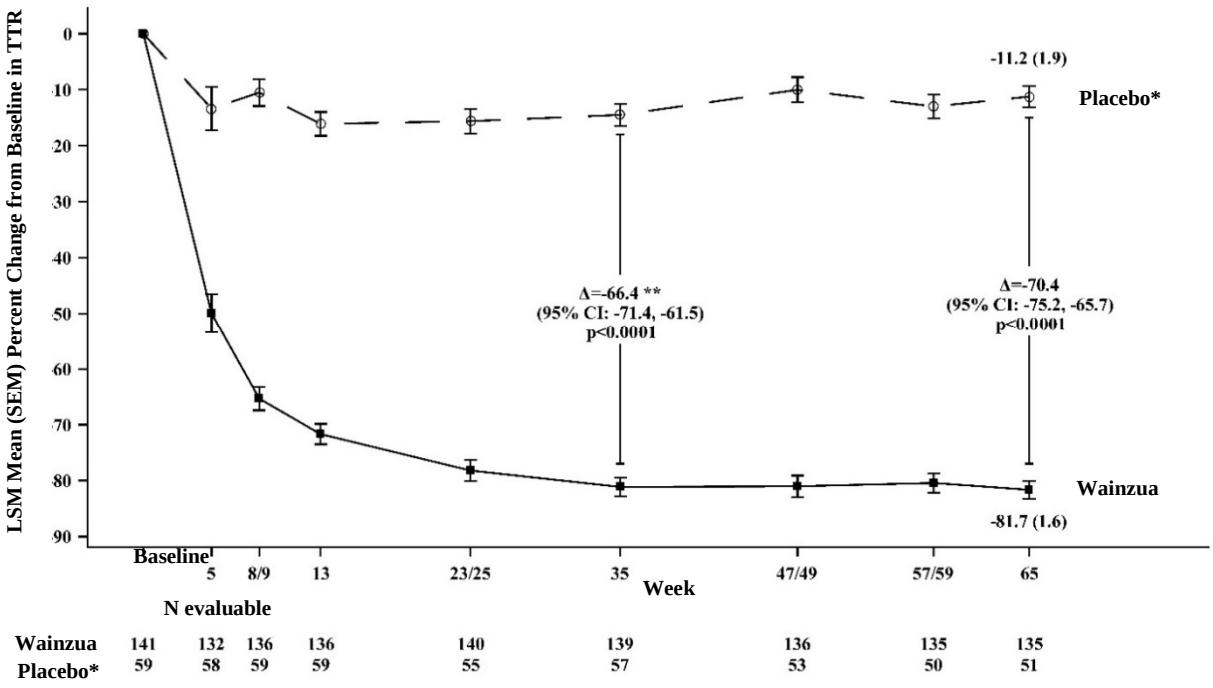
[2] Based on an ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, Val30M mutation, previous treatment, and the baseline value. Only data up to Week 35 are included in the interim analysis.

[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.

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 patients at Week 35 and 141 patients at Week 66. One patient 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.

The secondary endpoint of change from baseline in PND score at Week 65 was statistically significant in favor of eplontersen (p=0.02). More patients in the eplontersen group experienced improvement from baseline in PND score than in the external placebo group (5.7% vs 3.4%) and fewer patients in the eplontersen group experienced a worsening from baseline than in the external placebo group (12.8% vs. 22.0%).

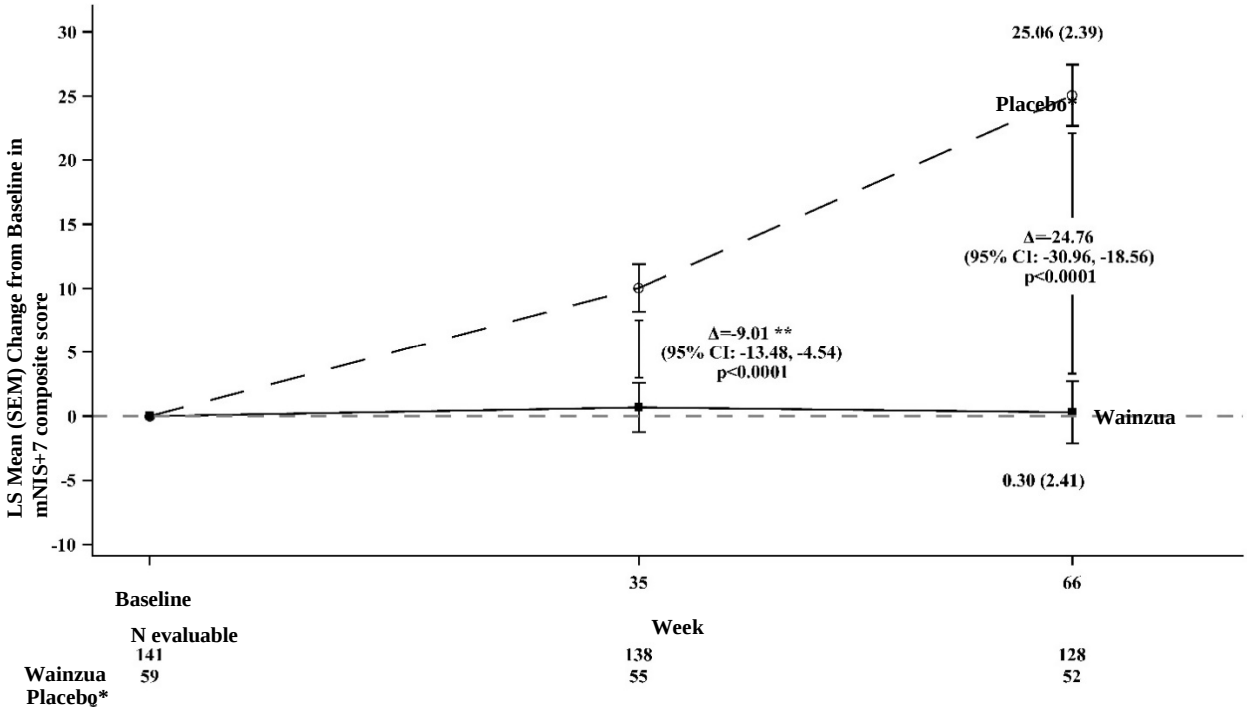
Figure 1: LSM percent change in serum TTR concentration from baseline to Week 65, Wainzua vs. placebo* through Week 65 (NEURO-TTRansform study) (full analysis set)



* 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, disease stage, Val30Met mutation, previous treatment, 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. Wainzua was assessed at baseline, Weeks 5, 9, 13, 25, 35, 49, 57 and 65.
The Week 35 and Week 65 LS mean treatment difference (Wainzua - 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.

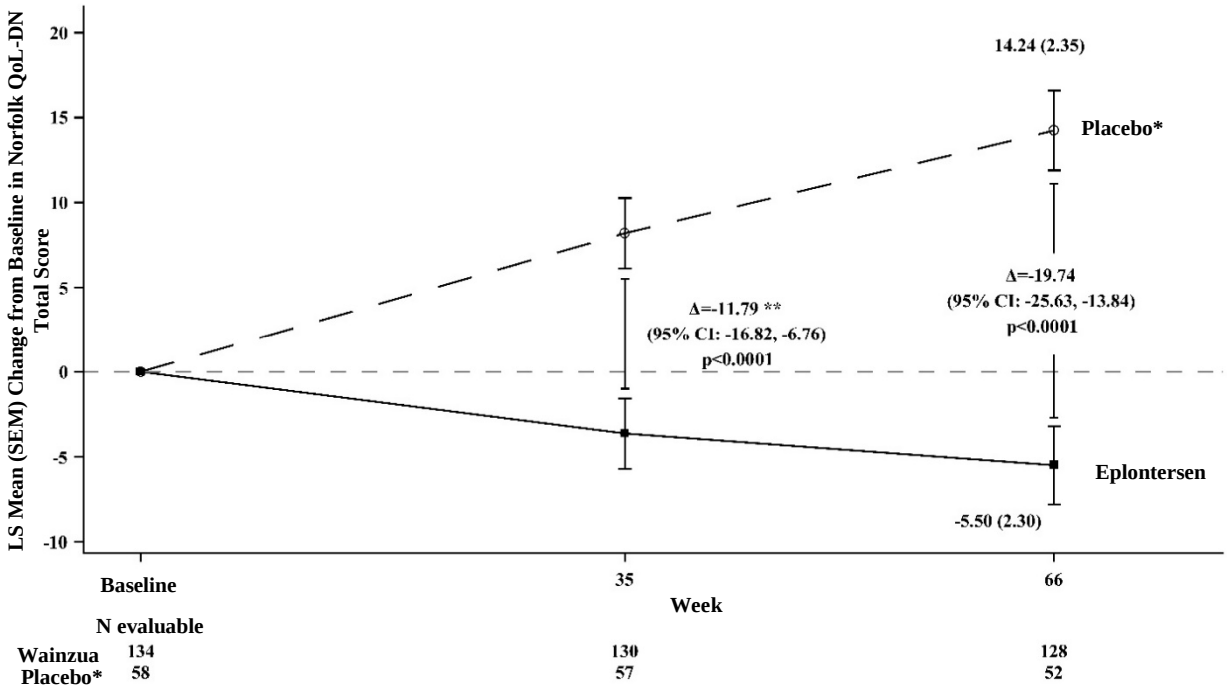
Figure 2: Change from baseline in mNIS+7 composite score (comparison of wainzua treatment in NEURO-TTRansform study to a placebo control*)



* 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 65 LS Mean treatment difference (WAINZUA – 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 3: Change from baseline in Norfolk QoL-DN total score (comparison of Wainzua treatment in NEURO-TTRansform study to a placebo control*)



* 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 65 LS Mean treatment difference (WAINZUA – Placebo) with 95% CI (unadjusted) are presented.
CI = confidence interval; LS mean = least squares mean; MI ANCOVA = multiple imputation analysis of covariance; MMRM = mixed effects model with repeated measures.

Patients receiving Wainzua experienced similar improvements relative to placebo in the reduction of serum TTR concentration, mNIS+7 composite and Norfolk QoL-DN

scores across all subgroups including age, sex, race, region, Val30Met mutation status, cardiomyopathy status, familial amyloid cardiomyopathy clinical diagnosis at baseline and disease stage.

In an exploratory analysis of cardiac assessments with serial echocardiograms, eplontersen 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 eplontersen 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.

Through the end of treatment with Wainzua at Week 85, reduction of TTR concentration and the observed effect in mNIS+7 composite score were sustained, and the mean Norfolk QoL-DN total score remained stable.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with eplontersen in all subsets of the paediatric population in ATTRv (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Wainzua were evaluated by measuring plasma concentrations of eplontersen 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 the systemic circulation with the time to maximum plasma concentrations of approximately 2 hours, based on population estimates. Population estimates of steady state maximum concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_{τ}) 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 C_{max} and AUC was observed in plasma after repeated dosing (once every 4 weeks). Accumulation was observed in C_{trough}, and steady-state was reached after approximately 17 weeks.

Distribution

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. Based on animal studies (mouse, rat, and monkey), eplontersen distributes primarily to the liver and kidney cortex after subcutaneous dosing.

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 C_{max} 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.

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 pharmacokinetics. 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.

5.3 Preclinical safety data

General toxicology

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.

Genotoxicity/Carcinogenicity

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

Reproductive toxicity

Eplontersen had no effects on fertility or embryo-foetal development in mice 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 medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Wainzua 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.

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 a pre-filled pen.

Pack size of one single-use pre-filled pen.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
1 Francis Crick Avenue
Cambridge
CB2 0AA
UK

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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