Date: 09.05.2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

WAINZUA

International non-proprietary name:	eplontersen
Pharmaceutical form:	solution for injection in pre-filled pen
Dosage strength(s):	Each pre-filled pen contains 45 mg
Route(s) of administration:	subcutaneous
Marketing authorisation holder:	AstraZeneca AG
Marketing authorisation no.:	69332
Decision and decision date:	approved on 14.02.2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for eplontersen in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a[decies] no. 2 TPA.
Orphan drug status was granted on 23 August 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with polyneuropathy.

2.2.2 Approved indication

Wainzua is indicated for the treatment of adult patients with stage 1 and 2 polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).

2.2.3 Requested dosage

Summary of the requested standard dosage:
45 mg

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20. October 2023
Formal control completed	3 November 2023
List of Questions (LoQ)	1 March 2024
Response to LoQ	25 June 2024
Preliminary decision	23 September 2024
Response to preliminary decision	18 November 2024
Final decision	14 February 2025
Decision	approval

3 Medical context

ATTRv is a rare, under-recognised, debilitating, rapidly progressive, irreversible, and fatal disease caused by autosomal dominant mutations in the gene that codes for TTR protein (Ando et al 2013, Benson et al 2018, Conceicao et al 2016, Gertz 2017, Gertz and Dispenzieri 2020). A mutated TTR gene results in an unstable TTR tetramer that dissociates into TTR monomers that are prone to aggregation into amyloid fibrils that deposit within multiple tissues.
ATTRv manifests predominantly as PN and/or CM phenotypes, with most patients having mixed phenotypes (Conceicao et al 2016, Finsterer et al 2019, Sekijima 2015). The worldwide prevalence of ATTRv-PN is estimated to be between 10,000 and 50,000 patients (Gertz 2017, Schmidt et al 2018). For patients with ATTRv-PN, the amyloid fibril deposits cause progressive peripheral sensorimotor and autonomic neuropathy (Conceicao et al 2016, Finsterer et al 2019, Sekijima 2015). Sensorimotor neuropathy leads to a loss of ambulatory function, and severe autonomic neuropathy impacts the cardiovascular, gastrointestinal, and genitourinary systems, resulting in declines in QoL (Aimo et al 2021, Sekijima 2015). Patients typically die due to malnutrition and cachexia, renal failure, and cardiac disease (Coelho et al 2008). Patients with ATTRv-PN have a median life expectancy of 5 to 15 years after diagnosis (Hawkins et al 2015). Thus, ATTRv-PN is both severely debilitating and life-threatening. The disease course can be classified into 3 stages based on ambulatory status (Coutinho et al 1980): Stage 1 does not require assistance with ambulation, Stage 2 requires assistance with ambulation, and Stage 3 is bedridden or wheelchair bound.
Current treatment options for ATTRv-PN in the EU and the US include the TTR-silencing agents TEGSEDI™ (inotersen), ONPATTRO™ (patisiran), and AMVUTTRA™ (vutrisiran). Inotersen is also approved in Canada. Patisiran is also approved in Canada and Japan. An additional drug, the TTR tetramer stabilising agent VYNDAQEL™/VYNDAMAX™ (tafamidis), is approved in the EU, Japan, and China for the treatment of patients with Stage 1 ATTRv-PN.

Approval status in Switzerland:
Inotersen: "*Tegsedi ist zur Behandlung von Polyneuropathie der Stadien 1 oder 2 bei erwachsenen Patienten mit hereditärer Transthyretin-Amyloidose (hATTR) indiziert.*"
Patisiran: "*Onpattro wird zur Behandlung der hereditären Transthyretin-Amyloidose (hATTR-Amyloidose) bei erwachsenen Patienten mit Polyneuropathie der Stadien 1 oder 2 angewendet.*"
Vutrisiran: "*Amvuttra wird zur Behandlung der hereditären Transthyretin-Amyloidose (hATTR-Amyloidose) bei erwachsenen Patienten mit Polyneuropathie der Stadien 1 oder 2 angewendet.*"
Tafamidis: "*Vyndaqel ist indiziert zur Behandlung der Transthyretin-Amyloidose bei erwachsenen Patienten mit Wildtyp- oder hereditärer Kardiomyopathie zur Verringerung der Gesamtmortalität und der kardiovaskulär bedingten Hospitalisierung.*"

Prior to the authorisation of these drugs, the only effective therapy for neuropathy related to ATTRv was orthotopic liver transplantation, which removes the main production site of the mutant TTR amyloidogenic protein. After the approval of these drugs, the role of liver transplantation in ATTR amyloidosis has been reduced significantly in the US, Canada, Europe, China, and Japan. Orthotopic liver transplantation, in general, will slow but not halt disease progression due to the continuous production and misfolding of wild-type TTR and, in some cases, accelerate heart disease (Liepnieks and Benson 2007, Liepnieks et al 2010, Yazaki et al 2000, Yazaki et al 2007). Therefore, to halt progression of the disease (i.e. to suppress both mutated TTR and wild-type TTR), TTR silencers could be a treatment option in post-liver transplant patients (Moshe-Lilie et al 2020).
In addition, off-label use of the NSAID diflunisal has been reported in patients with Stage 1 and Stage 2 disease (Adams et al 2016). However, the known cardiovascular and renal side effects associated with the NSAID class may limit the use of this drug in older patients with ATTRv-PN or severe renal impairment. Diflunisal is not approved in Switzerland.

4 Quality aspects

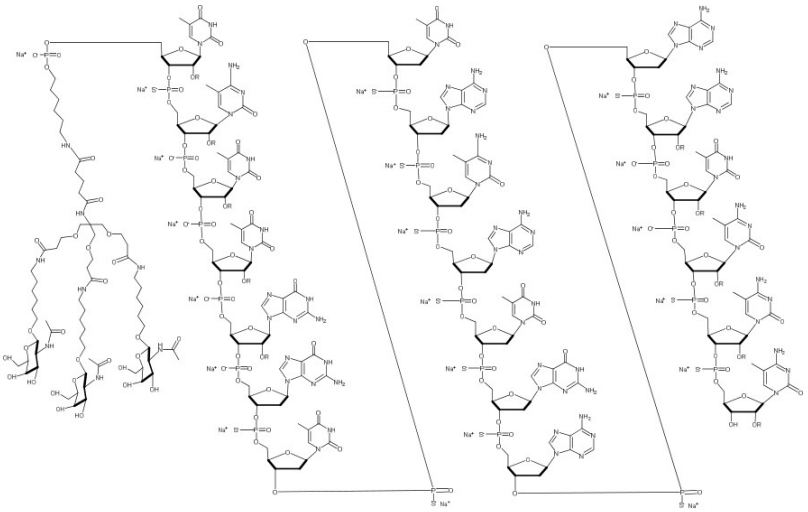
4.1 Drug substance

INN: Eplontersen
Molecular mass: Free-acid relative molecular mass: 8606.5
Sodiated relative molecular mass: 9046.1

Eplontersen drug substance is a synthetic antisense oligonucleotide with 20 base residues.

Molecular structure:

Figure 1 Structure of eplontersen sodium[a]



[a] R = $CH_2CH_2OCH_3$

Manufacture:
The drug substance is manufactured by solid-phase synthesis, using well defined and characterised starting materials. The synthesis and purification of the drug substance is described in sufficient detail, including a flow diagram, narrative of each step and appropriate in-process controls.

Specification and Analytical Procedures:
In order to ensure a consistent quality of eplontersen, the specifications include all relevant test parameters. Acceptance criteria are based on the results of toxicological studies, and release and stability studies on development and commercial batches. Detailed information on the analytical procedures and method validation reports have been provided. Impurities in the drug substance have been adequately discussed.

Container Closure System:
The bulk drug substance is packaged in HDPE bottles.

Stability:
Appropriate stability data have been presented. Based on the results, a satisfactory storage condition and retest period were established.

4.2 Drug product

Description and composition:
Eplontersen solution for injection, 45 mg, is a sterile, preservative-free, solution intended for subcutaneous (SC) administration. The formulation contains 56 mg/mL eplontersen (59 mg/mL eplontersen sodium) in 10 mM phosphate buffer, at pH 7.4. Sodium chloride is added to achieve an isotonic solution for SC administration. The solution appears clear and colourless to yellow.

Manufacture:
The drug product manufacturing process consists of dissolving the drug substance in appropriate buffer, sterile filtration, and aseptic filling into syringes, followed by autoinjector assembly and packaging. The manufacturing process is described in sufficient detail including a flow diagram and narrative of each step and is considered adequate. The process is sufficiently validated, and appropriate in-process controls are performed.

Specification and Analytical Procedures:
Release specifications have been defined based on the characteristics of the drug substance and the drug product, compendial requirements for the dosage form, and the results of the release and stability studies of development and commercial batches in order to ensure a consistent quality. The analytical methods used have been adequately described and appropriately validated.

Container Closure System:
Eplontersen solution for injection is filled into a sterile syringe, which is further assembled into an autoinjector for the final drug product presentation.

Stability:
The product is stable for the proposed shelf life and storage conditions, as demonstrated by the provided stability data.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated

5 Nonclinical aspects

5.1 Pharmacology

Eplontersen (Wainzua) consists of a mixed backbone with 20 nucleotides connected sequentially by phosphorothioate and phosphodiester linkages. The base sequence is identical to the already approved inotersen (Tegsedi), which solely consists of phosphorothioate linkages in the backbone. New to eplontersen is the fact that the 5′-end is covalently attached to triantennary N-acetyl galactosamine (GalNAc3) via a trishexylamino (THA)-C6 linker to form an antisense oligonucleotide (ASO) GalNAc conjugate. This conjugate interacts with the asialoglycoprotein receptor expressed on the surface of hepatocytes, thereby facilitating delivery to the hepatocytes and increasing the potency. Eplontersen binds to the 3′-untranslated region of the transthyretin (TTR) mRNA and inhibits expression of TTR protein. By decreasing the amount of liver-derived TTR in the plasma, eplontersen treatment is expected to result in decreased formation of TTR amyloid fibril deposits in organs and thus may slow disease progression.

In silico, *in vitro* and *in vivo* investigations have been conducted to characterise the primary pharmacology of eplontersen. For *in vivo* assessments, mice and non-human primates were used. The TTR mRNA target sequence in non-human primates is 100% identical to the human TTR target sequence. However, in mice the TTR target sequence differs by 8 bases as compared to the human TTR target sequence. Therefore, transgenic mice expressing the entire human genomic TTR transgene containing the Ile84Ser disease mutation were used.

Based on *in silico* analysis and analysis in human cells with inotersen, eplontersen is not predicted to target any other human gene, and its binding site is free of any reported mutation or SNP, suggesting that this ASO can be used to reduce TTR expression in the majority of patients. BLAST analysis revealed TCP11L1 as one potential liver target with a mismatch of 2 bases. No significant reduction of TCP11L1 mRNA by inotersen was measured in cells in culture at concentrations up to 8 µM. In addition, the thyroid cancer-associated transcript THCAT155 was identified by *in silico* analysis with a 2-base mismatch. This gene encodes a long non-coding RNA of unknown function and is expressed at low level in non-target tissues such as brain and testis. No risk has so far been associated with reduced THCAT155 expression.

In vitro analysis in human hepatocytes showed dose-dependent reductions of TTR mRNA and demonstrated that GalNAc3-conjugation dramatically increased the potency compared to unconjugated ASO by about 50-fold (IC_{50} = 0.06 µM vs. 3.01 µM, respectively).

In vivo studies included comparisons between eplontersen and inotersen in transgenic mice. Mice were subcutaneously (s.c.) injected with eplontersen (0.6, 2 and 6 mg/kg) or inotersen (6, 20 or 60 mg/kg). Liver TTR mRNA and plasma TTR protein levels were measured. After 3 weeks of treatment, eplontersen, demonstrated significantly improved inhibition of human TTR hepatic mRNA and plasma protein levels in human TTR transgenic mice (28-fold and 15-fold increases in potency, respectively), as compared to the unconjugated inotersen.

In non-human primates (cynomolgus monkeys), the pharmacodynamics was evaluated as part of the toxicology assessments with s.c. doses up to 24 mg/week in a 13-week study and up to 25 mg/kg/month in a 9-month study. Liver TTR mRNA expression and plasma TTR protein were dose-dependently reduced, by up to 62% and 70%, respectively. In addition, plasma retinol binding protein 4 (RBP4) protein levels were reduced, as TTR is a carrier protein for the retinol binding protein (RBP)-retinol complex. With a monthly s.c. treatment schedule, hepatic TTR mRNA and plasma TTR protein levels partially recovered, and plasma RBP4 protein levels returned to baseline by the end of a three-month recovery period.

No specific studies were submitted with respect to secondary pharmacodynamics and pharmacodynamic drug interactions. This can be accepted as the ASO is highly selective to its target

sequence and shows a very specific mode of action. No secondary off-target effects were noted in the toxicology studies. No plasma protein-binding displacement in vitro was observed between eplontersen and the highly plasma protein-bound drugs warfarin and ibuprofen. Eplontersen did not interfere with cytochrome P450 enzymes, drug or ion transporters.

Regarding safety pharmacology, eplontersen did not inhibit hERG currents *in vitro* up to the highest evaluated dose of 300 μM, and no cardiovascular, respiratory or neurobehavioural effects were noted in toxicology studies in monkeys.

5.2 Pharmacokinetics

The nonclinical pharmacokinetics (PK) of eplontersen was characterised in specific single-dose studies or in the context of the toxicology studies in mice, rats and monkeys. Single-dose PK studies included absorption, distribution, metabolism, and excretion (ADME) evaluations and mass balance and quantitative whole body autoradiography studies in rats. The tritium (3H) radiolabelled oligonucleotide and the THA-linker portion of the molecule were both evaluated. Validated bioanalytical methods used to characterise the PK of eplontersen in mouse and monkey toxicology studies included a quantitative hybridisation-based enzyme-linked immunosorbent assay (ELISA) for plasma and a high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method for tissues.

After a single s.c. dose of 2 mg/kg, eplontersen is rapidly absorbed (T_{max} in monkeys: 1 to 2 hours; T_{max} in rats: 0.5 to 1 hour). Eplontersen plasma levels declined in a biphasic manner with an initial distribution half-life of about 2 hours in rats and monkeys due to rapid tissue distribution and a second slow elimination half-life of about 2-4 weeks. Eplontersen is highly bound to plasma proteins (monkeys: > 98%; mice: > 97%). The plasma PK was unaltered by repeated dosing, and no accumulation of the drug product was noted. In monkeys, anti-drug antibodies (ADA) were measured in some animals. The plasma PK was not affected by ADAs.

In mice, rats and monkeys, eplontersen rapidly and dose-dependently distributes from the plasma compartment to tissues where it accumulates less than dose proportionally as an unconjugated moiety in liver and kidneys. No notable sex differences were observed with respect to liver distribution. In female mice, there was a trend of higher kidney exposure as compared to male animals, which was not confirmed in monkeys. Whole body radiography in rats following single s.c. injections of radioactively labelled eplontersen backbone showed highest mean concentrations of radioactivity in the liver and kidney at 24 hours post-dose with concentrations 250- and 1,000-fold, respectively, above the mean circulating concentration in plasma. Low non-quantifiable levels of radioactivity were detected in the brain and spinal cord. In monkeys, tissue concentrations decreased in a monophasic pattern with an elimination half-life in liver and kidneys of about 3 weeks. In a combined fertility and embryo-fetal study in mice, no measurable levels of eplontersen were detected in placenta or fetal livers.

Following a single s.c. administration of eplontersen, radioactively labelled in the THA-linker, also showed highest concentrations of radioactivity in the kidney and liver. In addition, high levels of radioactivity were observed in the small and large intestine walls, with peak concentrations 2 and 8 hours post-dose, respectively. Again, very little radioactivity was associated with the brain and spinal cord.

In tissues, the THA-linker of eplontersen is rapidly removed, and the eplontersen backbone is degraded by endo- and exonuclease. Several chain-shortened oligonucleotides and THA-linker-related metabolites were identified in liver and kidneys of mice, rats and monkeys. The excretion of eplontersen was studied in rats with radioactively labelled oligonucleotides or the THA-linker. The

eplontersen oligos were mainly excreted by the renal route (60%), and the THA-linker was mainly eliminated in faeces (80%).

5.3 Toxicology

The toxicology assessment included GLP-compatible repeated-dose studies in mice and monkeys, *in vitro* and *in vivo* genotoxicity studies, a carcinogenicity study in Tg.rasH2 transgenic mice and a reproductive and developmental study in mice. In addition, dose range-finding studies in mice and rats, an immunogenicity study in monkeys and an impurity qualification study in mice were performed.

In mice, 13- and 26-week GLP repeat-dose toxicity studies with weekly s.c. injections of up to 150 mg/kg of eplontersen and 13-week recovery periods showed primarily class effects of chemically modified oligonucleotides. These effects included the presence of basophilic granules in the renal tubular epithelium and accumulation of vacuolated/granular macrophages in the liver (hepatic Kupffer cells), injection sites, skin, testes, and epididymis. Vacuolated/granular macrophages were also noted sporadically at doses of ≥ 25 mg/kg/week in the choroid plexus of the brain, pituitary gland, heart, biceps femoris, tibiofemoral joint, gastrointestinal tract, lung, lymph nodes, and pancreas. These findings were of low severity, with no associated cellular degenerations or necrosis, and were considered non-adverse. Eplontersen-related microscopic findings were reduced (basophilic granules in hepatic Kupffer cells, renal tubular epithelial basophilic granules, vacuolated/ granular macrophages in the skin, injection sites, epididymal and testicular interstitium) or absent following the recovery period, and tissue concentrations of unconjugated eplontersen were below the limit of quantitation in all animals.

In cynomolgus monkeys, 13- and 39-week GLP repeat-dose toxicity studies were conducted with weekly (13-week study) and monthly s.c. injections (39-week study) of up to 25 mg/kg of eplontersen and 13-week recovery periods. In contrast to mice, eplontersen is pharmacologically active in monkeys. Microscopically, similar class effects of chemically modified oligonucleotides were noted in monkeys as in mice, and no abnormalities associated with TTR inhibition were observed. In one female animal treated with 24 mg/kg/week in the 13-week toxicity study, a severe thrombocytopenia developed, associated with spontaneous bleeding events. This event recovered following steroid treatment and skipping of several treatments. Based on this event, a no observed adverse effect level (NOAEL) of 6 mg/kg/week was considered (corresponding to 73-fold the predicted human AUC). Monkeys are sensitive to complement activation after treatment with oligonucleotides. At the highest dose levels, the complement split product Bb was acutely elevated. There were no alterations in haemodynamic parameters or ECG findings, and no change in total complement factor C3 was observed, suggesting that circulating complement components were not depleted with chronic administration of eplontersen. Therefore, the effect of the complement system was not considered adverse.

The genotoxic potential of eplontersen was assessed *in vitro* using an Ames test (up to 5,000 μg per plate) and a chromosome aberration assay in CHL cells (up to 500 μg/mL) and *in vivo* in a mouse bone marrow micronucleus assay following (2 SC doses up to 2,000 mg/kg). Eplontersen did not induce any genotoxic effects.

No 2-year rat carcinogenicity study was conducted with eplontersen, as the toxicity and TK profiles of inotersen and eplontersen are very similar and the *in vivo* carcinogenicity profile of inotersen has been characterised. In Tg.rasH2 transgenic mice, a 26-week carcinogenicity study was performed with monthly s.c. eplontersen doses up to 1,500 mg/kg. There was no evidence in the Tg.rasH2 mouse model of eplontersen-mediated tumorigenesis.

The assessment of reproductive and developmental toxicity for eplontersen was conducted in a segment I/II study in mice. Potential effects of eplontersen on fertility, pregnancy, and fetal development were evaluated using eplontersen and surrogate oligonucleotide coding for a mouse-specific ASO (ION-1184986) that reduced the mouse liver TTR mRNA levels by more than 90%.

No adverse effects of the ASO treatment were noted in this study, and the NOAEL was considered the highest dose (75 mg/kg/week), which corresponds to about a 38-fold safety margin (based on human equivalent dose) for a monthly treatment with 45 mg.

Eplontersen impurities were qualified in a 13-week toxicity study in mice with weekly s.c. dosing, comparing an eplontersen batch to 3 batches of eplontersen that had enriched impurity mixtures. Those impurities were enhanced levels of impurities such as dithioate, MOE amidite impurities and GalNAc impurities. There were no discernible histological differences or additional toxicities that could be attributed to any of the 3 impurity mixtures.

The immunogenicity of eplontersen was evaluated in monkeys following SC administration during a 9-month repeat-dose toxicity study with a 3-month recovery. The presence of ADA was generally associated with an increase in plasma trough concentrations, although no differences in Cmax, AUC0-48 or tissue exposure between ADA-negative and ADA-positive animals were noted, and there was no consistent effect on reduction of liver TTR mRNA or TTR protein in plasma.

5.4 Nonclinical conclusions

The base sequence of eplontersen is identical to that of the already approved inotersen. Based on *in silico*, *in vitro* and *in vivo* evaluations, no risk for adverse off-target interactions are expected. The GalNAc conjugate results in an efficient uptake in liver cells by the asialoglycoprotein receptor and strongly increases the potency as compared to inotersen. Clinical data did not suggest a need for vitamin A level monitoring as vitamin A supplementation is recommended in the label. The pharmacokinetic and toxicity assessments of eplontersen did not result in new unexpected risks as compared to inotersen. No thrombocytopenia event was observed in monkeys at the NOAEL of 6 mg/kg/week, which indicates an acceptable safety margin of 73-fold with respect to the predicted human exposure after a 45 mg dose of eplontersen. From the preclinical perspective, a positive benefit-risk ratio is expected, and the application can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

In study ION-682884-CS3 (NEURO-TTRansform), no accumulation in C_{max} or AUC_{0-6h} was observed following eplontersen 45 mg q4w SC dosing up to Week 66, consistent with the low observed C_{trough} in relation to the C_{max} and time-invariant plasma kinetics. Accumulation in C_{trough} was observed with eplontersen 45 mg q4w SC administration, and steady-state appeared to be reached by Day 169 based on C_{trough} in ADA-negative patients. Plasma exposure was lower (C_{max} > 30-fold lower and AUC_{0-6h} > 100-fold lower) following administration of a 45-mg q4w dose of eplontersen (free acid) compared 300 mg q1w SC inotersen sodium (284-mg free acid equivalent), irrespective of ADA status.
Eplontersen is a 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 bonds. The GalNAc conjugate enables the targeted delivery of the ASO into hepatocytes. The selective binding of eplontersen to the TTR messenger RNA (mRNA) in hepatocytes leads to the degradation of both mutant and (normal) wild-type TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in a significant reduction of mutant and wild-type TTR protein secreted by the liver into the circulation.
No clinical drug-drug interaction studies have been conducted. Considering that eplontersen is not a substrate/inducer/inhibitor for the classic cytochrome P450 metabolic pathways or transporters, and given the in vitro results of the lack of drug-drug interactions on the protein binding, eplontersen has a very low potential to have drug-drug interactions with other drugs via CYPs, transporters, or protein binding. Nevertheless, TTR is a carrier protein of retinol-binding protein 4 (RBP4), the main carrier of vitamin A (retinol). Therefore, it is expected that a reduction of plasma TTR would result in a decrease of plasma retinol levels below the lower limit of normal.

6.2 Dose finding and dose recommendation

In study ION-682884-CS3 (NEURO-TTRansform), no accumulation in C_{max} or AUC_{0-6h} was observed following eplontersen 45 mg q4w SC dosing up to Week 66, consistent with the low observed C_{trough} in relation to the C_{max} and time-invariant plasma kinetics. Accumulation in C_{trough} was observed with eplontersen 45 mg q4w SC administration and steady-state appeared to be reached by Day 169 based on C_{trough} in ADA-negative patients. Plasma exposure was lower (C_{max} > 30-fold lower and AUC_{0-6h} > 100-fold lower) following administration of a 45 mg q4w dose of eplontersen (free acid) compared to 300 mg q1w SC inotersen sodium (284-mg free acid equivalent), irrespective of ADA status.
A flat exposure-response relationship was observed for TTR and for mNIS+7 and Norfolk QoL-DN total scores, suggesting that sufficient exposure was reached to achieve clinically relevant responses in nearly all eplontersen-treated patients.
An eplontersen dose of 45 mg q4w was determined as the optimal dose to evaluate in the Phase III clinical programme based on the achieved reduction in serum TTR concentration and the acceptable safety profile in the Phase I study ION-682884-CS1 in healthy subjects.

6.3 Efficacy

An interim analysis for study ION-682884-CS3 was conducted when all ongoing subjects progressed past Week 35. Analyses were performed for the PK, PD, and efficacy data collected through the data cut- off date of 18 April 2022, and the extended safety and IM data collected through the data cut-off date of 19 July 2022.
The efficacy objectives of the study were achieved with regard to the percent change from baseline in serum TTR concentration and change from baseline in mNIS+7, Norfolk QOL-DN. Percent changes from baseline in serum TTR concentration showed a statistically significant difference in favour of eplontersen at Week 35. Similarly, changes from baseline in mNIS+7 composite and Norfolk QOL-DN total scores showed a statistically significant difference in favour of eplontersen at Week 35. Score

change from baseline in mNIS+7 and Norfolk QOL-DN scores showed, on average, disease stabilisation in the eplontersen group, compared to disease progression in the external placebo group. Additional exploratory analysis of SF-36 physical and mental component scores showed nominally significant improvement in the eplontersen group compared with the placebo group. These results were confirmed by week 85 data.
Plasma exposures were substantially lower (by more than 30-fold) following dosing with eplontersen 45 mg Q4W, as compared to Q1W dosing with inotersen 300 mg. There was no accumulation in C_{max} or AUC_{0-6h} after 45 mg Q4W eplontersen treatment, irrespective of subject IM status. Plasma trough levels were substantially increased in ADA-positive subjects compared to negative subjects. Time to steady-state based on C_{trough} in ADA-negative subjects appeared to be reached by Day 169. C_{max} and AUC in subjects with TTR polyneuropathy were similar to those observed in Phase 1 studies, though higher inter-subject variability was observed in subjects.
When exposure-response relationship between C_{trough} at both Day 85 and Day 225 with serum TTR level on Week 35 was evaluated, a desired and favourable flat exposure-response relationship was observed, with a decreased serum TTR level of approximately 80%, which remained fairly consistent over the entire exposure range achieved. Therefore, sufficient exposure was reached to achieve a pharmacological response in eplontersen-treated subjects in the study.
Consistent with the serum TTR results, a desired and favourable flat exposure-response relationship was observed for both change from baseline in mNIS+7 and in Norfolk QOL-DN total score. These results suggest that sufficient exposure was reached to achieve clinically relevant responses in nearly all eplontersen-treated subjects.
The PK parameters (C_{max} and AUC_{0-6h}) were similar between ADA-positive and ADA-negative subjects. Although higher C_{trough} was observed ADA-positive subjects, decreases in TTR levels were maintained, with a flat exposure-response relationships for both ADA-negative and ADA-positive subjects, indicating that anti-eplontersen antibodies did not affect pharmacological response. Analyses of clinical endpoints by immunogenicity status and peak titre quartiles showed no clinically relevant differences based on ADA status or between quartiles of peak titres, indicating that ADA status did not affect pharmacological response and had no impact on clinical efficacy.

6.4 Safety

The Summary of Clinical Safety includes safety data from 2 ongoing Phase III studies with eplontersen in patients with ATTRv-PN: the pivotal study ION-682884-CS3 and the long-term extension study ION-682884-CS13. The external placebo group and historical inotersen group from a completed Phase II/III historical study (ISIS 420915-CS2) were used to compare the safety data from the pivotal study ION-682884-CS3. Additionally, safety data for eplontersen in healthy volunteers from 3 completed Phase I studies are included in this document: ION-682884-CS1, ION-682884-CS20, and ION-682884-CS21.
The incidence of any TEAEs (97.2% versus 100%), study drug-related TEAEs (36.8% versus 38.3%), TEAEs leading to discontinuation of the study drug including death (4.2% versus 3.3%), TEAEs leading to withdrawal from the study (2.8% versus 1.7%), and TEAEs leading to dose interruption (stop/delay) (8.3% versus 5.0%), was generally similar between the eplontersen and external placebo groups. The severity of TEAEs was mostly mild or moderate in the eplontersen group and moderate or severe in the external placebo group.
The incidence of serious TEAEs was lower in the eplontersen group compared to the external placebo group (14.6% versus 20.0%). Discontinuation of the study drug due to serious TEAEs, including deaths, was reported in 2.8% of patients in the eplontersen group compared to none in the external placebo group. A total of 2 fatal TEAEs were reported in the eplontersen group compared to none in the external placebo group. The serious TEAEs, including deaths, reported in the eplontersen group were assessed as not related to the study drug by the Investigator. The incidences of AESIs in the eplontersen and the external placebo groups were 28.5% and 20.0%, respectively. The incidences of OAEIs in the eplontersen and the external placebo groups were 60.4% and 78.3%, respectively.
In the eplontersen group, the incidence of TEAEs in the Week 85 + data was generally consistent with the data up to Week 66. The incidences of TEAEs were generally consistent between the eplontersen-treated set and the eplontersen group with the data up to Week 66. The overall

EAER (event rate per 100 PY) in patients with at least one TEAE was 513.3 in the eplontersen-treated set and 565.99 in the eplontersen group in the data up to Week 66.
The incidence of TEAEs in infections and infestations SOC was 59.0% in the eplontersen group, primarily due to PTs of COVID-19 and UTI. The other SOCs with the most reported TEAEs (> 25% of patients) in the eplontersen group were gastrointestinal disorders; musculoskeletal and connective tissue disorders; nervous system disorders; and general disorders and administration site conditions; none of these SOCs had an incidence that was higher than the external placebo group.
The SOCs with > 5% higher incidence in the eplontersen group than in the external placebo group were metabolism and nutrition disorders (primarily driven by vitamin A deficiency); blood and lymphatic system disorders; and ear and labyrinth disorders. Vitamin A deficiency may cause lesions of the skin, including dryness of the skin. The incidence of TEAEs within the SOC of skin and subcutaneous tissue disorder was similar between the eplontersen group and the external placebo group (21.5% versus 25.0%).
In the eplontersen-treated set, the incidence of most commonly reported TEAEs by PTs (≥ 10%) was COVID-19, UTI, diarrhoea, nausea, and vitamin A deficiency. In the eplontersen-treated set, SOCs with the most reported TEAEs (> 25% of patients) were infections and infestations; gastrointestinal disorders; musculoskeletal and connective tissue disorders; nervous system disorders; general disorders and administration site conditions; investigations; renal and urinary disorders; eye disorders; and injury, poisoning and procedural complications.
The severity of TEAEs was mostly mild or moderate in the eplontersen-treated set which was consistent with the data up to Week 66 in the eplontersen group. The proportion of patients and number of events with severe TEAEs were higher in the eplontersen-treated set compared to the data up to Week 66 in the eplontersen group, while it was lower than the external placebo group. The exposure-adjusted event rate (i.e. EAER per 100 PY) was 22.8 in the eplontersen-treated set, 15.6 in the eplontersen group (up to Week 66 data), and 27.82 in the external placebo group (up to Week 66 data). The TEAEs with severe intensity reported in more than one patient in the eplontersen-treated set were vomiting (3 patients) and UTI (2 patients). None of the severe TEAEs in the eplontersen group were assessed as related to the study drug by the Investigator.
The incidence of study drug-related TEAEs as assessed by the Investigator in the eplontersen-treated set was consistent with the data up to Week 66 in the eplontersen group (36.5% versus 36.8%). The EAER (per 100 PY) of study drug-related TEAEs was 59.7 in the eplontersen-treated set and 72.99 in the eplontersen group with the data up to Week 66. None of the study drug-related TEAEs were reported with an incidence of ≥ 10% in the eplontersen-treated set. None of the study drug-related TEAEs were reported as serious events in the eplontersen-treated set.
A total of 6 deaths were reported in the eplontersen-treated set up to the DCO (07 April 2023). None of the deaths were assessed as related to the study drug by the Investigator. After the Week 85 analysis was completed, an additional patient was confirmed to have died before the Week 85 analysis cut-off. A total of 2 fatal TEAEs (PT arrhythmia and PT cerebral haemorrhage) occurred in the eplontersen group, and no deaths occurred in the external placebo group. The deaths reported in the eplontersen group were not considered related to the study drug by the Investigator.
A total of 3 fatal TEAEs were reported in the eplontersen group of study ION-682884 with Week 85 + data. Of these, one fatal TEAE (PT Acute myocardial infarction) was reported after Week 66.
After the Week 85 analysis was completed in Study ION-682884-CS3, an additional patient was confirmed to have died before the Week 85 analysis cut-off. The patient died 103 weeks after enrolment in the study (Study Day 726) due to pneumonia sepsis. The patient discontinued treatment 64 weeks (Study Day 272) before the death, having received 5 doses of eplontersen, and elected to continue for survival follow-up only.
The incidence of serious TEAEs in the eplontersen-treated set (20.4%) was generally consistent with the data up to Week 66 in the eplontersen group (14.6%) across individual PTs and SOCs, except for the cardiac disorder SOC. The incidence of serious TEAEs reported in the cardiac disorder SOC were higher in the eplontersen-treated set (7.2%) compared to the eplontersen group with the data up to Week 66 (2.8%), with no notable differences at the PT level. The EAER (per 100 PY) of serious TEAEs was 35.2 in the eplontersen-treated set, 29.76 in the eplontersen group with the data up to Week 66, and 19.47 in the external placebo group with the data up to Week 66.

Serious TEAEs reported in more than one patient in the eplontersen-treated set were: vomiting (3%); pneumonia (2.4%); UTI and syncope (1.8% each); AV block complete, nausea, sepsis, COVID-19 pneumonia, and dehydration (1.2% each). None of these serious TEAEs were assessed as related to the study drug by the Investigator. Among the serious TEAEs, 6 TEAEs were reported as fatal in the eplontersen-treated set (see above).
The incidence of TEAEs leading to discontinuation of the study drug, including fatal TEAEs, was similar between the eplontersen group and external placebo group (4.2% versus 3.3%). The incidence of TEAEs leading to discontinuation of the study drug, including fatal TEAEs, was consistent between the eplontersen-treated set and eplontersen group with the data up to Week 66 (6.6% versus 4.2%). The EAER of TEAEs leading to discontinuation of the eplontersen (patients with at least one TEAE) was 3.9 in the eplontersen-treated set and in the eplontersen group with the data up to Week 66. In the eplontersen-treated set, no TEAEs led to discontinuation of the study drug in more than one patient, except for TEAEs of proteinuria, which led to discontinuation in 2 patients. All TEAEs that led to study drug discontinuation in the eplontersen-treated set were serious, except for proteinuria and abnormal transaminases. The only events assessed as related to the study drug by the Investigator were proteinuria and abnormal transaminases (each in one patient).

Adverse Events of Special Interest
A thrombocytopenia AESI was defined as any AE with the PTs of thrombocytopenia or platelet count decreased. Review of platelet counts and AE data indicate that eplontersen treatment does not increase the risk of clinically meaningful platelet-related adverse effects. Decreases in platelet counts were observed more frequently in patients treated with eplontersen compared to patients on placebo, due to a higher frequency of decreases to Grade 1a: ≥ 100 × 109/L to < 140 × 109/L). Decreases to worse grades were few and similar in both groups. Overall, the decreases in platelet counts were mostly transient, resolved spontaneously while on continued treatment with eplontersen and did not have any clinical impact. No safety signals related to haemorrhages were identified in patients treated with eplontersen. In the eplontersen-treated set, all TEAEs of the thrombocytopenia AESI were mild in severity, non-serious, and resolved without interruption or discontinuation of the study drug, except in one patient who was reported with a severe, serious TEAE of thrombocytopenia that led to discontinuation of the study drug. None of these events led to concurrent bleeding.
Due to its mode of action, eplontersen reduces serum vitamin A concentration. The assessment of ocular TEAEs potentially related to vitamin A deficiency was conducted through a non-specific, concatenated MedDRA search that included a predefined set of PTs for either vitamin A deficiency or ocular AEs. Analyses of the data show that eplontersen in combination with vitamin A supplementation did not appear to increase the risk of symptomatic vitamin A deficiency. The incidence of TEAEs related to ocular AEs potentially related to vitamin A deficiency. AESIs in the eplontersen-treated set (28.7%) were similar to the data collected up to Week 66 in the eplontersen group (27.1%). The EAER (per 100 PY) was 21.5 in the eplontersen-treated set and 30.88 in the eplontersen group with the data up to Week 66. In the eplontersen-treated set, TEAEs were generally mild to moderate (except for one severe TEAE of ulcerative keratitis) and non-serious (except for one serious TEAE of blindness transient with moderate severity).
A serious TEAE with PT of blindness transient was reported in one patient. The event started on Study Day 3, was moderate in severity, and resolved with concomitant treatment on Study Day 6. The event was likely due to a concurrent, serious TEAE of cerebral infarction. The Investigator considered the event of blindness transient as not related to eplontersen. A non-serious, severe TEAE of ulcerative keratitis was reported in one patient on Study Day 462. The patient had a medical history of dry eye and left eye keratitis. The patient continued eplontersen treatment without interruption. The event was assessed as unlikely related to the study drug by the Investigator, treated with concomitant medication, and the event was ongoing at the time of DCO.
In the eplontersen-treated set, the incidence of PT vitamin A deficiency was 10.8% (18 patients, 19 events), and the incidence of PT vitamin A decreased was 4.2% (7 patients, 7 events). Most of the TEAEs with PTs of vitamin A deficiency and vitamin A decreased were assessed as related to the study drug by the Investigator, and TEAEs with the other PTs were mostly assessed as not related to the study drug by the Investigator. None of the events led to interruption or discontinuation of the eplontersen treatment. One patient who had a medical history of dry eyes and significant eye issues at

Screening (reported in the ocular screening questionnaire) was reported with a TEAE of xerophthalmia (mild, non-serious TEAE) on Study Day 518. The event was resolved on Study Day 540 while on continued treatment with eplontersen. The patient received concomitant treatment of hyaluronate sodium trehalose. The event was assessed as not related to the study drug by the Investigator.

Other Adverse Events of Interest
No TEAEs related to coagulation abnormalities OAEI were reported in the eplontersen group or the external placebo group. There were no clinically meaningful effects of eplontersen treatment on the coagulation parameters.
Overall, the review of renal laboratory data and TEAEs related to renal impairment OAEI did not suggest an increased risk of renal adverse effects with eplontersen treatment. In the eplontersen-treated patients, no TEAEs of glomerulonephritis AESI were reported. Overall, laboratory findings show that eplontersen treatment was not associated with clinically relevant changes in eGFR or other renal function laboratory parameters.
The incidence of abnormal liver function OAEI was similar between the eplontersen-treated set and the eplontersen group with the data up to Week 66 (8.4% versus 6.3%). The EAER was 12.4 in the eplontersen-treated set and 15.72 in the eplontersen group with the data up to Week 66. In the eplontersen-treated set, TEAEs of liver function OAEI were mild or moderate in severity, except for one severe TEAE of GGT increased. None of the TEAEs led to discontinuation of the study drug, except for one TEAE with PT of transaminases abnormal. Most of the events were assessed as not related to the study drug by the Investigator, and mostly resolved while on eplontersen treatment without any concomitant treatment. All TEAEs were non-serious, except for one patient with 2 serious TEAEs of ascites (moderate severity) which was assessed as not related to the study drug by the Investigator, and were resolved without dose interruption while on eplontersen treatment.
The results do not suggest that eplontersen has a clinically significant negative effect on the CNS. The incidence of CNS disorder OAEI was similar between the eplontersen-treated set, and the data collected up to Week 66 in the eplontersen group (32.3% versus 29.9%). The EAER (per 100 PY) in the eplontersen-treated set was 31.0 compared to 37.62 in the eplontersen group with the data up to Week 66. In the eplontersen-treated set, most of the TEAEs were mild in severity and non-serious. Most of the events resolved while continuing on eplontersen treatment without any concomitant treatment. None of these TEAEs led to the discontinuation of the study drug, except for the fatal event of cerebral haemorrhage. In the eplontersen-treated set, a total of 7 serious TEAEs were reported in 5 patients: 4 TEAEs with PT syncope (3 events with moderate severity and 1 severe event) in 3 patients; 1 TEAE with PT cerebral haemorrhage (severe and fatal) in 1 patient, 1 TEAE with PT cerebral infarction (moderate in severity) in 1 patient, and 1 TEAE with PT metabolic encephalopathy in one patient. No other severe events were reported. None of the serious TEAEs were considered as related to the study drug by the Investigator

The ADRs related to eplontersen are identified by ongoing signal evaluation based on emerging safety data from all data sources (non-clinical findings, clinical data from the ongoing clinical trial programme as well as comparative analyses of randomised comparator/placebo-controlled pivotal trials in the target populations). Based on this, the following ADRs were identified: vitamin A decrease, vomiting, injection site reaction, erythema, injection site pain, and injection site pruritus.

6.5 Final clinical benefit risk assessment

ATTRv is a rare, rapidly progressive debilitating disease that leads to premature death within 5 to 15 years after diagnosis (Hawkins et al 2015). The current pharmacological treatments approved for ATTRv-PN are the TTR tetramer stabilising agent tafamidis and the TTR-silencing agents inotersen, patisiran, and vutrisiran.
Data from the pivotal study ION-682884-CS3 up to Week 66 provide clear evidence of a favourable benefit-risk profile for eplontersen used per the proposed labelling as a new treatment option for adult patients with ATTRv-PN. The results of the eplontersen-treated set with longer exposure (i.e. the pooled analysis of the pivotal study ION-682884-CS3 and the LTE study ION-682884-CS13 with DCO

07 April 2023) were consistent with the data up to Week 66, with no new safety signals identified. The benefit risk ratio for eplontersen is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Wainzua was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

WAINZUA®, solution for injection

Composition

Active substances

Eplontersen (a synthetically produced chemically modified antisense oligonucleotide)

Excipients

Sodium dihydrogen phosphate dihydrate (corresp. max to 0.1 mg sodium per injection)
Disodium hydrogen phosphate anhydrous (corresp. 0.3 mg sodium per injection)
Sodium chloride (corresp. 1.9 mg sodium per injection)
Sodium hydroxide (for pH adjustment) (corresp. max to 0.01 mg sodium per injection)
Hydrochloric acid (for pH adjustment)
Water for injection ad solutionem pro 0.8 ml.

Pharmaceutical form and active substance quantity per unit

Solution for injection in a single-dose autoinjector (injection) for subcutaneous (s.c.) use.
Each mL contains 59 mg eplontersen sodium, equivalent to 56 mg eplontersen.
Each single dose autoinjector contains 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) in 0.8 mL solution.
Sterile, clear, preservative-free, colourless to yellow solution.

Indications/Uses

WAINZUA is indicated for the treatment of adult patients with stage 1 and 2 polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).

Dosage/Administration

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

Usual dosage

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

The decision to continue treatment in patients whose disease has progressed to stage 3 polyneuropathy should be made at the physician's discretion based on the overall benefit-risk assessment.

Patients with renal disorders

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 m2) (see section “Pharmacokinetics“). WAINZUA has not been studied in patients with eGFR<45 mL/min/1.73 m2 or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk.

Patients with hepatic disorders

No dose adjustment is necessary in patients with mild hepatic impairment (see section “Pharmacokinetics“). WAINZUA 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.

Elderly patients

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

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.

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.

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 WAINZUA.
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 WAINZUA 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’

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to composition.

Warnings and precautions

Reduced Serum Vitamin A Levels and Recommended Supplementation

Based on the mechanism of action, WAINZUA is expected to reduce serum vitamin A (retinol) below normal levels (see section “Properties/Effects”).
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 the daily recommended dose of vitamin A 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, and persistent dry eyes.
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 (see section “Pregnancy, lactation”).
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.
Other excipients
Sodium:
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Interactions

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

Pregnancy, lactation

Women of child-bearing potential / contraception in females

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 practise 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. Due to the long half-life of eplontersen (see section “Pharmacokinetics“), a vitamin A deficit may develop even after cessation of treatment.
Women of child-bearing potential should practise effective contraception.

Pregnancy

There are no data regarding the use of WAINZUA 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 “Preclinical data»).
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 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 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.
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.

Effects on ability to drive and use machines

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

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 WAINZUA and who received at least one dose of WAINZUA. 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 WAINZUA 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

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 WAINZUA 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 “Properties/Effects”).

Injection site reactions

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

N07XX21

Mechanism of action

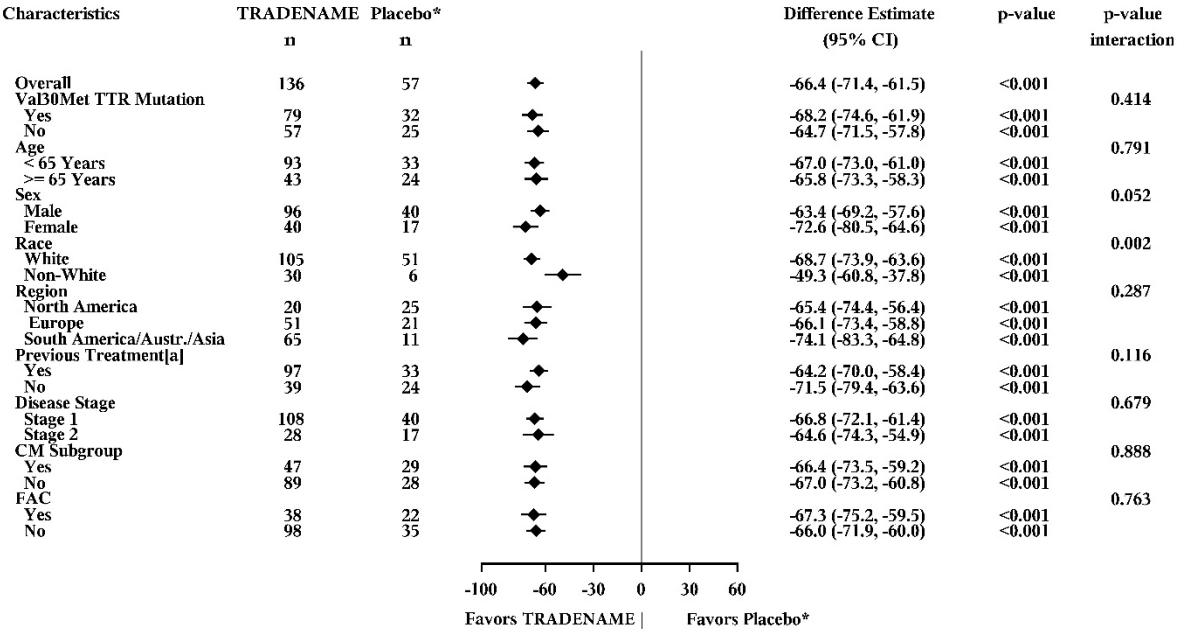
Eplontersen is a GalNAc conjugated 2′-O-2-methoxyethyl (2′-MOE)-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate (PS) and phosphate diester (PO) internucleotide linkages. The GalNAc conjugate enables targeted delivery of the ASO to hepatocytes. The selective 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).

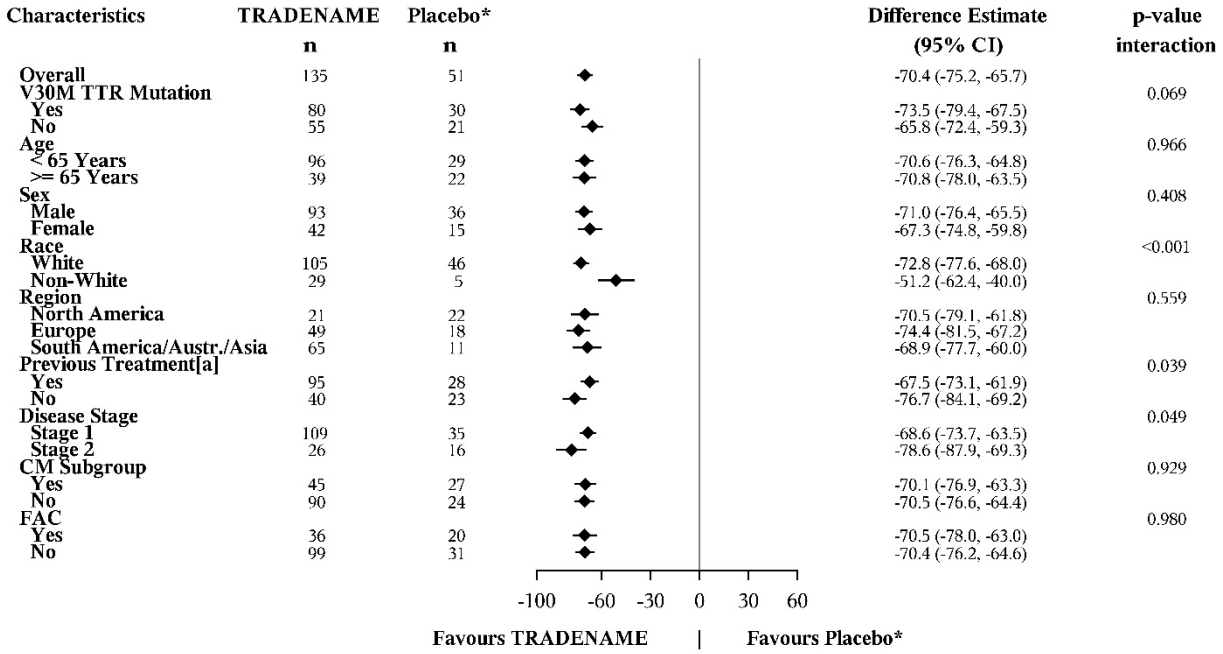
Figure 1: Forest Plot of Treatment Difference in LSM for Percent Change from Baseline in TTR (g/L) for Key Subgroups (NEURO-TTRansform Study) (full analysis set)

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 (WAINZUA – 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 randomized 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 (WAINZUA – 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 WAINZUA. 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 WAINZUA.

Clinical efficacy

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

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) 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	60	138
mean (SD)	1049.89 (228.43)	1025.78 (235.12)
Median (Min, Max)	1027.55 (668.7, 1710.0)	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, VAL122LLE 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.

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.
WAINZUA 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). WAINZUA 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). WAINZUA 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 acceptable method of assessing nutritional status in ATTR. Higher scores represent better nutritional status and is considered to be an indicator of longer survival in ATTRv-PN patients.

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]		WAINZUA – External Placebo* Difference in LSM (95% CI)	p-value
	External Placebo*	WAINZUA	External 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 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 WAINZUA versus external placebo*		
			Estimate	95% CI	p value
LSM change in NSC from baseline at Week 66					
WAINZUA (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					
WAINZUA (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					
WAINZUA (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					
WAINZUA (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					
WAINZUA(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.

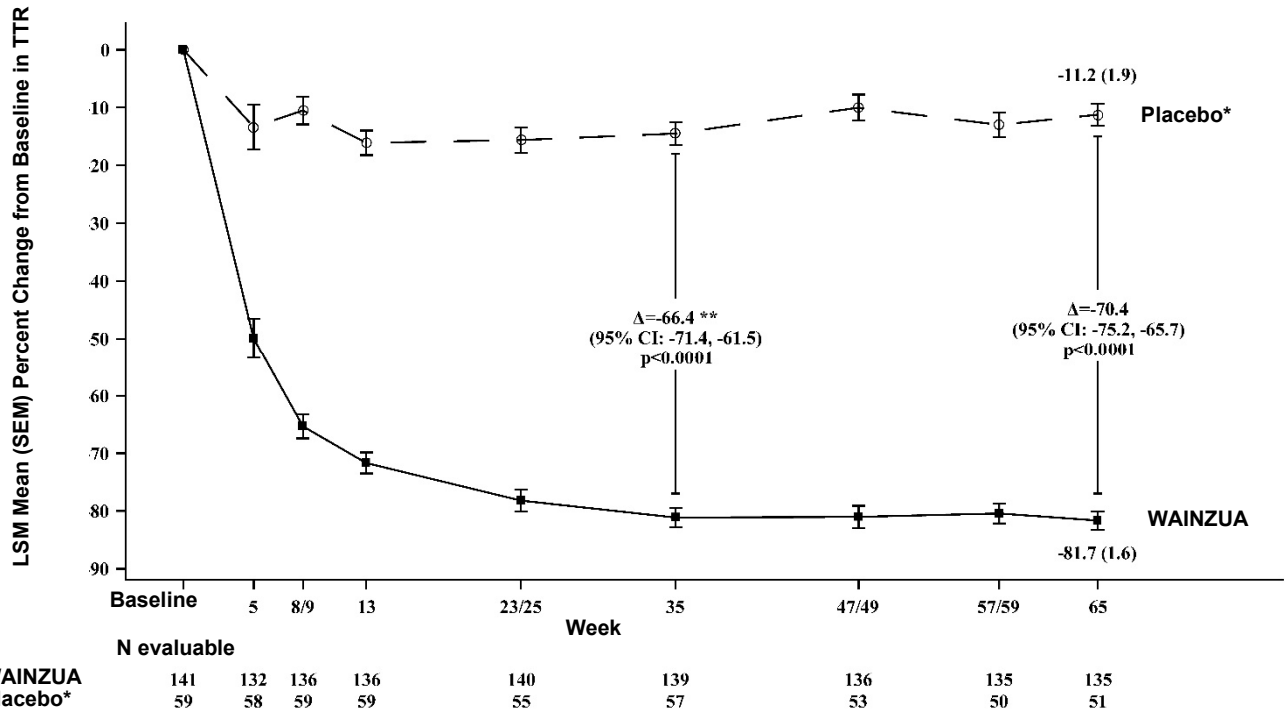
n=Number of patients with non-missing data on baseline covariates and change from baseline at the time point.

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, WAINZUA 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.

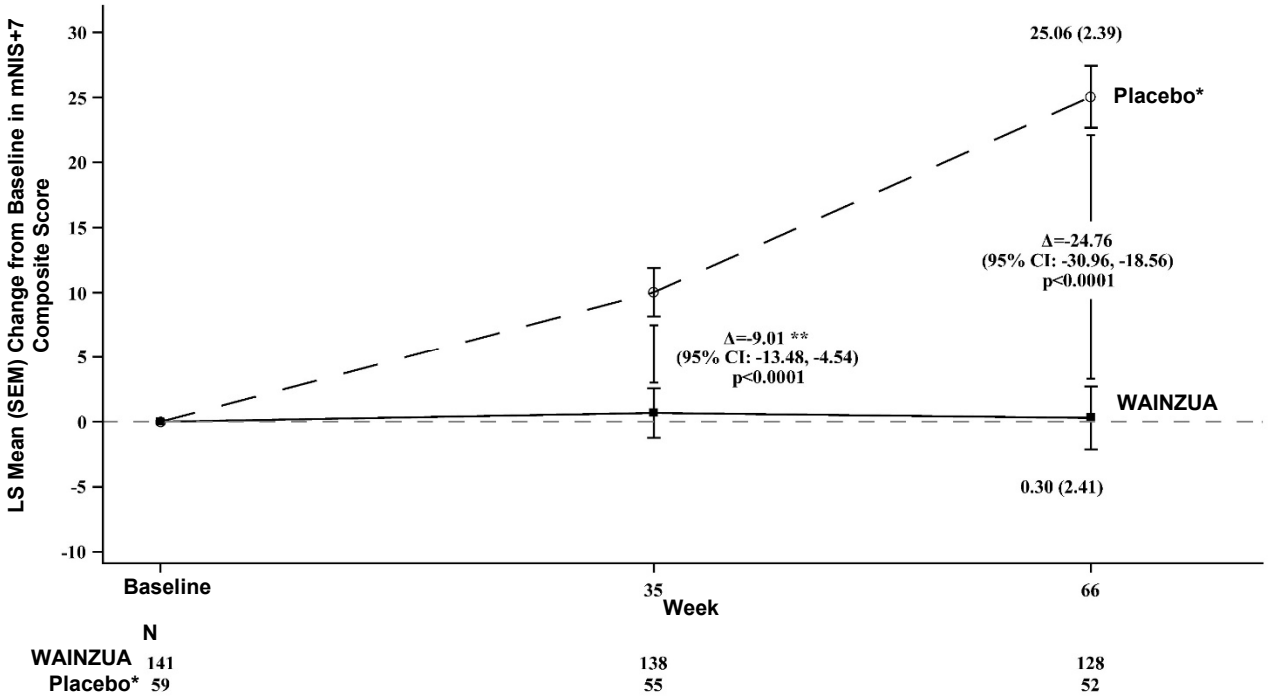
Based on MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time interaction.

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, 57 and 65, WAINZUA assessed at Baseline, Weeks 5, 9, 13, 25, 35, 4, 59 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.

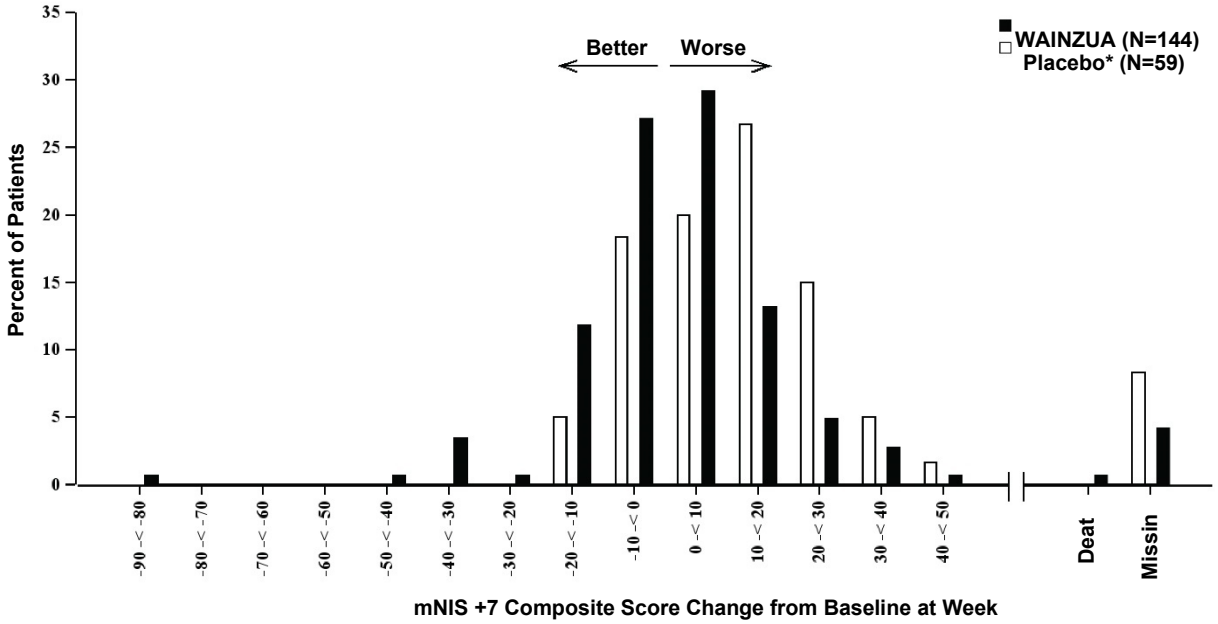
Figure 3: LSM Change in mNIS+7 Composite Score from Baseline (NEURO-TTRansform Study) (full analysis set)



* 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 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.

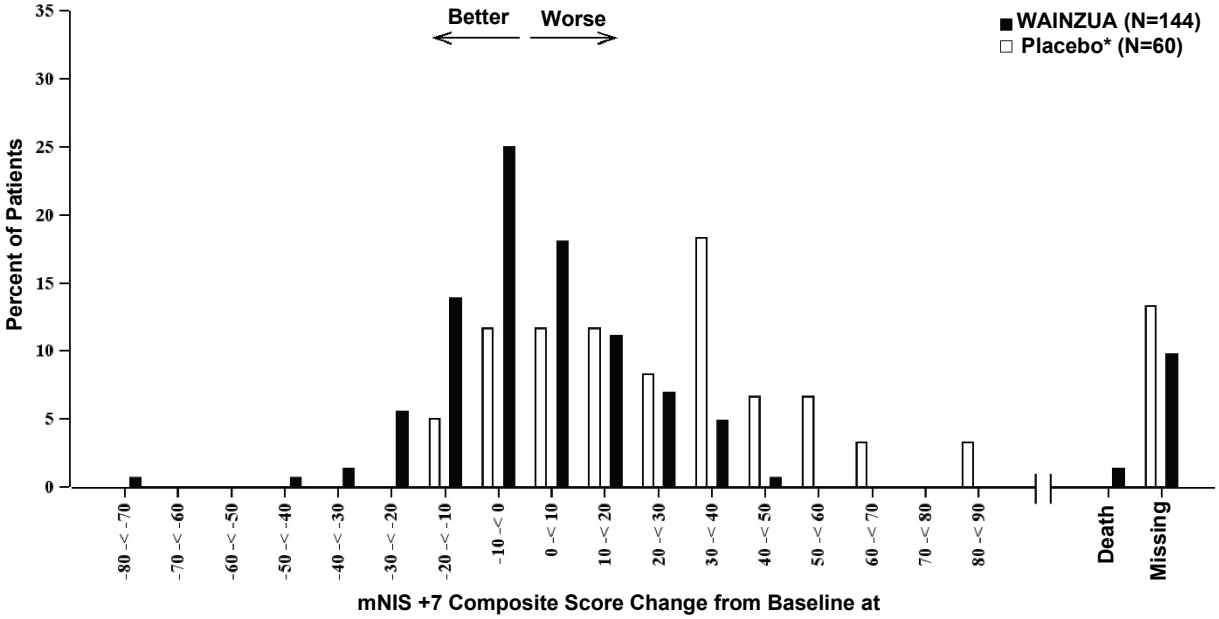
Figure 4: Histogram of mNIS+7 Composite Score Change from Baseline (NEURO-TTRansform Study) (safety analysis set)

a) at Week 35



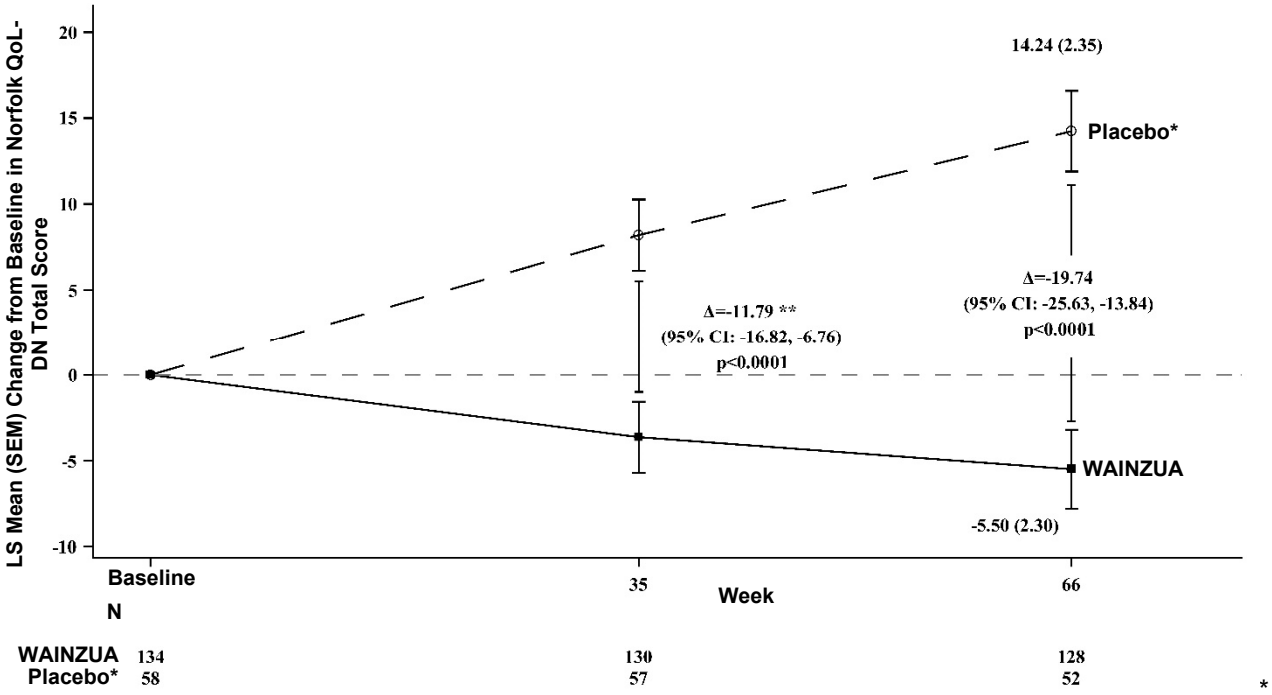
* External placebo group from another randomised controlled trial (NEURO-TTR).

b) at Week 66



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

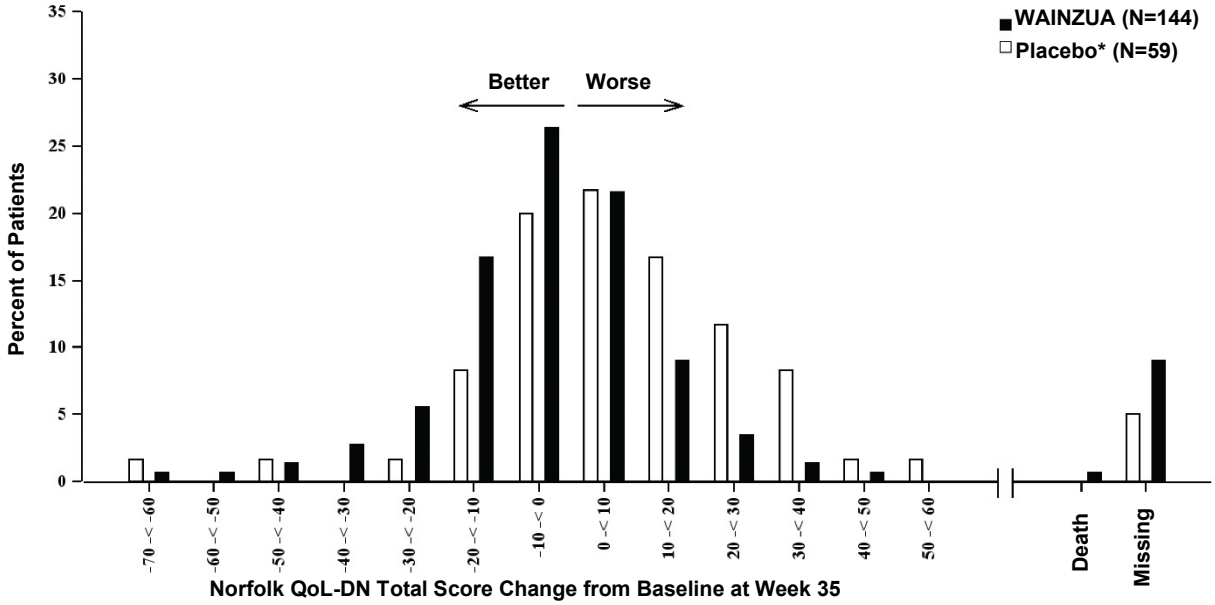
Figure 5: LSM Change in Norfolk QoL-DN Total Score from Baseline (NEURO-TTRansform Study)



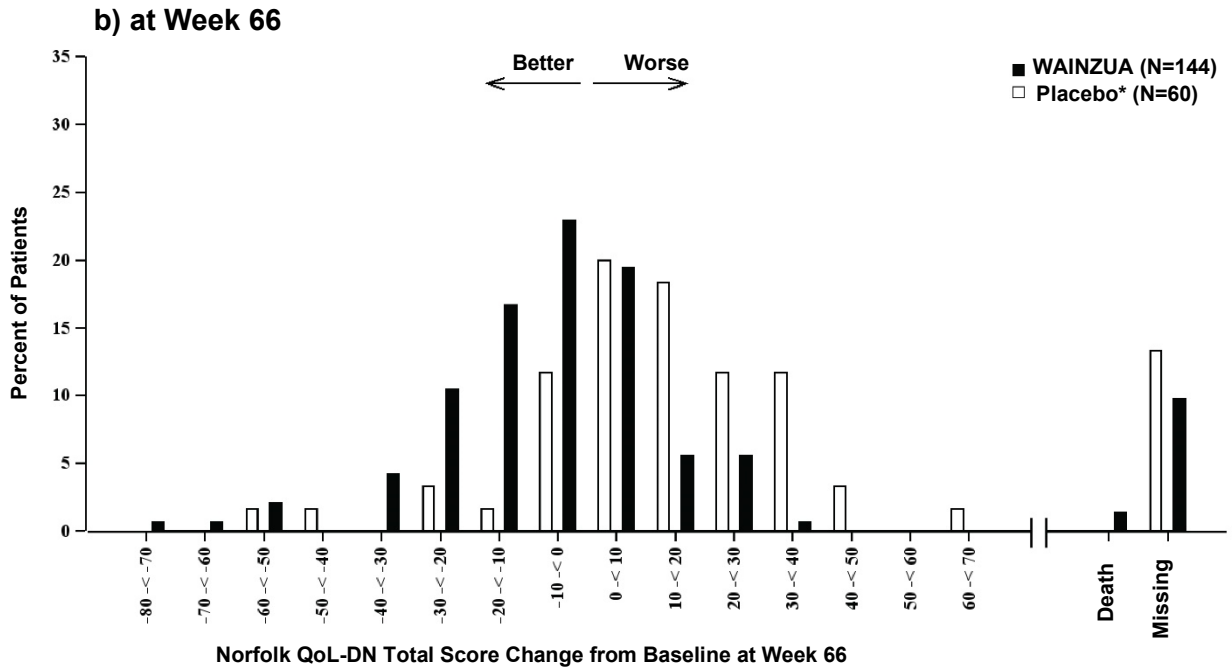
External placebo group from another randomised controlled trial (NEURO-TTR).
** Treatment difference presents results from formal Week 35 interim analysis. Based on MI ANCOVA adjusted by propensity score weights with fixed categorical effects for treatment, disease stage, Val30Met mutation, previous 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 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 6: Histogram of Norfolk QoL-DN Total Score Change from Baseline (NEURO-TTRansform Study) (safety analysis set)

a) at Week 35



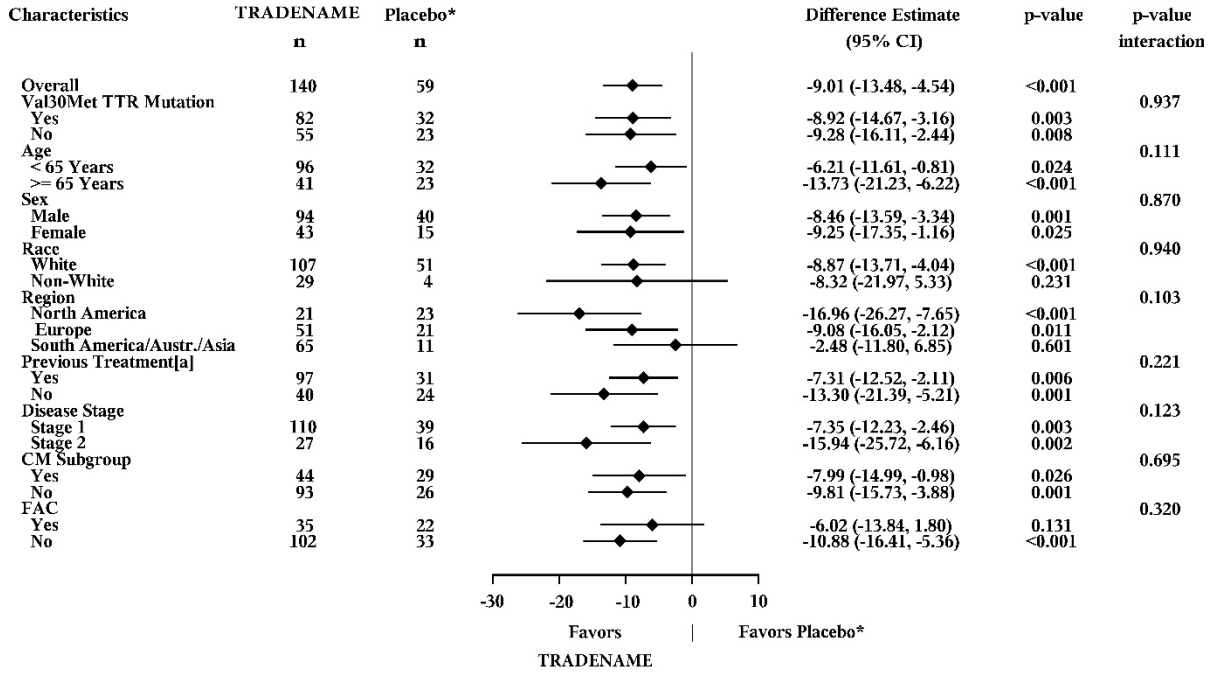
* External placebo group from another randomised controlled trial (NEURO-TTR).



* External placebo group from another randomised controlled trial (NEURO-TTR).
At both Week 35 and Week 65/66, patients receiving WAINZUA 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, baseline NIS score, 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)

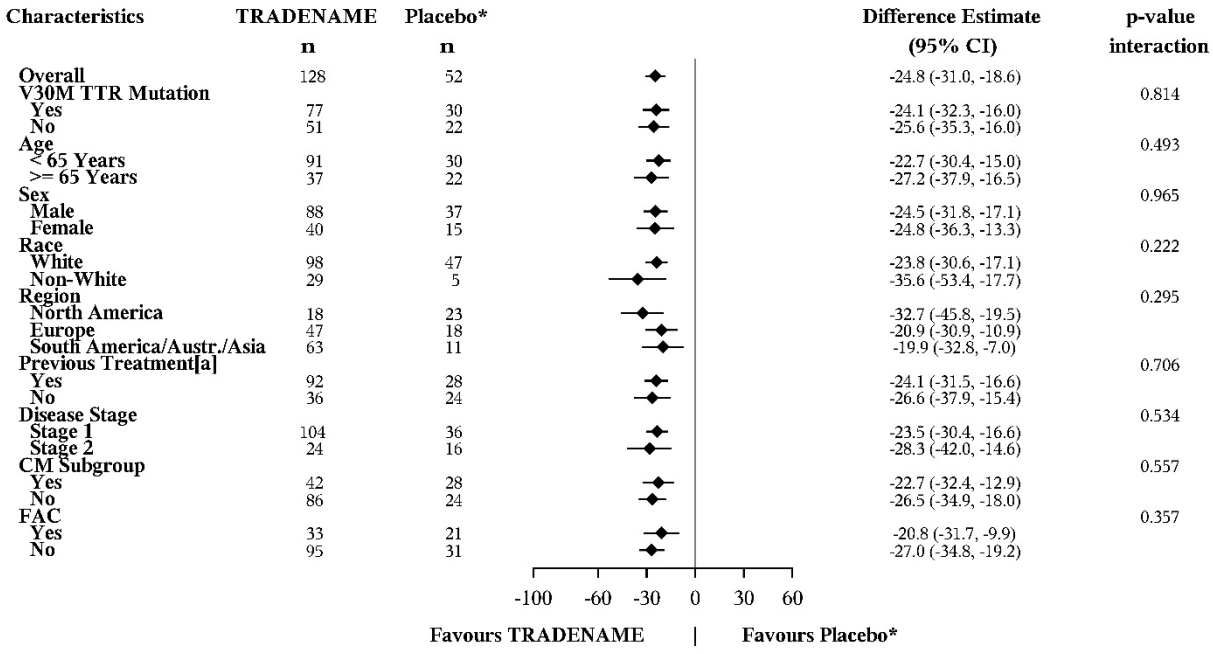
a) at Week 35



* 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.

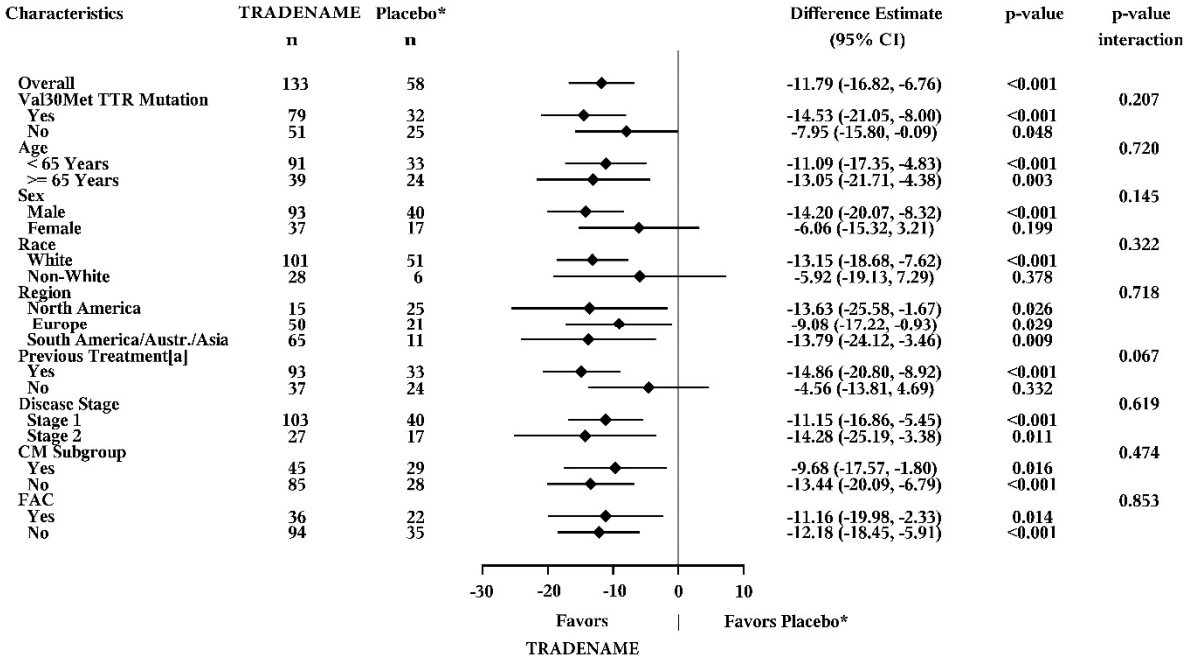
b) at Week 66



* 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 (WAINZUA – 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



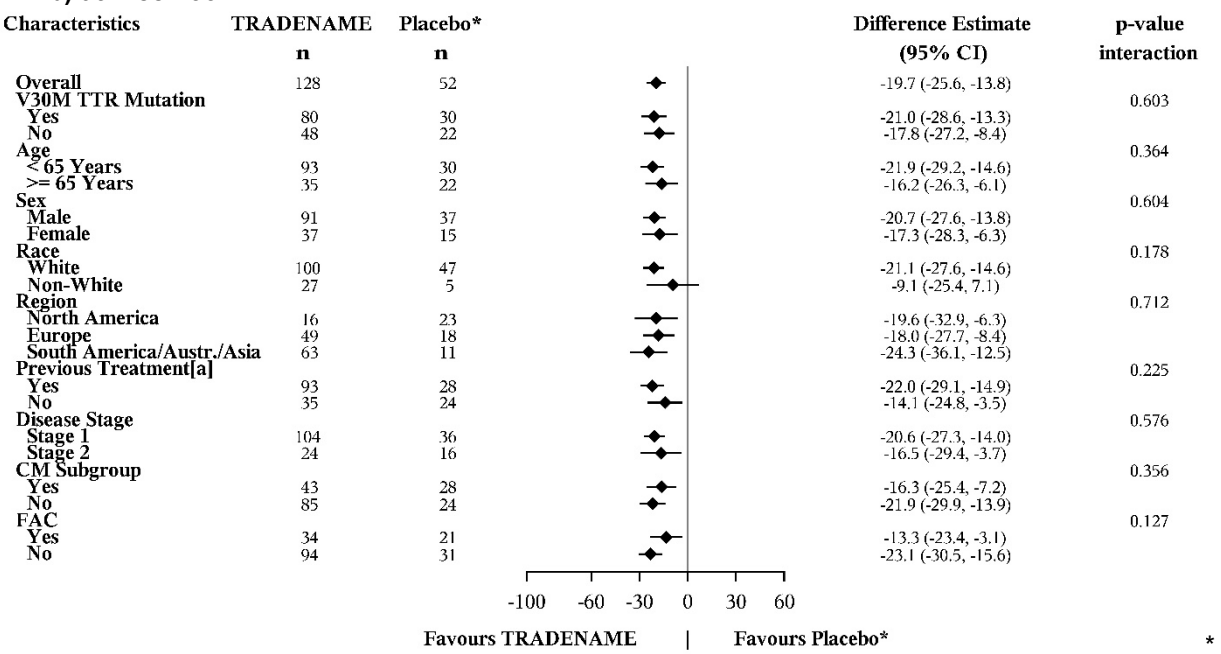
* External placebo group from another randomised controlled trial (NEURO-TTR).

[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 (WAINZUA– 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, WAINZUA 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 WAINZUA 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 WAINZUA 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.

Pharmacokinetics

The pharmacokinetic (PK) properties of WAINZUA 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 (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 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.

Kinetics in specific patient groups

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 patients

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

Preclinical 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.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the 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 in order to protect from light.
Do not freeze. Do not expose to heat.
Keep out of the reach of children.

Instructions for handling

WAINZUA should be inspected visually prior to administration. The solution should be clear and colourless to yellow. Do not use WAINZUA 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.
Additional information and instructions for the preparation and administration of WAINZUA using the pre-filled autoinjector are given in the package leaflet and the separate ‘Instructions for Use’.

Authorisation number

69332

Packs

WAINZUA solution for injection: Pack size of 1 pre-filled autoinjector for single use [B]

Marketing authorisation holder

AstraZeneca AG, Baar

Date of revision of the text

February 2025