



Australian Government

Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Wainua

Active ingredient: Eplontersen

Sponsor: AstraZeneca Pty Ltd

October 2026

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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List of abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibodies
AEs	Adverse event(s)
AESI	Adverse event(s) of special interest
AI	Automatic injector
ARTG	Australian Register of Therapeutic Goods
ASO	Antisense oligonucleotide
ATTRv	Hereditary transthyretin-mediated amyloidosis
AUC	Area under the concentration-time curve
CIs	Confidence interval(s)
CMI	Consumer Medicines Information
C _{max}	Maximum plasma concentration
C _{trough}	Trough plasma concentration; the lowest concentration of a drug in the blood plasma between doses
CV	Coefficient of variation
eGFR	Estimated glomerular filtration rate
GalNAc	N-acetylgalactosamine
ISRs	Injection site reaction(s)
LLN	Lower limit of normal
mNIS+7	Modified Neuropathy Impairment Score + 7
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
popPK/ PD	Population pharmacokinetics/pharmacodynamics
PN	Peripheral neuropathy
PSUR	Periodic safety update report
Q4W	Dose once every 4 weeks
QoL-DN	Norfolk Quality of Life – Diabetic Neuropathy
RMP	Risk management plan
SC	Subcutaneous
SD	Standard deviation
TEAEs	Treatment emergent adverse events

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
T _{max}	Time to maximum concentration
TTR	Transthyretin
ULN	Upper limit of normal

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Wainua
Active ingredient:	eplontersen (as sodium)
Decision:	Approved
Approved therapeutic use for the current submission:	Wainua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy
Date of decision:	2 June 2026
Date of entry onto ARTG:	5 June 2026
ARTG number:	490449
▼ Black Triangle Scheme	Yes
Sponsor's name and address:	AstraZeneca Pty Ltd, 66 Talavera Road, Macquarie Park, NSW 2113
Dose form:	Solution for injection
Strength:	Each pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 mL of solution. Each mL contains 56 mg eplontersen (as eplontersen sodium).
Container:	Single-use, type I glass syringe with a staked 27-gauge ½ inch (12.7 mm) stainless steel needle, rigid needle shield, and siliconised chlorobutyl elastomer stopper in a pre-filled pen.
Route of administration:	Subcutaneous injection
Dosage:	45 mg administered monthly For further information regarding dosage, refer to the Product Information .
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by AstraZeneca Pty Ltd (the Sponsor) to register Wainua (eplontersen) for the following proposed indication:¹

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

Disease or condition

Hereditary transthyretin-mediated amyloidosis (ATTRv; 'v' denotes 'variant') is a rare disorder caused by mutations in the transthyretin gene which are inherited in an autosomal dominant manner.² Transthyretin normally functions primarily as a carrier protein for thyroxine (T4) and, via association with retinol-binding protein, also mediates vitamin A transport.² These mutations serve to destabilise the transthyretin protein favouring the formation of amyloid fibrils which may deposit throughout the body, serving as the pathophysiologic basis for this multi-system disease. The peripheral nervous system, both somatic and autonomic systems, and the heart are the most commonly affected sites, resulting in peripheral sensorimotor neuropathy, autonomic neuropathy, and cardiomyopathy, or a combination of the three, being common clinical phenotypes.²

Typical clinical findings include a slowly progressive sensorimotor and/or autonomic neuropathy frequently accompanied by one or more of cardiac conduction blocks, cardiomyopathy, nephropathy, vitreous opacities or glaucoma.³ Supportive imaging findings include typical features on echocardiogram, gadolinium enhanced cardiac MRI and amyloid PET scan. Tissue biopsy can be undertaken to identify amyloid deposits, with Congo red staining identifying amyloid deposits via a characteristic yellow-green birefringence under polarised light.² Given the autosomal dominant inheritance pattern, family history should also be sought. Identification of a pathogenic variant in the transthyretin *TTR* gene on molecular genetic testing can confirm the diagnosis in a patient with suggestive clinical findings.³

Among persons from specific endemic foci in Portugal and Japan, mean age at onset is around 40 years, though in other patients is typically much later in life.³ Typically sensory neuropathy starts in the lower extremities followed by motor neuropathy within years.^{2,3} Over time sensorimotor neuropathy follows a glove and stocking distribution. Most patients develop cardiac manifestations, reflecting conducting system amyloid deposition and cardiomyopathy, after 50 years of age.³ Whilst the liver is the primary site of TTR production it also occurs in the choroid plexus, which may result in CNS manifestations, most commonly transient focal neurologic episodes, even among those on disease-modifying therapy for whom treatment does not target choroid plexus TTR production.³ Most patients will develop ocular involvement, manifesting as vitreous opacity, glaucoma, dry eyes, and ocular amyloid angiopathy.³ Kidney involvement is also typical which may result in proteinuria and chronic kidney disease.³

The TTR pathogenic variant p.Val50Met is the most common pathogenic variant in endemic regions of Portugal and Japan and one of the most common variants worldwide.³ Global prevalence is low, estimated at around 10,000 individuals. Retrospective analysis on data from

¹ This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

² Manganelli F et al. Hereditary transthyretin amyloidosis overview. *Neurological Sciences*. 2022;43(Suppl 2):5595-5604.

³ Sekijima Y and Nakamura K. Hereditary Transthyretin Amyloidosis. *GeneReviews*. Updated 30 May 2024.

<https://www.ncbi.nlm.nih.gov/books/NBK1194/>.

the Australian Amyloidosis Network clinics between 2007 and 2022 identified 161 individuals with ATTRv, an average age of 59.4 years, with 24 different genetic variants identified.⁴

ATTRv is distinct from wild type ATTR which results from deposition of wild type TTR predominantly in the heart, but with deposition also seen in the lungs, blood vessels and kidneys.³ It typically affects elderly patients and may not be diagnosed during life, with autopsy studies suggesting a prevalence of up to 10-25% in those aged over 80 years.³ Carpal tunnel syndrome is a common presentation in wild type ATTR, along with slowly progressive heart failure.³

Current treatment options

Historically treatment was supportive and symptomatic in nature, with liver transplant providing a disease modifying option. In recent years a number of disease-modifying therapies have become available, including those which function to inhibit synthesis of amyloidogenic TTR such as the *TTR* silencer therapies inotersen, patisiran, and vutrisiran, and those which function to stabilise the native TTR tetramer such as tafamidis.³ Published US-based expert consensus guidelines advocate initiation of disease-modifying therapy as soon as possible after diagnosis of ATTRv with polyneuropathy, though note a lack of head-to-head studies to guide choice of specific agent.⁵ Current products in the Australian Register of Therapeutic Goods (ARTG) with approved indications for ATTRv are summarised in Table 1.

Table 1. Products included in the Australian Register of Therapeutic Goods with approved indications for hereditary transthyretin-mediated amyloidosis.

Active ingredient (product name)	Approved therapeutic indication	Dosing and administration
Vutrisiran (Amvuttra), Aust R 422290	For the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy	25 mg via subcutaneous injection once every 3 months
Patisiran (Onpattro), Aust R 380813	For the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.	300 micrograms per kg body weight via IV infusion once every 3 weeks.
Tafamidis (Vyndamax), Aust R 314813, and 316241	For the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy.	61 mg orally once daily.

Inotersen (Tegsedi), an antisense oligonucleotide which inhibits synthesis of transthyretin, is not included in the ARTG but is approved overseas in the European Union (EU), United States of America (USA) and Canada for treatment of ATTRv with polyneuropathy.

⁴ Carroll AS et al. The spectrum of neuropathy in hereditary transthyretin amyloidosis (ATTRV) in Australia. *BMJ Neurol Open.* 2023;5(suppl 1):A1-A63.

⁵ Karam C et al. Diagnosis and treatment of hereditary transthyretin amyloidosis with polyneuropathy in the United States: Recommendations from a panel of experts. *Muscle and Nerve.* 2024;69:273-287.

Clinical rationale

Eplontersen is an antisense oligonucleotide (ASO) that is selectively delivered to the liver via conjugation to a N-acetylgalactosamine (GalNAc) ligand. This liver-targeted approach is intended to increase potency, allowing TTR reduction with monthly subcutaneous dosing. Hybridisation of eplontersen to hepatic TTR mRNA leads to its cleavage by ribonuclease H1, thus preventing production of TTR protein in the liver. Decreased production of liver-derived TTR protein in the circulation decreases the formation of TTR amyloid fibril deposits, which may slow the symptoms of ATTR disease.

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 2 summarises these submissions and provides the indications where approved.

Table 2. International regulatory status at the time the TGA considered this submission

Country	Submission date	Approval date	Comment
Canada	21 Apr 2023	19 June 2024	<i>Approved indication:</i> Treatment of polyneuropathy associated with stage 1 or stage 2 hereditary transthyretin-mediated amyloidosis (hATTR) in adults.
European Union ^a	05 Oct 2023	6 Mar 2025	<i>Approved indication:</i> Treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.
Singapore	28 Mar 2024	Under evaluation	
Switzerland	19 Oct 2023	14 Feb 2025	<i>Approved indication:</i> Treatment of adult patients with stage 1 and 2 polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).
United Kingdom ^b	30 Oct 2023	14 Oct 2024	<i>Approved indication:</i> Treatment of hereditary transthyretin-mediated amyloidosis (ATTRv amyloidosis) in adult patients with Stage 1 and 2 polyneuropathy.
United States	22 Dec 2022	21 Dec 2023	<i>Approved indication:</i> Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

^a Centralised Procedure Rapporteur (Germany) and co-rapporteur (Poland).

^b National application.

Registration timeline

Table 3 captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

Table 3. Registration timeline for Wainua (eplontersen), submission PM-2025-02079-1-5

Description	Date
Submission dossier accepted evaluation commenced	30 June 2025
Evaluation completed	17 April 2026
Registration decision (Outcome)	2 June 2026
Registration in the ARTG completed	5 June 2026
Number of working days from submission dossier acceptance to registration decision*	171

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Eplontersen, obtained as eplontersen sodium, is a synthetic oligonucleotide conjugated to a GalNAc ligand *via* an aminohexyl linker on the 5' terminus. The oligonucleotide part consists of 20 nucleosides (20-mer) in a 5-10-5 structure of 2'-O-(2-methoxyethyl) nucleosides (5 and 5) and 2'-deoxynucleosides (10). The backbone is mixed between phosphate diester and phosphorothioate linkages.

Eplontersen sodium structure is shown in Figure 1 and key physiochemical properties are presented in Table 4.

Figure 1. Chemical structure of eplontersen sodium

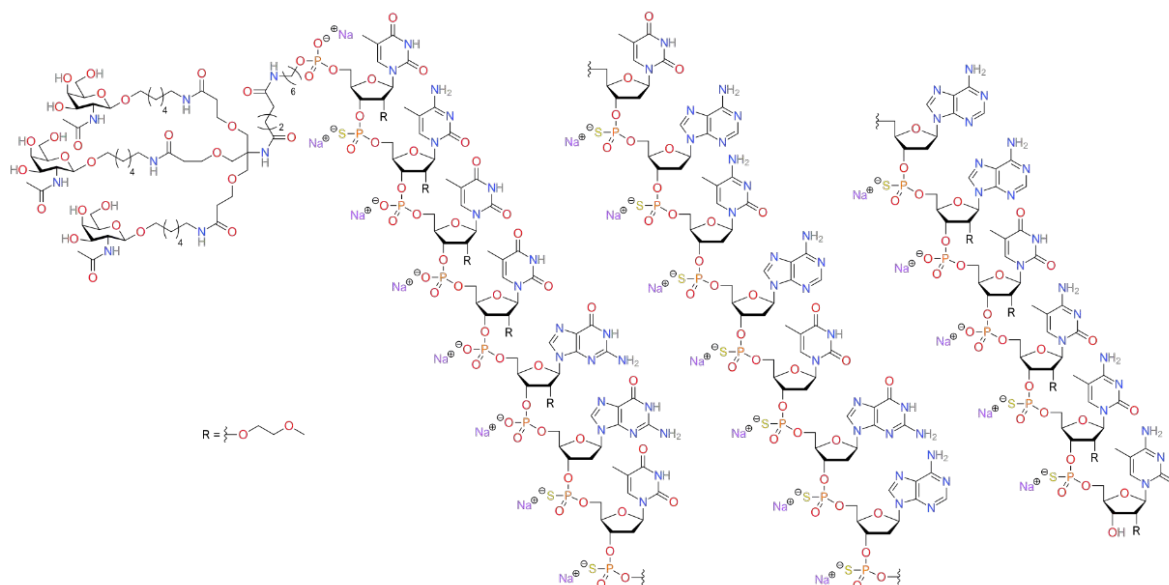


Table 4. Physiochemical properties of eplontersen sodium

Melting point	No melting point was determined. Differential scanning calorimetry shows peaks at 104 °C, attributed to water loss, and at 223 °C, due to decomposition.
Polymorphism	The drug substance is amorphous.
Solubility	Freely soluble in water, acetate buffer (pH 3) and phosphate buffered saline (pH 7.4).
pH	pH of a 5% (w/v) aqueous solution of eplontersen sodium is approximately 6.
Partition coefficient	The determined Log ₁₀ Mean D _{ow} of eplontersen sodium is -0.805 at pH 5, -1.325 at pH 7, and -1.313 at pH 9.
Molecular formula	Free acid: C ₂₉₆ H ₄₃₇ N ₇₇ O ₁₅₆ P ₂₀ S ₁₃ Sodium salt: C ₂₉₆ H ₄₁₇ N ₇₇ O ₁₅₆ P ₂₀ S ₁₃ Na ₂₀
Molecular weight	Free acid: 8606.5 amu Sodium salt: 9046.1 amu

The oligonucleotide portion of the drug substance is synthesised via solid-phase oligonucleotide synthesis on a solid support. The sequence of the oligonucleotide is established during the synthetic process. The oligonucleotide is then subsequently modified via conjugation with a GalNAc derivative.

A risk evaluation on the potential presence of elemental and nitrosamines were performed by the Sponsor. No significant risk was identified.

Impurities for oligonucleotide drug substances are not covered by ICH Q3A requirements⁶. The impurity limits are qualified based on advice from the Toxicology section. The drug substance specifications are sufficient to ensure the drug substance quality and consistency. The drug substance specifications acceptable from a quality perspective is notably identical to those approved in the EU.

The analytical methods used to analyse the drug substance were adequately described and appropriately validated.

Wainua is a sterile, colourless to yellow solution for injection containing 45 mg eplontersen (added as 47 mg eplontersen sodium) in 0.8 mL 10 mM phosphate buffered saline with a pH of 7.4.

The drug product is supplied in a Type I glass syringe, with a staked 27-gauge ½ inch stainless steel needle and closed with a chlorobutyl plunger stopper. The pre-filled syringe is assembled into an autoinjector for the final drug product presentation. Wainua is supplied in cartons containing one autoinjector.

The manufacturing process includes sterile filtration and syringe filling under aseptic conditions.

Sterility, endotoxin, container safety aspects were separately assessed by the TGA Laboratories Branch, and these were found to be acceptable.

All excipients used in the formulations are conventional. The drug product is a phosphate buffered aqueous solution in water for injection, at pH 7.4. The solution has a target osmolality

⁶ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Q3A. [Impurities in New Drug Substances](#). 25 October 2006.

250 – 330 mOsm/kg (comparable to human plasma 275-299 mOsm/kg). The viscosity of the solution is ~10 cP at 25 °C.

The drug product specifications are sufficient to ensure drug product quality and consistency. The drug product specifications are acceptable from a quality perspective and are notably identical to those approved in the EU.

The analytical methods used to analyse the product were adequately described and validated.

A risk assessment on the potential contamination of the product with nitrosamine impurities did not identify any significant risk.

Stability data did not show any significant degradation trends or changes for any of the specification parameters tested. The data supports a shelf-life of 36 months when stored at 2 – 8 °C. Additionally, the stability data supports the proposed in-use storage of the drug product for 6 weeks when stored below 30 °C. The drug product is discarded after 6 weeks if not used.

There are no objections to registration from a pharmaceutical chemistry perspective.

Nonclinical evaluation summary

The scope and quality of the submitted nonclinical dossier was acceptable, with studies consistent with the principles of ICH guidance for the nonclinical testing of pharmaceuticals. All pivotal safety-related studies were conducted according to Good Laboratory Practice.

The oligonucleotide sequence of eplontersen is complementary to a sequence in the 3'-UTR of the human *TTR* mRNA. The sequence matches the same region of the cynomolgus monkey *TTR* mRNA but significant mismatches exist with rodent and rabbit *TTR* mRNA, suggesting a lack of responsiveness in these species. *In vitro*, the oligonucleotide sequence of eplontersen inhibited *TTR* mRNA in monkey hepatocytes and mice hepatocytes overexpressing human *TTR*. In mice expressing the human mutant *TTR* variant and monkeys, eplontersen caused reductions in hepatic *TTR* mRNA and plasma TTR protein levels, thus lending support for the proposed clinical indication. No studies were submitted to determine if eplontersen could suppress progression or ameliorate disease symptoms. Therefore, no comment in regard to efficacy can be given based on nonclinical data.

Considering its sequence and enhanced hepatic delivery conferred by GalNAc conjugation no significant off-target effects for eplontersen are expected

A safety pharmacology study conducted in cynomolgus monkeys that covered the cardiovascular, respiratory and central nervous systems did not reveal any adverse or treatment-related effects. No significant inhibition of hERG K⁺ channel tail current was observed at clinically relevant concentrations. The safety pharmacology studies do not raise any concerns regarding effects on respiratory, CNS or cardiovascular function in patients.

Overall, the pharmacokinetic profile of eplontersen was consistent with the class of GalNAc-THA-conjugated synthetic oligonucleotides and was qualitatively similar in animals and humans. Plasma half-life was similar between monkeys and humans. Plasma protein binding is high in humans and animal species. Tissue distribution of the ASO component was primarily distributed to the intended target tissue (liver) and the main route of elimination (kidneys). Eplontersen is metabolised by exonucleases in all species, that degrade eplontersen to shorter nucleotides of varying length. The GalNAc-THA component is rapidly metabolised.

Pharmacokinetic drug interactions involving eplontersen are considered unlikely, consistent with chemically-similar oligonucleotide therapeutics.

Eplontersen had a low order of acute toxicity via the subcutaneous (SC) route in mice and monkeys.

Key repeat-dose toxicity studies using the clinical route (SC) were conducted in mice (up to 26 weeks) and cynomolgus monkeys (up to 39 weeks). Target organs for toxicity were associated with areas of high uptake and distribution of drug. These included the liver (target organ), the kidneys (elimination), the injection site – site of administration, and the lymph nodes. The effects were non-adverse, showing reversal during recovery phase. Thrombocytopenia was seen in monkeys at high relative doses.

Eplontersen was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in Chinese hamster lung cells) or *in vivo* (in the mouse micronucleus test). No treatment related increase in tumour incidence was observed in a mouse carcinogenicity study with eplontersen. In a 2-year rat carcinogenicity study with a related oligonucleotide, there were no systemic tumours related to treatment. Tumours at the injection site were considered of low relevance to the clinical situation.

No adverse effects on fertility, embryofetal development or pre/postnatal development were seen in animal studies with eplontersen, a mouse surrogate (in mice) or a non-GalNAc-conjugated oligonucleotide with the same pharmacological target. However, the negative embryofetal development findings should be considered with caution, given the important roles of thyroid hormones and vitamin A in fertility and embryofetal development. A pregnancy category D is warranted given the potential adverse embryofetal development effects associated with an imbalance in vitamin A levels that may occur with eplontersen treatment.

Injection site reactions to eplontersen in mice and monkeys included minimal/slight mononuclear or mixed inflammatory cell infiltrates with vacuolated macrophages.

No adverse effects on immune function were seen in mice or monkeys.

The primary pharmacology studies lend some support for the proposed indication.

Eplontersen was well-tolerated in the repeat-dose toxicity studies, with minor treatment-related findings observed that are related to the class effects of the drug. Thrombocytopaenia seen at high doses in animals is considered of low concern for patients.

There are no nonclinical objections to the registration of eplontersen for the proposed indication.

Clinical evaluation summary

Pharmacology

Pharmacokinetics

Evaluable pharmacokinetic (PK) data was provided in 4 clinical studies, a population PK (popPK) report, and a PK/pharmacodynamics (PD) report. Each study is briefly summarised below:

- Study CS1, a phase 1, double-blind, placebo-controlled, single- and multiple-dose study evaluating safety, tolerability and PK of single and multiple doses of eplontersen:
 - 30 healthy volunteers receiving multiple doses (45 mg, 60 mg, and 90mg Q4W for 12 weeks), and 9 receiving single 120 mg dose.

- Study CS20, a phase 1, double-blind, randomised, placebo-controlled, single-dose escalation of eplontersen to evaluate safety, tolerability, PK, and PD of single doses:
 - 18 healthy volunteers of Japanese descent, dose escalation 45 mg, 60 mg, 90 mg.
- Study CS21, a phase 1, randomised, open-label, single dose, 3-period, crossover study to assess bioequivalence of 45 mg eplontersen from 3 different drug product presentations:
 - 57 healthy volunteers, presentations including pre-filled syringe (N= 48), autoinjector (N= 51), and vial and syringe (N= 50), 45 mg dose, with 4-week washout between doses.
- CS3, a phase 3, global, randomised, open-label study to evaluate efficacy and safety of eplontersen in subjects with ATTRv associated peripheral neuropathy (ATTRv-PN), and to evaluate trough and post-treatment concentrations, and PK parameters in a subset of participants:
 - 144 in eplontersen treatment arm, and 28 in PK subgroup, receiving eplontersen 45 mg Q4W for 84 weeks.
- Population PK report incorporating data from studies CS1, CS20, CS21, and CS3, comprising 5,525 observations from 230 participants.
- Population PK/PD report, including data from studies CS1, CS20, CS21 and CS3, comprising 2,722 observations from 258 participants.

Based on population estimates following SC administration, eplontersen is rapidly absorbed into the systemic circulation, with peak plasma levels reached approximately 2 hours post-dose. After reaching maximum observed eplontersen concentration in plasma (C_{max}), plasma concentrations of eplontersen decline in a biphasic fashion with an initial, relatively fast disposition phase that dominates the plasma clearance followed by a much slower elimination phase. Plasma C_{max} and area under the plasma concentration-time curve (AUC) increased slightly greater than dose proportionally over a dose range of 45 to 120 mg of eplontersen. Geometric mean eplontersen plasma concentrations decreased > 95% from the C_{max} at 24 hours following SC injections. The apparent terminal elimination half-life ranged from 3 to 4 weeks over a dose range of 45 to 120 mg and appeared to be independent of dose. Steady state is reached after approximately 17 weeks.

No accumulation in C_{max} or AUC was observed after repeated SC administrations once every 4 weeks (Q4W), consistent with the low observed trough of eplontersen concentration in plasma (C_{trough}) in relation to the C_{max} and time invariant plasma kinetics. C_{trough} levels were < 0.2% of C_{max} after multiple SC administrations of 45 mg eplontersen Q4W. However, accumulation in C_{trough} levels was observed, reflective of drug accumulation in tissues. Interparticipant variability in eplontersen pharmacokinetic parameters was moderate in healthy volunteers (percent coefficient of variation (%CV) 24.1–76.7%) and higher in participants with ATTRv-PN (up to 109%).

Table 5 summarises key PK parameters for eplontersen across the phase 1 studies conducted in healthy volunteers, and the phase 3 study CS3 conducted in patients with ATTRv-PN, at the 45 mg Q4W dosing which is sought in this application.

Table 5. Summary of eplontersen pharmacokinetic parameters, 45 mg 4 weekly dosing.

Study Type	Study Code	N	Dosing Day	PK parameter					
				$t_{\max}$ (h)	$C_{\max}$ (µg/mL)	AUC ^b (µg*h/mL)	C_{trough} ^c (µg/mL)	$t_{1/2\lambda}$ (days)	CL _{0-24/F} (L/h)
Phase I (healthy volunteers)	ION-682884-CS1	10	Day 1 ^d	2.01 (1.00, 4.00)	0.143 (39.3)	1.21 (24.1)	NA	NC	37.3 (24.1)
Phase I (healthy volunteers)	ION-682884-CS1	10	Day 85 ^e	3.00 (1.00, 3.00)	0.215 (66.1)	1.40 (35.4)	0.000260 (71.9) ^g	22.0 (72.1)	32.1 (35.4)
Phase I (healthy volunteers)	ION-682884-CS20	6	Day 1 ^e	1.75 (0.50, 2.00)	0.307 (52.7)	1.73 (34.3)	NA	NA	26.1 (34.4)
Phase I (healthy volunteers)	ION-682884-CS21 ^j	47	Days 1, 29, 57 ^e	2.50 (1.00, 8.00)	0.216 (52.6)	1.68 (25.2)	NA	NC	NC
Phase III (patients with ATTRv-PN)	ION-682884-CS3	23	Day 1 ^{d, e}	2.17 (1.00, 6.00)	0.204 (109)	0.871 (98.9)	NA	NC	NC
Phase III (patients with ATTRv-PN)	ION-682884-CS3	19	Day 225 ^{d, e, f}	2.05 (0.967, 6.00)	0.215 (83.0)	0.836 (72.1) ^j	0.000186 (66.0) ^h	NC	NC
Phase III (patients with ATTRv-PN)	ION-682884-CS3	25	Day 449	2.00 (1.00, 6.00)	0.201 (87.7)	0.829 (72.8)	0.000262 (60.4) ^h	NC	NC

a The PK parameters $C_{\max}$, AUC, $t_{1/2\lambda}$ and CL_{0-24/F} are presented as geometric mean (geometric %CV). $t_{\max}$ is presented as median (minimum, maximum). C_{trough} is presented as arithmetic mean (%CV) due to many individual BLQ values.

b AUC_{0-24h} was calculated for studies ION-682884-CS1 and ION-682884-CS20; AUC_{0-168h} was calculated for study ION-682884-CS21; AUC_{0-6h} was calculated for study ION-682884-CS3.

c The C_{trough} values presented in this table are from overall ADA-negative subjects.

d Injection site: arm.

e Injection site: abdomen.

f Injection site: thigh.

g The C_{trough} presented here is the concentration at steady-state (Day 113) in overall ADA-negative subjects (N = 7). %CV was calculated as SD/Mean × 100, ie, (0.000187/0.000260) × 100=71.9

h The C_{trough} presented here is from overall ADA-negative subjects in the eplontersen group of study ION-682884-CS3 PK Set (N = 67 for Day 225 and N = 68 for Day 449).

i N = 18

j The presentation of eplontersen product administered in studies was vial and syringe, except for study ION-682884-CS21, in which all the 3 presentations (PFS with safety device, autoinjector [intended commercial product presentation], and vial and syringe) were administered, whereas only PK parameters from vial and syringe is presented in this table.

%CV = percent coefficient of variation; ADA = antidrug antibody; ATTRv-PN = hereditary transthyretin mediated amyloidosis with polyneuropathy; AUC = area under the concentration-time curve; AUC_{0-168h} = AUC from time 0 to 168 hours post-dose; AUC_{0-24h} = AUC from time 0 to 24 hours post-dose; AUC_{0-6h} = AUC from time 0 to 6 hours post-dose; BLQ = below the lower limit of quantification; CL_{0-24/F} = apparent clearance assessed over the time interval of 0 to 24 hours post-dose; $C_{\max}$ = maximum plasma concentration; C_{trough} = trough plasma concentration; h = hour(s); L = liter(s); N = number of subjects with PK results at the specified dosing day; NA = not applicable; NC = not calculated; PFS = prefilled syringe; PK = pharmacokinetic(s); SD = standard deviation; $t_{1/2\lambda}$ = elimination half-life; $t_{\max}$ = time to maximum concentration.

Population PK analysis identified injection site as a statistically significant covariate for absorption rate, with injections in the arm associated with slower absorption rate, with a 23% lower mean $C_{\max}$ at steady-state compared to abdomen or thigh injection sites, though impact on steady-state AUC and C_{trough} was minimal.

The population PK estimates of volume of distribution of the central compartment (V_c/F) and volume of distribution of the peripheral compartment (V_p/F) were 12.9 L and 11,100 L, respectively. The Sponsor reported a pre-clinical study found eplontersen is highly (> 98%) bound to plasma proteins, with little change over a clinically relevant range of 0.1 to 5 µg/mL. The Sponsor reported a pre-clinical study found the human blood to plasma ratio for eplontersen was between 0.632 and 0.739 over a concentration range of 0.01 to 1 µg/mL. These data suggest that eplontersen distributes mostly in the plasma compartment and that no plasma protein-binding displacement is expected between eplontersen and other highly plasma protein-bound drugs.

Metabolism is nuclease mediated in tissues, with shortened oligonucleotides rapidly eliminated in the urine. Urinary excretion of eplontersen as total full-length ASO within the first 24 hours post-dose represented a small fraction (< 1%) of the administered dose and was dose independent.

The primary route of elimination of eplontersen is initial rapid hydrolysis of GalNAc conjugate following uptake into tissues, where the unconjugated eplontersen is slowly metabolised by endo- and exonucleases. Terminal elimination half-life is approximately 3 weeks, after which there is rapid urinary excretion of the slowly formed fragmented oligonucleotide metabolites. The trishexylamino-linker undergoes rapid oxidative metabolism in tissues, followed by elimination (> 90%) via biliary excretion, and to a lesser extent, renal excretion, within 24 hours of administration.

Eplontersen has not been studied in patients with moderate or severe hepatic impairment or in patients with prior liver transplant. The population PK analysis did not identify mild hepatic impairment category or baseline aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin as statistically significant covariates impacting eplontersen PK. No dose adjustment is suggested for patients with mild hepatic impairment (total bilirubin $\leq 1 \times$ upper limit of normal (ULN) and AST $> 1 \times$ ULN, or total bilirubin > 1.0 to $1.5 \times$ ULN and any AST).

Eplontersen has not been studied in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m² or with end-stage renal disease. The population PK analysis identified baseline eGFR (mL/min/1.73m²) as a statistically significant covariate on eplontersen PK, where lower baseline eGFR was associated with lower eplontersen clearance. This was based on limited data, with only 3 (1%) participants with moderate renal impairment (defined as eGFR 30 to < 60) and 59 (26%) participants with mild renal impairment (eGFR 60 to < 90) included in the analysis. Whilst modelling suggested higher steady-state $AUC_{0-\tau}$, C_{max} , and C_{trough} values compared to an individual with normal renal function, the Sponsor noted these differences in exposures were small compared with the within-group variability and were not considered clinically meaningful. No dose adjustment is suggested in patients with mild to moderate renal impairment (eGFR ≥ 45 to < 90).

In the population PK analysis, age was not identified as a statistically significant covariate impacting eplontersen PK. No dose adjustment is suggested based on age. The age range of participants in clinical studies was 23 to 82 years old. Of note, anti-drug antibody (ADA) positive participants were excluded from PK modelling.

Based on totality of evaluable PK data, at 45 mg Q4W dosing, no dose adjustments were recommended based on body weight, sex, age, race, disease stage, drug product presentation, or injection site.

In vitro studies were reported by the Sponsor to show that eplontersen is not an inhibitor or an inducer of CYP enzymes nor a substrate or inhibitor of transporters, and it does not interact with highly plasma protein-bound drugs. No drug-drug interaction was reported to be observed in vitro with regard to plasma protein binding displacement between eplontersen and highly

plasma protein-bound drugs, warfarin and ibuprofen. Dedicated clinical drug interaction studies with eplontersen were not conducted.

The PK for eplontersen were comprehensively characterised and all three proposed administration sites, namely abdomen, thigh and arm, are suitable for clinical use on the basis of PK data.

Bioequivalence of different presentations

A vial and syringe presentation (eplontersen 150 mg/mL, 0.3 mL) was used in the clinical development program. The intended commercial presentation includes a pre-filled syringe with an automatic injector (AI; 56 mg/mL, 0.8 mL).

Study CS21 was conducted to determine the bioequivalence between three product presentations (including vial and syringe and AI). While the study demonstrated no difference between AUC_{0-168h} when using the AI when compared to the vial and syringe, the 90% confidence intervals (CIs) of the geometric mean ratio for C_{max} exceeded the standard bioequivalence upper boundary criteria of 125% by 3.17%.

Based on the population PK and PK/PD analysis, the AI presentation had a slightly higher (6.25%) nominal delivered dose and faster absorption rate compared with vial and syringe. These differences resulted in a 23% higher steady-state C_{max} , 7% higher C_{trough} , and 6% higher $AUC_{0-\tau}$.

The differences in PK parameters identified between the AI and vial and syringe presentations did not translate into any differences in serum TTR concentration reduction, suggesting no clinically meaningful effect on PD. The overall clinical development program showed consistent safety profile between different presentations. The Sponsor contends that small observed differences in PK parameters with the AI presentation are not expected to have any clinically meaningful effect on safety or efficacy of eplontersen.

It was concluded that the AI presentation was likely therapeutically equivalent to the vial and syringe presentation, notwithstanding bioequivalence criteria for C_{max} not being met in study CS21.

Pharmacodynamics

Evaluable PD data was included in studies CS1, CS20 (healthy participants of Japanese ancestry), CS3, a population PK/PD report, QT studies (CS1 and CS20), CS21 (bioequivalence studies), and via an exposure-response report.

PD data were analysed as change and percent change from baseline (Δ) in serum TTR concentration following SC administration of single (45 to 120 mg) and multiple (45 to 90 mg) doses for eplontersen in studies CS1, CS20, CS21, and CS3.

In healthy volunteers, a reduction in serum TTR concentration was observed across all studies from the first post-dose measurement on day 8 and remained reduced through the last day of each study (up to 3 months post-dose). The administration of single and multiple doses of eplontersen resulted in dose-dependent reductions in serum TTR concentrations in healthy volunteers.

In participants with ATTRv-PN, a reduction in serum TTR concentration was observed from the first assessment (week 5) and the mean percent serum TTR concentration reduction was 82-83% across the major analysis time points of week 35, 65 and 85.

Based on the popPK/PD analysis, steady-state for serum TTR concentration reduction was reached after approximately 17 weeks in participants with ATTRv-PN following SC administration of 45 mg eplontersen q4w.

In study CS3, mean serum vitamin A concentrations at baseline were similar in the eplontersen and external placebo groups (52.2 and 53.1 µg/dL, respectively). Most of the participants in the eplontersen group (95.1%) and historical inotersen group (90.1%) had post-baseline vitamin A value < lower limit of normal (LLN) compared with 3.3% of participants in the external placebo group. In the eplontersen group the mean vitamin A level reduced from baseline by 70.5% and 62.6% at week 37 and 65, respectively. Of all participants treated with eplontersen, 87.2 % of participants who had normal vitamin A levels at baseline had low vitamin A levels during treatment. Whilst mean retinyl palmitate levels measured in study CS3, representing an alternative source of vitamin A, remained steady across study duration in both eplontersen and external control groups, the dossier did not include evidence to contextualise the clinical implications of this.

There was no evidence of clinically significant effect on corrected QT interval, though a thorough QT study was not conducted owing to the lack of known class effect for 2'-O-methoxyethyl ASOs.

The clinical treatment target of reduction in serum TTR level greater than 80% from baseline supports the clinical relevance of the PD data obtained in patients with ATTRv-PN included in the dossier.

Efficacy

Dose finding

Based on known characteristics of ASOs, being hydrophilic and distributing predominantly to the lean body mass, and results from nonclinical studies the Sponsor proceeded with fixed dosing as opposed to dosing by body weight. An eplontersen dose of 45 mg Q4W was determined as the optimal dose to evaluate in the phase 3 clinical program, based on the achieved reduction in serum TTR concentration and acceptable safety profile in study CS1 in healthy volunteers.

A comparison of the Q4W with monthly administration frequency was performed using the final population PK and PK/PD models and applying the covariate distribution from study CS3 in patients with ATTRv-PN. The comparison between the Q4W and monthly dosing regimens showed no clinically meaningful differences in the simulated PK exposure metrics (steady-state C_{max} , C_{trough} , and $AUC_{0-\tau}$) or serum TTR concentration reduction. The Sponsor's position therefore is that monthly dosing is expected to result in comparable safety and efficacy to Q4W administration, with the proposed dosing in this application being monthly.

Studies providing evaluable efficacy data

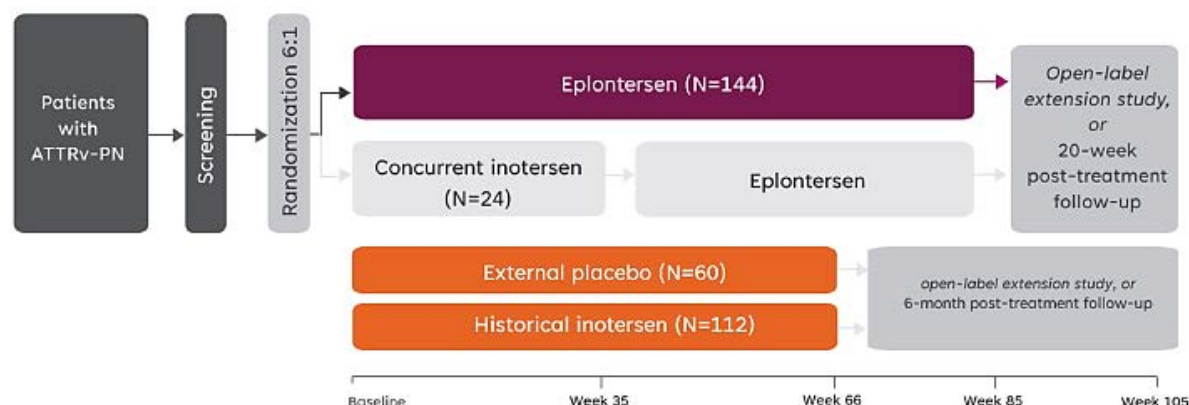
The dossier included 1 pivotal phase 3 clinical study, CS3 (NEURO-TTRransform). Study CS13, a phase 3 long-term extension study up to 3 years enrolling subjects completing study CS3 or study CS101, remains ongoing and efficacy data was not provided in the dossier.

Pivotal study: CS3

This was a phase 3, multicentre, open-label, external control, randomised study designed to evaluate superiority of eplontersen versus external placebo control in slowing disease progression of ATTRv-PN, conducted between December 2019 and March 2023 across 17 international sites, including Australia. The Sponsor's rationale for external control groups was that administration of a placebo would be unethical given the availability of approved therapies

for what constitutes a progressive and life-threatening condition. Efficacy of eplontersen was evaluated by comparison with 3 other treatment groups, as outlined in Figure 2, namely an external placebo group sourced from study ISIS 420915-CS2 which was conducted from March 2013 to March 2017, a concurrent inotersen group, and a historical inotersen group. The primary objective was to evaluate the efficacy of eplontersen, compared with external placebo, with regards to serum TTR concentration, modified Neuropathy Impairment Score + 7 (mNIS+7) composite score, and Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) total score over 65 weeks of treatment. Study ISIS 420915-CS2, from which the external placebo control group was sourced, was a phase 2/3 randomised, double-blind, placebo-controlled study to assess efficacy and safety of eplontersen in subjects with amyloid polyneuropathy.

Figure 2. Study scheme for clinical study CS3.



Key inclusion criteria for study CS3 were adults aged 18 to 82 years, with ATTRv-PN defined as stage 1 (ambulatory without assistance) or stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy or Coutinho Stage, documented genetic mutation in the TTR gene, and Symptoms and signs consistent with neuropathy associated with ATTR, including Neuropathy Impairment Score (NIS) ≥ 10 and ≤ 130 . Key exclusion criteria included features on medical history including certain infections, malignancy within 5 years, and other causes of sensorimotor or autonomic neuropathy, diabetes mellitus, certain abnormalities on laboratory results at screening, notably $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$, and current treatment with any approved drug for ATTRv or previous treatment with inotersen or patisiran or other oligonucleotide or RNA therapeutic (excluding COVID-19 vaccines). Concomitant treatment with tafamidis was also excluded. Of note, for study ISIS 420915-CS2 participants were excluded with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$.

Eligible patients were randomised 6:1 to eplontersen or inotersen. Patients in the eplontersen group received 45 mg eplontersen SC (0.3 mL) Q4W up to and including week 81. Patients in both inotersen cohorts received 300 mg SC Q1W. For those in study CS3 randomised to inotersen this was administered up to week 34, and from week 37 to week 81 these subjects switched to eplontersen 45 mg Q4W. The historical inotersen cohort received 300 mg Q1W up to week 65. All participants were required to take daily oral supplemental doses of the recommended daily allowance of vitamin A (defined as approximately 3000 IU) during the treatment and post-treatment evaluation periods.

Table 6 summarises efficacy endpoints according to both interim and final analysis, with analysis of efficacy endpoints proceeding as comparison between eplontersen treatment group and historical placebo control group.

Table 6. Efficacy endpoints, clinical study CS3.

Final Analysis Co-Primary Efficacy Endpoints	• Percent Δ in serum TTR concentration at week 65 • Δ in mNIS+7 at week 66 • Δ in Norfolk QOL-DN at week 66
Final Analysis Secondary Endpoints	• Δ in Neuropathy Symptom and Change (NSC) at week 66 • Δ in NSC at week 35 • Δ in the physical component summary score of 36-Item Short Form Survey (SF-36 PCS) score at week 65 • Δ in polyneuropathy disability (PND) score at week 65 • Δ in mBMI at week 65
Interim Analysis Co-Primary Efficacy Endpoints at week 35	• Percent Δ in serum TTR concentration at week 35 • Δ in mNIS+7 at week 35
Interim Analysis Key Secondary Efficacy Endpoint at week 35	• Δ in Norfolk QOL-DN at week 35

It was noted that whilst serum TTR concentration is not a validated surrogate endpoint for clinical outcomes in ATTRv-PN, it has been used in previous studies, and that mNIS+7 is an accepted objective scale to measure neurological manifestations of ATTRv-PN. The Norfolk QoL-DN is a questionnaire to assess disease-specific changes in QoL in diabetic neuropathy. Results between -4 to 136 points were possible. Higher scores represent a greater severity of disease or impairment, respectively. While study treatment was open-label, evaluators completing mNIS+7 assessments were independent, blinded to the study treatment being received, and where possible, were the same for all assessment for an individual participant.

Study sites and participants were also blinded to PD marker data. Efficacy analyses were conducted on the full analysis set (FAS) which comprised all randomised subjects who received at least 1 dose of study treatment, had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 or Norfolk QOL-DN questionnaire. Other analysis sets were the randomised set, per-protocol set (PPS) and safety set.

Sample size estimates were based on data from study ISIS 420915-CS2. For study CS3, it was projected that participants treated with eplontersen would experience at least an 80% mean reduction in TTR from baseline, with an estimated standard deviation (SD) of 13%. It was further anticipated that this group would have a 4.2-point increase in mNIS+7 (SD: 20) and no change (0-point increase, SD: 20) in Norfolk QOL-DN from baseline. Assuming a 10% dropout rate, enrolment was planned for 140 participants, resulting in 108 evaluable participants receiving eplontersen.

This cohort size was calculated to provide at least 95% power to detect a 70.3% difference in percent Δ in TTR between the eplontersen and external placebo cohorts, using a two-sided alpha level of 0.025. Additionally, the sample size allowed for at least 90% power to observe a 19.6-point difference in mNIS+7 scores and 80% power to detect a 10.7-point difference in Norfolk QOL-DN scores between the two study groups, both with a two-sided alpha level of 0.025.

There were 52 evaluable placebo participants in the PPS for study ISIS 420915-CS2 which comprised the external historical placebo group.

Interim analysis at 35 weeks considered the 2 co-primary endpoints first, percent change in TTR and change in mNIS+7 from baseline, and if both were significant at 2-sided alpha of 0.025, the change in Norfolk QOL-DN from baseline co-primary endpoint was to be tested at the same 2-sided alpha level. If all co-primary endpoints were found to be statistically significant at this interim analysis no formal testing would be conducted at the final analysis. Prespecified sensitivity analysis included analyses using all data, different missing data imputation approaches, and subgroup analyses. Testing of secondary efficacy endpoints proceeded by a hierarchical approach.

Of note, the EMA questioned the rationale for not formally testing co-primary efficacy endpoints at week 66, concluding that whilst week 66 testing may have enhanced interpretation of clinical significance of efficacy results, that the impact of not performing this testing was likely minimal.

Study ISIS 420915-CS2 included 60 participants randomised to and who received at least one dose of placebo, who formed the external placebo group. At week 66, 52 (86.7%) participants had completed treatment and of the remaining who discontinued treatment, majority were as a result of voluntary withdrawal (3) or disease progression (3). A total of 218 participants were screened for the study CS3 and 168 participants were randomised (eplontersen: 144, concurrent inotersen: 24), all of whom received at least one dose of study drug.

The majority of participants assigned to receive eplontersen completed study treatment (135 (93.8%)) through week 66. In the historical and concurrent inotersen groups, 87 (77.0%) and 19 (79.2%) participants completed study treatment through week 66, respectively. The majority of participants had at least 1 major protocol deviation, with the most common study procedure deviation due to assessments performed outside defined windows, and drug error deviations due to dosing in the absence of evaluable platelet count.

In terms of baseline patient demographics, it is notable that mean age was lower in the eplontersen treatment group in study CS3 (53.0 years) compared to historical placebo group (59.5 years), with 15% in the placebo group in the ≥ 75 years group compared to 5.6% in the eplontersen group. Further, in terms of race, there was a higher proportion of participants of Asian ethnicity in the eplontersen group (15.4%) compared to historical placebo group (5.0%).

Demographics were otherwise comparable between groups. In terms of baseline disease characteristics the majority of subjects in all groups had stage 1 PN, and had received previous treatment. It is notable that subjects in the eplontersen group had lower mean serum TTR at baseline and lower disease severity at baseline compared to the historical placebo group. During EMA evaluation the Sponsor stated that use of propensity scores during analysis sought to match baseline characteristics between these two groups, with the EMA evaluation concluding that observed differences in baseline characteristics did not meaningfully impact conclusions on efficacy or magnitude of treatment effect, which was also accepted by the TGA.

All primary and secondary efficacy endpoints were met, with statistically significant results favouring eplontersen at week 35 interim analysis, and sustained effects observed at week 66. Table 7 shows results of interim and final analysis for co-primary efficacy endpoints, comparing historical external placebo control group to eplontersen treatment group.

Table 7. Results of interim analysis and final analysis, co-primary efficacy endpoints, study CS3

	Baseline, mean (SD)		LS mean Δ^a /percent Δ^b , (SE) [95% CI]		Treatment difference (95% CI)	
Analysis/endpoint	CS2 External Placebo	CS3 Eplontersen 45 mg q4w	CS2 External Placebo	CS3 Eplontersen 45 mg q4w	Eplontersen minus Placebo	p-value ^c
Week 35						
Full analysis set	N = 59	N = 140	N = 59	N = 140		
Serum TTR, g/L ^{b, d}	0.15 (0.038)	0.23 (0.076)	-14.8% (1.98) [-18.73, - 10.80]	-81.2% (1.70) [-84.55, - 77.84]	-66.4% (-71.39, - 61.47)	< 0.0001
mNIS+7 composite score ^{a, e, f}	74.1 (39.03)	79.6 (42.32)	9.2 (1.88) [5.54, 12.91]	0.2 (1.87) [-3.46, 3.89]	-9.0 (-13.48, - 4.54)	< 0.0001
Norfolk QoL-DN total score ^{a, e, f}	48.6 (26.97)	43.5 (26.25)	8.7 (2.11) [4.53, 12.81]	-3.1 (2.08) [-7.19, 0.96]	-11.8 (-16.82, - 6.76)	< 0.0001
Week 66						
Full analysis set	N = 59	N = 141	N = 59	N = 141		
Serum TTR, g/L ^{b, g}	0.15 (0.038)	0.23 (0.075)	-11.2% (1.91) [-15.06, - 7.41]	-81.7% (1.61) [-84.82, - 78.48]	-72.5 % (-79.18, - 65.72)	< 0.0001
mNIS+7 composite score ^{a, d, f}	74.1 (39.03)	79.8 (42.25)	25.1 (2.39) [20.23, 29.88]	0.3 (2.41) [-4.46, 5.06]	-24.8 (-30.96, - 18.56)	< 0.0001
Norfolk QoL-DN total score ^{a, d, f}	48.6 (26.97)	43.3 (26.21)	14.2 (2.35) [9.51, 18.97]	-5.5 (2.30) [-10.03, - 0.96]	-19.7 (-25.63, - 13.84)	< 0.0001

a Change from baseline

b Percent change from baseline

c At the week 35 interim analysis, all 3 endpoints were statistically significant within the confirmatory testing strategy. In accordance with the prespecified testing strategy, none of the 3 co-primary endpoints at week 66 was therefore formally tested within the prespecified testing strategy.

d Based on an 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 value and the baseline-by-time interaction.

e Based on an ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, Val30Met mutation, previous treatment, and the baseline value

f Patients with a missing mNIS+7 composite score or Norfolk QoL-DN total score had value multiply imputed using an imputation model. Each of 500 imputed data sets was analysed using simple ANCOVA model and the 500 ANCOVA model results were combined using Rubin's rules.

g Based on non-parametric Wilcoxon Rank Sum Test (prespecified sensitivity analysis 1, as the Shapiro-Wilks test rejected the assumption of normal distribution).

With respect to the mNIS+7 co-primary endpoint week 66 results demonstrated stability in the eplontersen group, with an increase over time in the external placebo group indicative of disease progression. Overall, sensitivity analyses and subgroup analyses across the co-primary endpoints were supportive of the primary analyses. Results for other secondary efficacy endpoints and exploratory endpoints were also supportive. Inotersen treatment arms in study CS3 were used to compare treatment responses between study CS3 and study ISIS 420915-CS2, with meaningful comparison hampered by small sample sizes.

Overall, it was observed that the complex study design was similar to those used for other ATTR treatments, with measures such as propensity scoring and inotersen treatment groups to allow

cross-study comparison acting to address potential bias due to open-label design and historical, external control group. The clinically meaningful nature of results was noted, with concern about interim analysis at week 35 for a chronic and progressive condition, offset by consistency of results at week 66.

Safety

Evaluable safety data was submitted in the pivotal phase 3 study CS3, pooled data from study CS3 and its long-term extension CS13 up to data cut-off of 7 April 2023, as well as data from 3 phase 1 studies, CS1, CS20 and CS21. Concomitant use of vitamin A supplements is recommended during treatment with eplontersen, including for all clinical trial participants. Vitamin A deficiency was monitored through laboratory results, and during studies CS3 and CS13 through the periodic (2-3 monthly) administration of a short ocular questionnaire which was designed to screen for vitamin A deficiency. During studies in the target population, participants who presented with new and persistent ocular symptoms compatible with vitamin A deficiency (e.g., night blindness or dry eyes) were to be referred for an ophthalmology examination and, if findings were consistent with vitamin A deficiency, referral to a corneal specialist. Participants were to be permanently discontinued from study drug administration if they demonstrate clear signs of vitamin A deficiency confirmed by an ophthalmologist and discussed with the Investigator. Identified adverse events of special interest (AESIs) included thrombocytopenia, glomerulonephritis, coagulation abnormalities, renal impairment, abnormal liver function, injection site reactions (ISRs), flu-like symptoms, central nervous system (CNS) disorders, and reduced thyroxine.

An integrated summary of safety data pooled from studies CS3 and CS13 was the basis for evaluation of safety, in which 167 participants received at least 1 dose of eplontersen, mean exposure of 628 days, and mean of 22 doses administered.

Treatment emergent adverse events

Table 8 summarises common (occurring in $\geq 2\%$ of subjects receiving eplontersen) treatment emergent adverse events (TEAEs) according to study CS2 external control group, study CS3 eplontersen treatment group, and pooled data for eplontersen-treated subjects. By preferred term (PT), TEAEs that occurred in $\geq 5\%$ of subjects receiving eplontersen, and at a higher rate compared to placebo, included Vitamin A deficiency, vomiting, proteinuria and blurred vision. Most TEAEs were classified as mild or moderate in severity with no severe TEAEs considered related to study treatment by investigators. The incidence of TEAEs was highest in the first 6 months of treatment and declined over time.

Table 8. Treatment emergent adverse events.

Preferred term	CS2 placebo (N=60)		CS3 eplontersen (N=144)		Eplontersen treated set ^a (N=167)	
	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)
Urinary tract infection	10 (16.7)	12 (16.69)	24 (16.7)	41 (23.02)	36 (21.6)	74 (24.1)
Diarrhoea	11 (18.3)	14 (19.47)	24 (16.7)	28 (15.72)	33 (19.8)	39 (12.7)

Preferred term	CS2 placebo (N=60)		CS3 eplontersen (N=144)		Eplontersen treated set ^a (N=167)	
	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)
Vitamin A deficiency^b	0	0	17 (11.8)	17 (9.55)	18 (10.8)	19 (6.2)
Nausea	7 (11.7)	9 (12.52)	16 (11.1)	21 (11.79)	17 (10.2)	22 (7.2)
Vomiting	3 (5.0)	3 (4.17)	12 (8.3)	23 (12.91)	16 (9.6)	31 (10.1)
Proteinuria	2 (3.3)	2 (2.78)	12 (8.3)	13 (7.30)	16 (9.6)	18 (5.9)
Oedema peripheral	5 (8.3)	5 (6.95)	12 (8.3)	14 (7.86)	15 (9.0)	17 (5.5)
Arthralgia	5 (8.3)	7 (9.74)	9 (6.3)	9 (5.05)	14 (8.4)	21 (6.9)
Headache	7 (11.7)	10 (13.91)	9 (6.3)	10 (5.61)	13 (7.8)	14 (4.6)
Dizziness	6 (10.0)	6 (8.35)	10 (6.9)	11 (6.18)	12 (7.2)	13 (4.2)
Fall	13 (21.7)	16 (22.26)	8 (5.6)	9 (5.05)	12 (7.2)	17 (5.5)
Pain in extremity	8 (13.3)	12 (16.69)	9 (6.3)	11 (6.18)	11 (6.6)	13 (4.2)
Fatigue	12 (20.0)	14 (19.47)	7 (4.9)	8 (4.49)	11 (6.6)	15 (4.9)
Cough	8 (13.3)	8 (11.13)	7 (4.9)	7 (3.93)	11 (6.6)	11 (3.6)
Nasopharyngitis	6 (10.0)	7 (9.74)	8 (5.6)	11 (6.18)	10 (6.0)	13 (4.2)
Thermal burn	6 (10.0)	6 (8.35)	6 (4.2)	8 (4.49)	8 (4.8)	10 (3.3)
Vision blurred	1 (1.7)	1 (1.39)	8 (5.6)	11 (6.18)	8 (4.8)	11 (3.6)

Preferred term	CS2 placebo (N=60)		CS3 eplontersen (N=144)		Eplontersen treated set ^a (N=167)	
	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)	Patients n (%)	Events N (Rate ^e)
Anaemia	1 (1.7)	1 (1.39)	6 (4.2)	6 (3.37)	8 (4.8)	10 (3.3)
Syncope	2 (3.3)	2 (2.78)	7 (4.9)	7 (3.93)	7 (4.2)	9 (2.9)
Dry eye	2 (3.3)	2 (2.78)	6 (4.2)	6 (3.37)	6 (3.6)	6 (2.0)
Neuralgia	9 (15.0)	9 (12.52)	4 (2.8)	6 (3.37)	6 (3.6)	8 (2.6)
Constipation	6 (10.0)	6 (8.35)	4 (2.8)	4 (2.25)	6 (3.6)	6 (2.0)
Injection site pain	5 (8.3)	8 (11.13)	5 (3.5)	8 (4.49)	5 (3.0)	8 (2.6)
Injection site erythema	0	0	5 (3.5)	7 (3.93)	5 (3.0)	7 (2.3)
Injection site pruritus	0	0	3 (2.1)	5 (2.81)	3 (1.8)	5 (1.6)
Asthenia	8 (13.3)	11 (15.30)	3 (2.1)	3 (1.68)	4 (2.4)	5 (1.6)

^a Week 85+ includes data up to 7 April 2023.

^b Vitamin A laboratory-related treatment-emergent adverse events (TEAEs) were not reported in the ISIS 420915-CS2 study because the results were blinded to the investigator and Sponsor.

Bold rows indicate an incidence at least 2 percentage points higher in the eplontersen group than in the external placebo group.

Analysis of TEAEs across subgroups undertaken as part of the EMA evaluation demonstrated higher rates of cardiac, renal and urinary disorders among participants >75 years of age compared to younger subgroups, and high incidence of eye disorders in non-White participants compared to White participants, however, low overall numbers limited clinical interpretability.

Treatment related adverse events (adverse drug reactions)

TEAEs determined to be related to study drug administration occurred in 61 (36.5%) of eplontersen-treated subjects and 23 (38.3%) placebo-treated subjects. In the eplontersen set the most common treatment related TEAE was vitamin A deficiency (9.6%). 14 (8.4%) also experienced ISRs following administration of eplontersen.

Adverse events of special interest

Vitamin A deficiency was recorded for 10.8% of eplontersen-treated subjects, with a further 4.2% recorded as vitamin A decrease. None of the events led to interruption or discontinuation

of eplontersen treatment. The incidence of ocular AEs potentially related to vitamin A deficiency in subjects treated with eplontersen was 28.7%. These TEAEs were generally mild to moderate and non-serious. None of the ocular AESIs potentially related to vitamin A deficiency led to discontinuation of eplontersen. The most common ocular AEs related to vitamin A deficiency were blurred vision and dry eye, which were reported in 4.8% and 3.6% of participants who received eplontersen, respectively. One severe and 1 serious ocular AEs related to vitamin A deficiency were reported. Both events were assessed as unlikely related to eplontersen use by investigators.

With respect to the AESI of thrombocytopenia, overall, observed decreases in platelet count during eplontersen use were mostly mild and transient, and resolved while on continued treatment. No events led to concurrent bleeding. No safety signals related to haemorrhages were identified in participants treated with eplontersen. Decreases in platelet count were observed more frequently in subjects treated with eplontersen; platelet count $<140 \times 10^9/L$ was recorded in 11 (18.3%) of subjects in the historical placebo control group, compared to 60 (35.9%) in the eplontersen-treated set, with $\geq 30\%$ decreased from baseline recorded in 4 (6.7%) in the placebo group and 52 (31.1%) in the eplontersen-treated set, and $\geq 50\%$ reduction from baseline recorded in 1 (1.7%) in the placebo group and 8 (4.8%) in the eplontersen-treated set. The median time to first occurrence of abnormal platelet counts ($< 140 \times 10^9/L$) was 23.4 weeks and median duration of abnormal counts was 6.1 weeks. One subject was noted to have severe thrombocytopenia (nadir platelet count of $16 \times 10^9/L$) that led to discontinuation of eplontersen. This event occurred 77 days after the last dose of eplontersen and was considered unlikely related to eplontersen use. In study CS3, the mean platelet count ($10^9/L$) was similar between the eplontersen and external placebo groups at baseline (223 vs 212). The mean Δ (SD) in nadir platelet count was -53 (34) in the eplontersen group and -35 (27) in the external placebo group. The EMA evaluation conducted additional analysis by concomitant antiplatelet or anticoagulant use, with no signal for bleeding events identified among those treated with eplontersen.

No TEAEs of glomerulonephritis were reported in subjects treated with eplontersen.

No TEAEs related to coagulation abnormalities were reported in subjects treated with eplontersen.

With respect to the AESI of ISR, 14 (8.4%) subjects experienced 27 AEs involving ISRs with the administration of eplontersen, in comparison to 11.7% of participants receiving placebo (noting that placebo was administered more frequently (Q1W) than eplontersen (Q4W)). TEAEs associated with the injection site were mild in severity (with no severe or serious events), mostly transient, and mostly resolved within a day. None of the TEAEs led to discontinuation of eplontersen treatment.

With respect to the AESI of CNS disorders, the incidence of CNS disorder was lower in subjects treated with eplontersen (32.3%) compared to placebo (53.3%). The most commonly reported TEAEs for eplontersen subjects were headache (13 [7.8%]), dizziness (12 [7.2%]) and syncope (7 [4.2%]). A total of 7 serious TEAEs were reported in 5 subjects: 4 episodes of syncope in 3 subjects; 1 cerebral haemorrhage (severe and fatal) in 1 subject, 1 cerebral infarction in 1 subject, and 1 TEAE of metabolic encephalopathy in 1 subject. None of the serious TEAEs were considered as related to eplontersen use by investigators.

With respect to hypersensitivity, the rate of TEAEs of hypersensitivity was lower in eplontersen-treated subjects (20.4%) compared to placebo-treated (26.7%), with the majority classified mild to moderate in severity, and no cases of anaphylaxis or angioedema recorded. The most common recorded hypersensitivity reactions were skin rash, erythema and pruritis.

Deaths and other serious adverse events

A total of 7 deaths were reported in the eplontersen-treated set, with no deaths occurring in the external placebo group. Reported causes of death included arrhythmia, acute myocardial infarction, cardiac arrest, cardiogenic shock, cerebral haemorrhage, gastrointestinal haemorrhage, and sepsis, with no deaths determined related to study treatment by investigators. Brief case narratives were provided in the dossier. Underlying ATTR diagnosis, or ATTR related cardiomyopathy, was considered a contributing factor in most cases.

Up to week 66 in study CS3 the incidence of serious adverse events (SAEs) was lower in eplontersen treated subjects (14.6%) compared to placebo (20%). SAEs reported in more than 1 subject treated with eplontersen included vomiting, nausea, UTI, COVID-19 pneumonia, and syncope. No SAEs were considered related to study treatment by investigators. In the pooled eplontersen-treated set the incidence of TEAEs was slightly higher, 20.4%, with SAEs occurring in more than 1 subject including vomiting, pneumonia, UTI and syncope, AV block complete, nausea, sepsis, COVID-19 pneumonia and dehydration, none of which were considered related to study treatment by investigators. The proportion of subjects with TEAEs leading to discontinuation of study drug was 6.6% in the eplontersen-treated set and 3.3% in the external placebo group.

Laboratory results and vital signs

With respect to liver function, 14 (8.4%) subjects were found to have TEAEs related to abnormal liver function during treatment with eplontersen. Most commonly this was increased ALT (3.0%) or gamma glutamyl transferase (3.0%). One subject was found to have ALT levels $\geq 8 \times$ ULN, two participants had AST levels $\geq 5 \times$ ULN and two participants had total bilirubin levels $> 2 \times$ ULN. However, no cases met Hy's law criteria. Only 1 TEAE of abnormal transaminases resulted in eplontersen discontinuation, which was considered as possibly related to eplontersen by investigators.

With respect to renal function, there were higher recorded rates of $\geq 25\%$ and $\geq 50\%$ decrease from baseline eGFR in the eplontersen-treated set (22.8% and 1.2%, respectively) compared to those in the historical placebo control group (10% and 0, respectively). Increases in laboratory measures of proteinuria, including albumin-to-creatinine ratio and protein-to-creatinine ratio, occurred at similar rates across historical placebo group and eplontersen-treated set. Table 9 summarises post-baseline renal function parameters across treatment groups.

Table 9. Post-baseline renal function parameters.

	Up to Week 66 ^a			On study ^b
	ISS 420915-CS2		ION-682884-CS3	Eplontersen Treated Set ^d (N=167)
	Placebo (N=60)	Inotersen 300 mg q1w (N=112)	Eplontersen 45 mg q4w ^c (N=144)	
eGFR by CKD-EPI $\geq 25\%$ decrease from baseline	6 (10.0)	30 (26.8)	27 (18.8)	38 (22.8)
eGFR by CKD-EPI $\geq 50\%$ decrease from baseline	0	8 (7.1)	2 (1.4)	2 (1.2)
urine albumin-creatinine ratio $>5 \times$ ULN	14 (23.3)	32 (28.6)	25 (17.4)	33 (19.8)
Urine Protein-to-Creatinine Ratio $>5 \times$ ULN	5 (8.3)	17 (15.2)	10 (6.9)	14 (8.4)
Serum creatinine increase $>44.2 \mu\text{mol/L}$ (0.5 mg/dL) from baseline	1 (1.7)	12 (10.7)	3 (2.1)	5 (3.0)
Urine Protein-to-Creatinine Ratio, n (%)				
$>3 \times$ baseline and $>1000 \text{ mg/g}$	5 (8.3)	13 (11.6)	9 (6.3)	12 (7.2)
$>5 \times$ baseline and $>1500 \text{ mg/g}$ or absolute value $\geq 2000 \text{ mg/g}$	2 (3.3)	11 (9.8)	5 (3.5)	7 (4.2)
$>5 \times$ baseline and $>1500 \text{ mg/g}$	2 (3.3)	6 (5.4)	5 (3.5)	7 (4.2)
$\geq 2000 \text{ mg/g}$	2 (3.3)	11 (9.8)	4 (2.8)	6 (3.6)

a Up to Week 66: Time from first dose up to Study Day 456 or up to last contact, whichever comes first.

b On study: Time from first dose of eplontersen up to the data cut-off or up to last contact, whichever comes first.

c Includes patients from the ION-682884-CS3 study "Eplontersen 45 mg q4w" arm only and excludes patients from the inotersen/eplontersen arm.

d Eplontersen Treated Set: Includes all patients who received at least one dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

Four subjects experienced serious or severe TEAEs related to renal impairment, leading to interruption and discontinuation of eplontersen for 1 subject each, respectively. Investigators determined that 1 of these events, proteinuria, was possibly related to eplontersen use.

In terms of haematological parameters, data from pivotal study CS3 showed that white cell counts less than the lower limit of normal at any time post-baseline were more frequent among those treated with eplontersen compared to historical placebo, including leukopenia (36.1% in the eplontersen group, 8.3% in the historical placebo group, respectively), lymphopenia (62.5% and 28.3%, respectively), and neutropenia (13.9% and 6.7%, respectively).

However, there was higher frequency of sampling among the eplontersen treatment group, and there was no difference overall between groups in terms of TEAEs in the SOC infections and infestations (59.0% in the eplontersen group, 63.3% in the historical placebo group).

Noting high rates of cardiac involvement in ATTRv and effect of concomitant medications, there was no cardiac or cardiovascular safety signals identified during clinical development for eplontersen. The incidence of TEAEs related to cardiac disorders during studies in subjects with ATTRv-PN was similar between eplontersen-treated subjects (34 (20.4%) subjects) and those who received placebo (13 (21.7%) subjects). A total of 12 subjects who received eplontersen reported 17 serious TEAEs related to cardiac disorders, of these 13 events were severe. Among the serious TEAEs, 4 TEAEs had fatal outcomes (arrhythmia, acute myocardial infarction, cardiac arrest, cardiogenic shock). None of the severe, serious or fatal TEAEs were assessed as related to eplontersen by investigators.

Immunogenicity

In the pivotal study CS3 6.9% of subjects in the eplontersen group had ADAs detected at baseline, with 58/144 (40.3%) showing treatment emergent or boosted ADAs throughout the study. The median time to onset of treatment emergent ADA was 223 days (range 24 to 603) and the median peak titre was 200 (range 50 to 25600). Most ADA-positive subjects had persistent responses. Presence of ADA had no impact on C_{max} or AUC, while higher plasma eplontersen C_{trough} levels were observed in both healthy volunteers and subjects with ATTRv-PN who had treatment emergent ADAs. The observed reductions in serum TTR concentrations were maintained in subjects with treatment-emergent ADAs, suggesting that ADAs did not affect pharmacological response. There was no clinically meaningful impact of ADA positivity on safety of eplontersen.

Pregnancy and lactation

During the clinical development program, subjects who were at risk of pregnancy and/or lactating were excluded from participating in clinical trials to avoid potential harm to an unborn fetus or breastfed infant. During the clinical development program, no pregnancies were reported in subjects or partners of male participants who had been treated with eplontersen. No reports for lactation are available.

Post-marketing safety data

In their response to Round 1 clinical evaluation the Sponsor provided international post-market safety data to June 2025, with estimated post-approval international patient exposure of 441.75 patient-years, with no new safety signals identified.

Risk management plan

AstraZeneca Pty Ltd submitted EU-RMP version 1 succession 4 (dated 10 September 2024; DLP 7 April 2023) and Australia-Specific Annex version 1 succession 1 (dated 19 May 2025) in support of this application.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 10. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Ocular adverse events due to vitamin A deficiency	✓*	✓†	✓	–
Missing information	Use in pregnant women and effects on pregnancy outcomes	✓	–	✓	–

* Specific adverse reaction follow-up questionnaires

† Study ION-682884-CS13

The Sponsor has proposed routine pharmacovigilance activities for all safety concerns that includes specific adverse events follow-up questionnaire for ocular adverse events due to vitamin A deficiency. Additional pharmacovigilance activities have been proposed in the form of an open-label extension study to address the safety concern of ocular adverse events due to vitamin A deficiency. The pharmacovigilance plan is acceptable from an RMP perspective.

The Sponsor has proposed routine risk minimisation activities for all safety concerns in the form of a PI and CMI. The risk minimisation plan is acceptable from an RMP perspective.

Risk-benefit analysis

This Category 1, type A application seeks to register the new therapeutic entity eplontersen, a ligand-conjugated antisense-oligonucleotide targeting hepatic transthyretin mRNA, for the following indication: *'for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.'* Efficacy has been primarily established via 1 pivotal phase 3 clinical study, CS3, a multicentre, randomised, open-label study comparing eplontersen to placebo, via an historical external control group, among adult patients with stage 1 or stage 2 ATTRv-PN. The safety profile of eplontersen has been evaluated based on data from the same pivotal study, a long-term extension study, and 3 phase 1 studies. Eplontersen is registered in the EU (under the tradename WAINZUA), the United Kingdom, Switzerland and Canada with approved indications that mirror that sought in Australia and is registered in the US (under the tradename Wainua) with an approved indication that does not specify stage of disease for peripheral neuropathy. There are no outstanding clinical, nonclinical, quality or manufacturing evaluation issues that would preclude approval of the application.

Proposed indication

The proposed therapeutic indication is acceptable on the basis that it reflects the study population in the pivotal efficacy study, CS3. Inclusion criteria for this study specified stages 1 or 2 polyneuropathy, and required documentation of a genetic mutation in the

TTR gene. It is biologically plausible that eplontersen will have efficacy for patients with ATTRv and stage 3 polyneuropathy, a patient cohort with high unmet clinical need, and despite the lack of evaluable clinical data in patients with stage 3 polyneuropathy finds the following statement

in the proposed Australian PI to be acceptable, and aligned with other products on the ARTG with similar approved indications: *'The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.'*

This statement implies that patients were initiated on eplontersen when experiencing stage 1 or 2 polyneuropathy and derived some clinical benefit from treatment and given that ATTRv-PN is typically a progressive disease, represents a pragmatic balance with uncertainty around clinical efficacy.

During evaluation, the prospect of broadening the approved indication to cover wild-type ATTR-PN patients was raised, citing high unmet clinical need, the relative rarity of this condition in an Australian context, biological plausibility, and phase 1 clinical study data suggesting efficacy outcomes could also be expected in this cohort.

The likelihood of benefit for this patient cohort, is not disputed, however, in the absence of robust clinical data, efficacy and safety has not been satisfactorily established for treatment of wild-type ATTR-PN. The TGA is also cognisant of products in the ARTG with similar approved indications to that sought by the Sponsor in this application which reflect the evaluable clinical data submitted for those products, and the consistency of the indication sought here with approved indications for eplontersen in comparable overseas jurisdictions.

Pharmacokinetics and pharmacodynamics

PK and PD aspects were adequately evaluated and detailed in the dossier. Terminal elimination half-life was approximately 3 weeks, with steady-state concentration achieved after around 17 weeks of Q4W dosing. Repeated administration did not show accumulation in C_{max} or AUC values.

Modelling did not provide any rationale for dose adjustment based on various intrinsic and extrinsic factors. Compared to the vial and syringe presentation used in the pivotal study the autoinjector presentation resulted in slightly higher nominal dose delivered, translating to 23% higher steady-state C_{max} , with nominal increases observed in steady-state C_{trough} and $AUC_{0-\tau}$.

Clinical study CS21 was designed to assess bioequivalence between 3 different subcutaneous presentations, including the vial and syringe used in the pivotal study and the pre-filled syringe with autoinjector sought in this application. Whilst prespecified bioequivalence criteria were met between these 2 presentations for the AUC_{0-168H} endpoint, the upper boundary of the 125% was exceeded for C_{max} .

There is no evidence of clinically meaningful impact of these differences in PK parameters between the presentations. Population PK modelling suggested that moderate renal impairment, $eGFR < 45 \text{ mL/min/1.73m}^2$, would result in modest increases in steady-state $AUC_{0-\tau}$, C_{max} , and C_{trough} values; this risk can be adequately mitigated via the Australian PI. PD data showed reduction in serum TTR from week 5 assessment in subjects with ATTRv-PN with mean reduction in serum TTR 82-83% from baseline, in line with a generally accepted threshold for clinical effect of 80% reduction from baseline.

Efficacy

The pivotal clinical study, CS3, included 144 subjects randomised to receive eplontersen 45 mg Q4W up to study week 81 with the external historical placebo control cohort of 60 subjects derived from study ISIS 420915-CS2.

In the eplontersen treatment group the majority of subjects were male (69.4%), White ethnicity (78.3%), with a mean age of 53.0 years and mean weight 70.319 kg. Study CS3 also included a historical inotersen treatment group comprising 113 subjects, and a concurrent inotersen group with 24 subjects. The majority of subjects across all treatment groups had stage 1 polyneuropathy at baseline.

The rationale for the inotersen treatment groups was to assess for meaningful differences in treatment response between populations in study ISIS 420915-CS2 and study CS3. An interim analysis at week 35 compared 2 co-primary endpoints between the eplontersen and historical placebo control groups, namely percent change in serum TTR concentration, and change in mNIS+7. If primary and secondary efficacy endpoints were found to be statistically significant at interim analysis, no formal testing was planned for final analysis at study week 66.

Propensity scoring was used to counteract bias arising from the use of a historical placebo control group applying a logistic regression model with baseline covariates. Baseline demographic and disease characteristics were generally consistent between treatment groups. Observed differences in baseline disease characteristics are likely of minimal clinical consequence when considered against the magnitude of treatment effect demonstrated.

At week 35 interim analysis all efficacy endpoints were met; serum TTR reduction was -14.8% (95% CI -18.73%, -10.80%) in the external placebo group compared to -81.2% (95% CI -84.55%, -77.84%) in the eplontersen group (treatment difference -66.4% [-71.39%, -61.47%] $p < 0.0001$), change in mNIS+7 composite score 9.2 (95% CI 5.54, 12.91) in the external placebo group compared to 0.2 (95% CI -3.46, 3.89) in the eplontersen group (treatment difference -9.0 [95% CI -13.48, -4.54] $p < 0.0001$), with Norfolk QoL-DN results also favouring eplontersen and reaching statistical significance. Week 66 results supported durability of response. Analyses for other efficacy endpoints and sensitivity analyses supported the primary efficacy analysis.

The complex pivotal study design and use of historical external control group as limitations of pivotal study design are noted, however, the rationale for this approach, namely that it would be unethical to proceed with a concurrent placebo control group for a progressive and debilitating condition with approved treatment options is accepted.

It is also accepted that ATTRv-PN is a rare disease with consequent difficulty recruiting adequate participants. It is also noted that design of study CS3 is similar to studies supporting regulatory approval for products with similar approved therapeutic indications. Choice of efficacy endpoints is considered adequate to support claims of efficacy in ATTRv-PN.

Overall, efficacy results in study CS3 are considered clinically meaningful, with a large magnitude of clinical effect, and met prespecified criteria for statistical significance. Changes in the surrogate marker of serum TTR were correlated with stabilisation in deficits due to neuropathy, and improved subject-reported quality of life. Subgroup analysis found similar magnitude of effect across subgroups including age, sex, race, pathogenic variant TTR mutation and disease stage. The TGA accepts that a recommendation in the PI for monthly dosing, as opposed to Q4W dosing as used in the pivotal study, is reasonable.

Safety

The safety profile of eplontersen was adequately described based on evaluable data from the pivotal study CS3, interim data from the long-term extension study CS13, and from 3 phase 1 studies, with an integrated safety summary comprising data from studies CS3 and CS13. There was mean exposure of 22 doses, and 628 days across 167 subjects.

Overall rates of TEAEs demonstrated vitamin A deficiency, vomiting, proteinuria and blurred vision occurring more frequently in eplontersen-treated subjects compared to historical

placebo. Injection site reactions were more common in those treated with eplontersen compared to placebo, but with low overall numbers.

Vitamin A deficiency is a known class effect for medicines that reduce serum TTR concentration and a predictable effect of eplontersen treatment. TTR protein functions as a carrier for vitamin A through its association with retinol binding protein 4 (RBP4), however, alternative pathways for vitamin A transport include transport of retinyl esters in chylomicrons, not related to serum TTR concentrations. PD results showed most participants having post-baseline vitamin A levels below the LLN after receiving eplontersen. Integrated safety data showed 19 events of vitamin A deficiency in 18 subjects (10.8%) treated with eplontersen, with the incidence of ocular adverse events potentially related to vitamin A deficiency 28.7%, with blurred vision and dry eye the most commonly reported.

Most reported ocular adverse events were mild to moderate in severity and none led to discontinuation of eplontersen. Presentation of this risk in the Australian PI, including recommendations for vitamin A supplementation while receiving eplontersen in section 4.2 of the PI, is considered adequate. It is highly likely that the risk of vitamin A deficiency will be appreciated by prescribers experienced in the management of ATTRv-PN, that supplementation is highly accessible in the Australian context, and that monitoring both of vitamin A levels and screening for clinical manifestations of vitamin A deficiency are achievable in clinical practice.

Whilst thrombocytopenia was observed more frequently in subjects treated with eplontersen compared to placebo, changes in platelet count were generally mild, transient and of no clinical consequence with no safety signal for bleeding episodes identified.

There were 7 deaths recorded across clinical development for subjects treated with eplontersen; based on brief case narratives provided the conclusions of the investigators that reported deaths were unlikely related to eplontersen treated, and more likely associated with underlying effects of ATTRv or other comorbidities, are accepted.

In terms of potential renal toxicity comparison of baseline eGFR to nadir post-baseline eGFR showed a change to a lower category in 73 (43.7%) of subjects treated with eplontersen, and a higher rate of subjects experiencing $\geq 25\%$ reduction in eGFR from baseline in those treated with eplontersen (38 subjects, 22.8%) compared to placebo (6 subjects, 10.0%), noting low numbers of subjects in each group. Proteinuria was reported as a TEAE in 16 (9.6%) subjects in the eplontersen-treated set.

Whilst declining renal function and proteinuria are potential disease manifestations of ATTRv, given apparent differences between placebo and eplontersen treatment groups, the Sponsor will be asked to discuss the clinical significance of these observations. The proposed Australian PI does not include information or recommendations for monitoring of renal function.

There was no evidence to suggest impact of treatment-emergent ADAs on PK parameters, efficacy or safety.

Long-term safety data is being collected as part of the ongoing long-term extension study CS13. The provision of the final clinical study report for study CS13 is included as a condition of registration.

Other considerations

The TGA tradename committee considered the proposed tradename, Wainua, and recommended it as acceptable according to TGA requirements for naming of therapeutic goods.

Whilst the name 'Wainua' could be interpreted as suggesting the product is newer than other therapeutic goods with a similar therapeutic indication, which in turn could be interpreted

suggesting superiority of the product compared to these other therapeutic goods, the name is not overtly misleading and does not make any claims with regard to safety and efficacy. The recommendation of the tradename committee was accepted.

With respect to bioequivalence between the autoinjector presentation and the vial and syringe presentation used in clinical development, the upper bound of bioequivalence criteria for $C_{\max}$ was exceeded in study CS21 during the comparison of these 2 presentations, with PK/PD modelling suggesting a slightly higher nominal delivered dose for the autoinjector presentation. Based on lack of significant differences in serum TTR concentration reduction, and no evidence to suggest differences in the safety profile of eplontersen between the 2 presentations, the presentations are considered therapeutically equivalent.

Conclusions

The submitted dossier contains adequate evidence to establish safety, quality and efficacy of eplontersen as sodium, in the tradename Wainua, for the proposed therapeutic indication:

‘...for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.’

There are no outstanding clinical, nonclinical, manufacturing or quality evaluation issues which would preclude approval of the application.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Wainua (eplontersen) for the following indications:

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

Specific conditions of registration

- Wainua (eplontersen sodium) is to be included in the Black Triangle Scheme. The PI and CMI for Wainua must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Wainua EU-Risk Management Plan (RMP) (version 1 succession 4, dated 10 September 2024, data lock point 7 April 2023), with Australia-Specific Annex (ASA) (version 1 Succession 1, dated 19 May 2025), included with submission PM-2025-02079-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Submission of final Clinical Study Report for study ION-682884-CS13

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA [PI/CMI search facility](#).

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