30 January 2025
EMA/CHMP/515905/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wainzua

International non-proprietary name: eplontersen

Procedure No. EMEA/H/C/006295/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

2’-MOE	2’-o-(2-methoxyethyl)
ADA	Antidrug antibody
ACE	Angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
ASGPR	Asialoglycoprotein receptor
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
ATTR	Transthyretin-mediated amyloidosis
ATTRv	Hereditary transthyretin-mediated amyloidosis
ATTRv-CM	Hereditary transthyretin-mediated amyloidosis with cardiomyopathy
ATTRv-PN	Hereditary transthyretin-mediated amyloidosis with polyneuropathy
AUC	Area under the concentration-time curve
AV block	Atrioventricular block
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
CI	Confidence interval
CI	Copy increments from Reference
CK	Creatinine kinase
CKD-EPI	Chronic kidney disease epidemiology collaboration
CK-MB	Creatine kinase-myocardial band
CL/F	Apparent clearance at steady-state
CM	Cardiomyopathy
C_{max}	Maximum plasma concentration
CR	Copy Reference
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
C_{trough}	Trough plasma concentration
CYP	Cytochrome p450
DBP	Diastolic blood pressure
DCO	Data cut-off
EAER	Exposure adjusted event rate (per 100 patient years)
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EOT	End-of-treatment
E-R	Exposure-response
FAC	Familial amyloid cardiomyopathy (also referred to as ATTRv-CM)
FAS	Full analysis set
GalNAc	N-acetyl-galactosamine
GGT	Gamma glutamyl transferase
HbA1c	Haemoglobin A1c
hERG	Human ether-à-go-go-related gene
Historical inotersen	Inotersen treatment group from study ISIS 420915-CS2
HPLC	High performance liquid chromatography
HR	Heart rate
hs-CRP	High sensitivity c-reactive protein
IC50	Half maximal inhibitory concentration

IEC	Independent ethics committee
IFN-β	Interferon β
IgG	Immunoglobulin g
IgM	Immunoglobulin m
IL	Interleukin
Imax	Maximal inhibition
INR	International normalized ratio
ION-682884	Eplontersen
ISR	Injection site reactions
ISS	Integrated summary of safety
IST	Investigator-sponsored trial
IVST	Interventricular septum thickness
J2R	Jump to Reference
ka1	Absorption rate constant for the slow pathway
ka2	Absorption rate constant for the fast pathway
Km	Michaelis Menten constant
Kout	First-order elimination rate
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LCRIS	Local cutaneous reactions at the injection site
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LSM	Least square mean
LTE	Long-term extension
LV	Left ventricular
MATE	Multidrug and toxin extrusion protein
mBMI	Modified body mass index
MedDRA	Medical dictionary for regulatory activities
MMRM	mixed effects model with repeated measures
mNIS+7	Modified neuropathy impairment score +7
NCI-ODWG	National cancer institute organ dysfunction working group
NIS	Neuropathy impairment score
Norfolk QoL-DN	Norfolk quality of life-diabetic neuropathy
NSC	Neuropathy symptoms and change
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New york heart association
OAEI	Other adverse event of interest
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptides
OCT	Organic cation transporter
P25	25th percentile
P75	75th percentile
PCS	Physical component score
PFS	Prefilled syringe
P-gp	P-glycoprotein
PND	Polyneuropathy disability
PO	Phosphodiester
popPK	Population pharmacokinetic
popPKPD	Population pharmacokinetic/pharmacodynamic
PPS	Per protocol set
PS	Phosphorothioate
PT	Preferred term
PY	Patient years
q1w	Once weekly
q4w	Once every 4 weeks
QRS	Combination of the q wave, r wave, and s wave on an electrocardiogram
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate calculated using Bazett’s formula
QTcF	QT interval corrected for heart rate calculated using Fredericia’s formula
RBP4	Retinol binding protein 4
SAE	Serious adverse event
SAP	Statistical analysis plan

SBP	Systolic blood pressure
SC (s.c.)	Subcutaneous
SD	Standard deviation
SE	Standard error
sec	Seconds
SF-36	Short form 36 item health survey (version 2)
SI	International system of units
SMQ	Standardized meddra query
SOC	System organ class
TEAE	Treatment-emergent adverse event
THA	Trishexylamino
t_{max}	Time to maximum plasma concentration
TNF-α	Tumor necrosis factor alpha
TTR	Transthyretin
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
UTI	Urinary tract infection
V30M	Val30met
Vc/F	Apparent volume of distributions for the central compartment
Vmax	Maximum metabolic rate
Vp/F	Apparent volume of distributions for the peripheral compartment
WBC	White blood cell
ΔQTcF	Change-from-baseline QT interval corrected by Fredericia formula
ΔΔQTcF	Placebo-adjusted change-from-baseline QT interval corrected by Fredericia formula

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 5 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Wainzua (eplontersen), through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2023.

Wainzua, was designated as an orphan medicinal product EU/3/23/2828 on 13 October 2023 in the following condition: *Treatment of transthyretin-mediated amyloidosis.*

The applicant initially applied for the following indication:

- *treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).*

The final indication for Wainzua is for the

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

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 06 November 2024 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Wainzua

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 13 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0534/2022 on the granting of a product-specific waiver.

The waiver covers all subsets of the paediatric population (0 to 18 years) on the grounds that eplontersen does not represent a significant therapeutic benefit as clinical studies are not feasible.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products Vyndaqel (tafamidis), Tegsedi (inotersen), Onpattro (patisiran) and Amvuttra (vutrisiran).

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance eplontersen contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
29 May 2019	EMA/CHMP/SAWP/277951/2019 EMEA/H/SA/4095/1/2019/III	*Marion Haberkamp and Mogens Westergaard*

The protocol assistance pertained to the following non-clinical and clinical aspects:

Non-clinical:

- Toxicity and carcinogenicity studies.

Clinical:

- Design of the phase 3 study, regarding the inclusion criteria, co-primary endpoints, efficacy analysis and statistical analysis plan, control group, timepoints for efficacy analyses, safety database, and overall clinical development plan.
- Platelet and renal monitoring in the clinical studies and foreseen frequency of such monitoring at the time of authorisation.
- Intended therapeutic indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig (DE) Co-Rapporteur: Ewa Balkowiec Iskra (PL)

The application was received by the EMA on	5 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	1 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 September 2024
SAG was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	10 September 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	18 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Wainzua on	17 October 2024
The CHMP adopted a report on similarity of Wainzua with Vyndaqel (tafamidis), Tegsedi (inotersen), Onpattro (patisiran) and Amvuttra (vutrisiran) on (see Appendix on similarity)	17 October 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	17 October 2024

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on request of the sponsor.	06 November 2024
The European Commission returned the Opinion to the Agency, requesting to further substantiate the scientific argumentation on which the CHMP concluded the non-similarity of eplontersen with authorised orphan medicinal products.	16 December 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a revised positive opinion for granting a marketing authorisation to Wainzua on	30 January 2025
The CHMP adopted a revised report on similarity of Wainzua with Vyndaqel (tafamidis), Tegsedi (inotersen), Onpattro (patisiran) and Amvuttra (vutrisiran) on (see Appendix on revised similarity assessment report).	30 January 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hereditary transthyretin-mediated amyloidosis (ATTRv amyloidosis, previously known as hATTR), also known as variant transthyretin-mediated amyloidosis, is a rare, autosomal dominant, rapidly progressive, multi systemic disease caused by variants in the *transthyretin* (*TTR*) gene that results in debilitating morbidity and high mortality. Amyloid deposits accumulate in multiple organs, particularly the peripheral nervous system, gastrointestinal tract, kidney, and heart, which manifests in progressive polyneuropathy including sensorimotor neuropathy and autonomic neuropathy. Cardiomyopathy, nephropathy, and gastrointestinal dysfunction frequently develop simultaneously. The phenotypic presentation of the disease is dependent on the pattern of affected organs. The most common manifestations of ATTRv amyloidosis are polyneuropathy and cardiomyopathy.

2.1.2. Epidemiology

The worldwide prevalence of ATTRv-PN is estimated to be between 10,000 and 50,000 patients. In Europe, the incidence is estimated from 0.003 to 0.10 cases per 10,000 per year (between 5,000 to 6,000 patients or 0.3 new cases per year per 1 million inhabitants), with the majority of cases in Portugal, France, Italy, and the United Kingdom. In Europe, the prevalence is highest in northern Portugal and northern Sweden (as high as 50 per 100,000 inhabitants).

2.1.3. Biologic features, aetiology and pathogenesis

In ATTRv amyloidosis, inherited variants in the *TTR* gene lead to destabilisation of the tetrameric protein and disassociation of the TTR subunits into dimers and individual variant and wild-type (wt) monomers, which subsequently misfold.

There are over 100 reported *TTR* genetic variants associated with ATTRv amyloidosis with some such as Val30Met (V30M) resulting in a predominately neuropathic phenotype, while others such as Val122Ile (V122I) are associated predominantly with cardiomyopathy. Some mutations have overlapping phenotypes such as Thr60Ala (T60A).

Worldwide, the most common disease-causing variant results in a valine to methionine mutation at position 30 in the TTR molecule, V30M (p. TTRV50M). V30M is predominantly associated with polyneuropathy and is found primarily in families with heritage from Portugal, Sweden, Japan, and Brazil. In the US, the isoleucine substitution for valine at position 122 in TTR, V122I (pV142I), is the most prevalent TTR-associated variant with a prevalence of approximately 4% in West Africans and African Americans. V122I is associated with predominantly cardiac manifestations but also can be associated with concurrent polyneuropathy.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Historically, due to incomplete understanding of aetiology and pathogenesis, 2 clinical syndromes of ATTRv amyloidosis have been described in the medical literature: ATTRv amyloidosis with polyneuropathy (previously known as familial amyloidotic polyneuropathy, or FAP) and ATTRv amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy, or FAC), both of which are characterized by amyloid deposits comprised of both mutant and wtTTR.

Many patients with ATTRv amyloidosis are not diagnosed until their neuropathy is already at least moderate in severity, with sensorimotor and autonomic abnormalities starting to impact ambulation.

The main clinical manifestations of ATTRv-PN are progressive peripheral sensorimotor and autonomic neuropathy. Non-specific and symmetrical numbness, pain, and temperature sensitivity typically begins in the lower extremities, progressing distal to proximal. In patients with ATTRv amyloidosis, sensory abnormalities include painful dysesthesias in the feet and hands, as well as loss of sensation, which may lead to thermal burns in these areas and to joint damage in the lower limbs. Progressive muscle atrophy and motor weakness in both lower and upper limbs lead to impaired ambulation and inability to perform activities of daily living. Autonomic dysfunction results in debilitating orthostatic hypotension leading to loss of consciousness, severe gastrointestinal symptoms (including early satiety, chronic nausea/vomiting, malnutrition/weight loss, and both diarrhoea and constipation), and bladder dysfunction with recurrent urinary tract infections, as well as cardiac arrhythmias. The rate of neuropathy progression is influenced by *TTR* genotype, age at symptom onset, and extent of neurologic impairment at time of diagnosis.

In the heart, infiltration of cardiac tissue with amyloid leads to wall thickening and cardiomyopathy, manifested by heart failure due to diastolic and systolic dysfunction, as well as conduction disturbances and arrhythmias. Cardiac involvement has been estimated to occur in 80% of ATTRv amyloidosis (Suhr et al, 2006). Similar to polyneuropathy, patients with more severe cardiac disease at the time of diagnosis experience rapid progression with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life, seen over a period of 18 months or less. Motor neuropathy follows within a few years, which affects ambulatory status.

ATTRv-PN is the most serious hereditary polyneuropathy of adult onset. Patients with this progressive, devastating, and life-threatening disease should not be left without any treatment. Diagnostic delay

varies in non-endemic regions from 3 to 4 years. Average survival from disease onset varies from 6 to 12 years, and cardiac involvement is often the cause of death. Furthermore, monitoring of disease progression is complicated by the considerable phenotypic heterogeneity seen among patients with the disease.

ATTRv-PN is classified into 3 stages based on ambulatory status of patients: in Stage 1, the patients present with weaknesses in the lower limbs and do not require assistance with ambulation, while they show gait dysfunctions, distal amyotrophies and hand involvement in Stage 2 and depend on assistance with ambulation, and are either wheel-chair bound or bedridden with generalised weakness and areflexia in Stage 3. This staging system was used to classify severity of disease in patients being considered for enrolment in the pivotal clinical study of inotersen (ISIS 420915-CS2) and also for eplontersen in study ION-682884-CS3. Disease severity can be also assessed using the Polyneuropathy Disability (PND) score, which is a 5-stage scoring system (Suhr et al, 1996).

Given the severity of ATTRv, there is a significant impact on patients' and caregivers' quality of life. Caregivers have moderate to high levels of fatigue and spend a significant amount of time caring for patients. Hereditary ATTR is associated with a substantial disruption in employment rates and work productivity. There is also a large mental health burden on both caregivers and patients.

The constellation of progressive morbidity from amyloid infiltration in patients with ATTRv amyloidosis results in severe disability, wasting due to gastrointestinal malabsorption, malnutrition, and cardiac cachexia. Death usually results from heart failure (including sudden death caused by ventricular arrhythmias or electromechanical dissociation) or infection. The survival after diagnosis is dependent on time from first symptom to diagnosis and also on age of onset. Survival after the onset of disease in patients who have ATTRv amyloidosis with polyneuropathy ranges from approximately 12 years in those with early-onset Val30Met disease to approximately 7 years in those with late-onset disease caused by other variants, such as Val30Met and Ile107Val with a reduced survival (3.4 years) for patients presenting with cardiomyopathy.

2.1.5. Management

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; EMEA/H/C/2294), is approved across the EU for the treatment of ATTR in adult subjects with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment and has also been licensed in Japan and several other countries.

Tafamidis binds to 1 of the 2 thyroxine binding sites on TTR in the native tetrameric form, thereby stabilizing the TTR tetramer and blocking its dissociation into monomeric subunits. Tafamidis is administered orally, once daily.

Inotersen contains an unconjugated 2'-MOE PS-modified ASO and silences or inhibits production of TTR protein through Ribonuclease H1-mediated degradation of TTR mRNA in cells, and is administered SC q1w by the patient and/or a caregiver. Inotersen can cause bleeding due to severe thrombocytopenia and can also cause glomerulonephritis. Patients receiving inotersen need routine frequent monitoring of platelet count, renal function, and liver function.

Patisiran is a synthetic double-stranded siRNA which, like inotersen, is a silencer of TTR protein production; in contrast to the Ribonuclease H1-mediated mechanism of inotersen, patisiran uses an RNA interference mechanism to inhibit TTR. It is administered as IV infusion every 3 weeks by a healthcare professional in a supervised setting. Patisiran is very commonly associated with infusion-

related reactions. To reduce the risk of infusion-related reactions, patients must be premedicated with several medications including IV corticosteroids along with antihistamines.

Vutrisiran is a synthetic double-stranded small siRNA GalNAc-conjugated oligonucleotide targeted against TTR mRNA and, like patisiran, uses a RNA interference mechanism to inhibit TTR. It is administered SC once every 3 months by a healthcare provider. Vutrisiran is associated with very common ADRs of arthralgia and pain in extremity. Additionally, dyspnoea, and increased blood alkaline phosphatase are common ADRs.

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. 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 (ie, to suppress both mutated TTR and wild-type TTR), TTR silencers are discussed in post-liver transplant patients (Moshe-Lilie et al, 2020).

Diflunisal is a non-steroidal anti-inflammatory drug (NSAID) that is presently used off-label in subjects with stage 1 or stage 2 disease; however, the cardiovascular and renal side effects associated with the NSAID class limit the use of this drug in older patients with ATTRv-PN or patients with ATTRv-CM.

2.2. About the product

Eplontersen (also termed ION-682884 in the submission dossier) has been developed by AstraZeneca AB in collaboration with Ionis Pharmaceuticals Inc. based on the scientific knowledge gained with inotersen (= ISIS 420915). Accordingly, eplontersen and inotersen share the identical nucleoside sequence and are both chimeric 20-mer ASOs consisting of ten 2'-deoxyribonucleotides that are flanked by five 2'-O-(2-methoxyethyl) (2'-MOE) ribonucleotides at each of the 5'- and 3'-termini (5-10-5 gapmer structure). Contrary to the phosphorothioate ASO inotersen, however, eplontersen contains a mixture of phosphorothioate and phosphodiester linkages. The 2'-MOE-modification of nucleotides in eplontersen was done aiming to increase affinity to the target mRNA and to improve resistance to exonucleases and endonucleases, thereby increasing stability in tissue, and ameliorating some of the high-dose toxicities relating to inflammation. Substituting the PO backbone linkages at 6 locations was done to reduce the pro-inflammatory profile that can be observed with ASOs. Importantly, the 5'-terminus of eplontersen is also covalently bound via a phosphodiester to a trishexylamino (THA)-C6 linker with triantennary GalNAc residues to facilitate the specific uptake of the ASO via endocytosis by asialoglycoprotein receptors (ASGPR) in the liver. This selective liver targeting enables the delivery of eplontersen at the principal site of TTR production. Compared to inotersen, the GalNAc conjugation therefore aims to reduce the dose and administration frequency required for effective TTR inhibition by eplontersen, while the mixed phosphorothioate and phosphodiester linkages in the backbone are thought to additionally lower pro-inflammatory side effects.

Like inotersen, eplontersen specifically binds to the 3'-untranslated region (UTR) of the cognate TTR mRNA, which leads to RNase H1-mediated degradation of this target mRNA. Consequently, mutated and wild-type TTR protein are no longer generated, which is expected to decrease the formation of amyloid fibril deposits and attenuate ATTRv progression.

TTR is a carrier protein for retinol binding protein 4, which is the principal carrier of vitamin A (retinol). Therefore, reduction in plasma TTR is expected to result in reduction of plasma retinol levels < LLN.

The following broad indication was initially proposed by the applicant: "*Eplontersen is indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).* After the discussions at CHMP and the Oral Explanation, the applicant agreed to restrict the indication to "*Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy*".

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

2.3. Type of application and aspects on development

The legal basis for this application refers to:

- Article 8.3 of Directive 2001/83/EC - complete and independent application

The applicant did not request an accelerated assessment.

Proof of GMP compliance for all manufacturing and testing sites is available. No inspection was deemed required.

Ionis, in collaboration with AstraZeneca, developed eplontersen.

The clinical development programme of eplontersen includes

1) two ongoing Phase 3 studies in patients with ATTRv-PN:
    a. pivotal study ION-682884-CS3 (NEURO-TTRansform; hereafter referred to as CS3) evaluating the superiority of eplontersen 45 mg q4w versus the external placebo group from the inotersen pivotal study (NEURO-TTR (ISIS 420915-CS2)) in slowing disease progression of ATTRv-PN over 65 weeks of treatment
    b. long-term extension study ION-682884-CS13 (hereafter referred to as CS13)
2) two completed Phase 1 ascending dose studies:
    a. study ION- 682884-CS1 (hereafter referred to as CS1)
    b. study ION- 682884-CS20 (hereafter referred to as CS20),
3) one completed Phase 1 bioequivalence study:

    study ION-682884-CS21 (hereafter referred to as CS21).

The clinical development programme also encompasses two Phase 3 studies in patients with ATTR-CM (ION- 682884- CS2 (CARDIO-TTRansform) and ION- 682884- CS12), which are not part of this application.

Eplontersen has not been studied in pregnant or lactating females, paediatric patients, patients with eGFR < 45 mL/min/1.73 m^2 or end-stage renal disease, patients with moderate or severe hepatic impairment, or in patients with prior liver transplant.

Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
ION-682884-CS3 (NEURO-TTRansform)	Ongoing Interim analysis (Week 35) data cut-off date: 18-Apr-2022 (efficacy) and 19-Jul-2022 (safety) Week 66 Analysis (Week 65/66) and Week 85 Analysis data cut-off date: 07-Apr-2023 Eplontersen: n = 144 randomized; n = 135 completed Week 66 Concurrent Inotersen: n = 24 randomized; n = 20 completed Week 66 External placebo (from Study ISIS 420915-CS2): n=60 randomized; n=52 completed Week 66 Historical Inotersen (from Study ISIS 420915-CS2): n=113 randomized; n=87 completed Week 66	Phase 3 randomized, open-label study with external placebo group to assess efficacy and safety of eplontersen 84 weeks treatment duration	<u>Eplontersen group</u> Eplontersen: 45 mg q4w (s.c.) <u>Inotersen-eplontersen group</u> Inotersen sodium (for first 34 weeks): 300 mg q1w (s.c.) Eplontersen (from Week 37): 45 mg q4w (s.c.) <u>Historical Inotersen group (from Study ISIS 420915-CS2):</u> 300 mg q1w	Male and female patients not of childbearing potential (post-menopausal and/or surgically sterile) aged 18 to 82 years with ATTRv-PN stage 1 or stage 2 according to the Familial Amyloid Polyneuropathy or Coutinho Stage, with documented genetic mutation in the TTR gene, and symptoms consistent with neuropathy associated with TTR mediated amyloidosis, including Neuropathy Impairment Score ≥ 10 and ≤ 130. Willingness to take to vitamin A suppl.
ION- 682884-CS13	Ongoing Interim 1 CSR data cut-off date: 19-Jul-2022 Interim 2 CSR data cut-off date: 07-Apr-2023 Enrolment: Eplontersen 165 (planned) 108 patients treated up to the data cut-off date	Phase 3 open-label, extension study to assess long-term safety and tolerability Up to 3 yrs treatment duration	Eplontersen (s.c.) 45 mg q4w	Completion of ION-682884-CS3 OR diagnosis of ATTRv-PN and satisfactory completion of either study ISIS 420915-CS101 (Investigator-Sponsored study with inotersen). Male and female patients not of childbearing potential (post-menopausal and/ or surgically sterile). Willingness to take to vitamin A suppl.
ION- 682884-CS1	Completed Eplontersen: 39 Placebo: 8	Phase 1/2 study to evaluate safety, tolerability, PK, PD of single and multiple doses of eplontersen	<u>Multiple dose:</u> 45, 60, and 90 mg eplontersen (s.c.) or placebo q4w (total of 4 doses) for 13 weeks <u>Single dose:</u> 120 mg eplontersen (s.c.) or placebo	Healthy volunteers (Cohorts A, B, C and E): Male and female HVs not of childbearing potential (post-menopausal and/ or surgically sterile), 18

		12 weeks treatment duration		to 65 years of age of Japanese descent. Willingness to take to vitamin A suppl. ATTRv patients (Cohort D): Male and female patients not of childbearing potential (post-menopausal and/ or surgically sterile) aged 18 to 82 years with ATTRv-PN stage 1-3, with documented genetic mutation in the TTR gene, and symptoms consistent with polyneuropathy as measured by including NIS score ≥ 10. Willingness to take vitamin A suppl.
ION-682884-CS20	Completed Eplontersen: 18 Placebo: 6	Phase 1 Randomized, double-blinded, placebo-controlled study to evaluate safety, tolerability, PK and PD of single doses of eplontersen treatment	<u>Single dose:</u> 45, 60, and 90 mg eplontersen (s.c.) or placebo	Healthy, male and female volunteers not of childbearing potential (post-menopausal and/ or surgically sterile), 18 to 65 years of age of Japanese descent. Willingness to take to vitamin A suppl.
ION-682884-CS21	Completed Eplontersen: 57	Phase 1, randomized, open-label, 3-period, crossover, bioequivalence study comparing three s.c. formulations: Sealed glass vials, prefilled syringe with safety device, autoinjector Single dose per period	Periods 1, 2, and 3 Eplontersen 45 mg (s.c.) with a 4-week (28 days) washout between study periods	Healthy, male and female volunteers not of childbearing potential (post-menopausal and/ or surgically sterile), 18 to 64 years of age. Willingness to take to vitamin A suppl.

The design of the Phase 3 study ION-682884-CS3 was discussed during the scientific advice procedure EMEA/H/SA/4095/1/2019/III in May 2019, including the following topics:

- Design of the phase 3 study, regarding the inclusion criteria, co-primary endpoints, efficacy analysis and statistical analysis plan, control group, timepoints for efficacy analyses, safety database, and overall clinical development plan.
- Platelet and renal monitoring in the clinical studies and foreseen frequency of such monitoring at the time of authorisation.
- Intended therapeutic indication.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection for subcutaneous (SC) administration in an autoinjector pre-filled pen containing 45 mg of eplontersen (as eplontersen sodium) in 0.8 mL of solution.

Other ingredients are: sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate anhydrous, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The product is available in a single use, type I glass syringe with a staked 27-gauge ½ inch (12.7 mm) stainless steel needle, rigid needle shield, and siliconised chlorobutyl elastomer stopper in a pre-filled pen.

2.4.2. Active substance

2.4.2.1. General information

The active substance, eplontersen sodium, is a synthetic 20-base oligonucleotide conjugated to tri-antennary trishexylamino GalNAc ligand via an aminohexyl linker on the 5’ terminus. The oligonucleotide consists of a mixed backbone of five 2’-O-(2-methoxyethyl) nucleosides at each end and ten 2’-deoxynucleosides in the centre. The internucleotide linkages are a mixture of seven phosphate diesters and 13 phosphorothioates. The active substance is a mixture of 2^{13} diastereoisomers and it is presented as an amorphous solid.

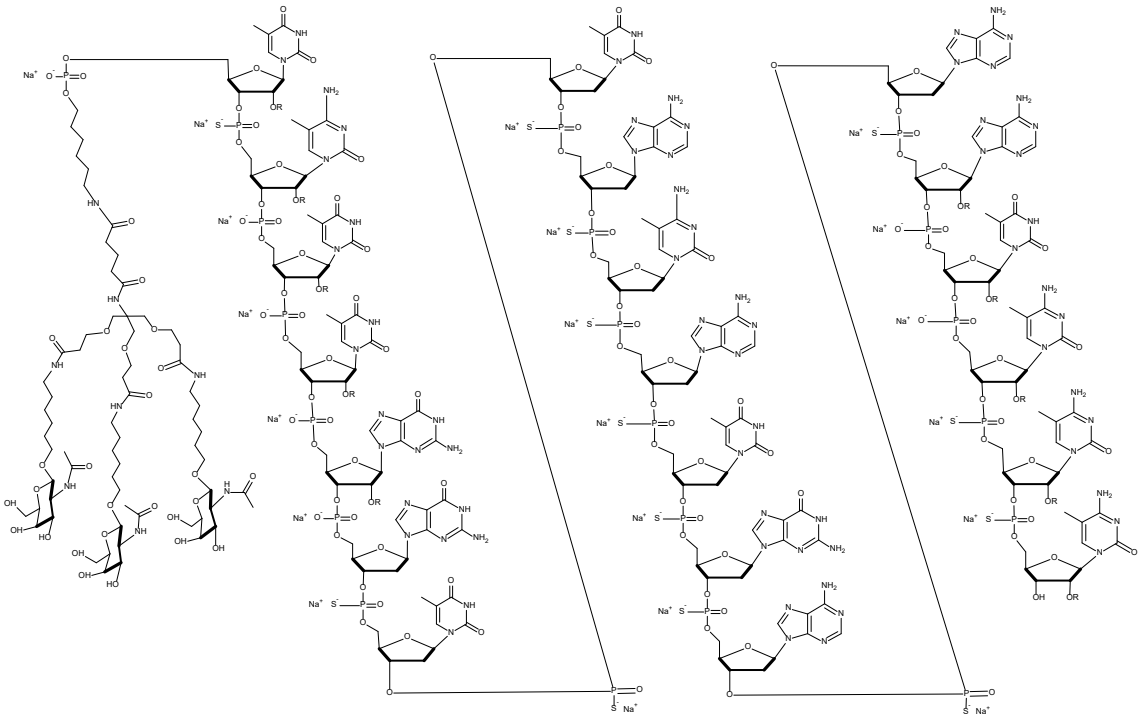
The chemical name of eplontersen is all-P-ambo-5'-O-(28-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]-16,16-bis{[3-({6-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]hexyl}amino)-3-oxopropoxy]methyl}-1-hydroxy-1,10,14,21 tetraoxo-2,18-dioxa-9,15,22-triaza-1λ5-phosphaoctacosan-1-yl)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methylcytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyluridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyluridylyl-(3'→5')-2'-O-(2-methoxyethyl)guanylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-P-thiothymidylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-5-methyl-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-O-(2-methoxyethyl)adenylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyluridylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')-2'-O-(2-methoxyethyl)-5-methylcytidine corresponding to the molecular formula $C_{296}H_{437}N_{77}O_{156}P_{20}S_{13}$ (free acid).

The eplontersen sequence can be written in shorthand as follows:

5’-THA-AH$_O$^{Me}U^{Me}C$_O$^{Me}U$_O$^{Me}U$_O$G$_O$GTTA^{Me}CATGAAA$_O$^{Me}U$_O$^{Me}C^{Me}C^{Me}C-3'

The underlined residues are 2’-O-(2-methoxyethyl) nucleosides; all other residues are 2’-deoxynucleosides. The locations of phosphate diester linkages are designated by O, all other linkages are phosphorothioate. AH designates the position of the aminohexyl linker; THA is 5-[(tris{3-[6-(2-acetamido-2-deoxy-β-D-galactopyranosyloxy)hexylamino]-3-oxopropoxymethyl})methyl]amino-5-oxopentanoyl.

Eplontersen sodium has a relative molecular mass of 9046.1 and the following structure:



R = $CH_2CH_2OCH_3$

Figure 1: Active substance structure

The chemical structure of eplontersen was elucidated by a combination of NMR spectroscopy (^{1}H, ^{13}C and ^{31}P), high resolution mass spectrometry (IP-HPLC-TOF-MS) for monoisotopic mass, failure sequence analysis and mass spectrometry fragmentation (both with IP-HPLC-TOF-MS) for sequence confirmation, elemental analysis (ICP-OES) for elemental composition of the icosasodium salt, UV spectrometry for determination of extinction coefficient and chromatographic separation of DMT-on shortmers after pause of the synthesis after addition of each nucleotide for diastereomeric composition. All results correspond with the expected identity and structure of the active substance. It is considered that the experiments on diastereoisomeric composition demonstrate inherent stereo control during the active substance synthesis. The active substance structure was confirmed also by COSY/HMBC/HSQC 2D NMR and respective results were provided, as requested during the MAA procedure. The primary and higher order/three-dimensional structure of the active substance was discussed in sufficient detail. Following CHMP request, the applicant justified that no stable three-dimensional structure is expected and provided CD spectroscopy data, which were considered representative for an antisense oligonucleotide.

The active substance is an amorphous white to yellow solid powder. It is freely soluble in water and hygroscopic.

Eplontersen exhibits stereoisomerism due to the presence of multiple chiral centres. The absolute configuration of each 2-deoxy-d-ribose unit is (1*R*, 3*S*, 4*R*). The absolute configuration of each 2'-*O*-(2-methoxyethyl)-d-ribose unit is (1*R*, 2*R*, 3*R*, 4*R*). The absolute configuration of each galactosamine unit is (1*R*, 2*R*, 3*R*, 4*R*, 5*R*). The absolute configuration at the phosphorus atom of each phosphorothioate diester is undefined; hence eplontersen sodium is a mixture of 2^{13} diastereoisomers.

Polymorphism has not been observed for eplontersen.

The applicant claimed eplontersen is a New Active Substance (NAS). Eplontersen was compared to inotersen sodium, (Tegsedi), volanesorsen sodium (Waylivra) and nusinersen sodium (Spinraza). A Major Objection (MO) was raised in this regard requesting the applicant to clarify under which indent

the NAS claim was made. The applicant claimed that eplontersen is a NAS under Indent 1 and provided the supporting information. The CHMP agreed and concluded that the naked oligonucleotide is the therapeutic moiety, which binds to the target RNA in vivo. Volanesorsen and nusinersen share only partial sequences with eplontersen and they bind to different RNA targets. Eplontersen and inotersen share the same base sequence. However, the phosphodiester backbone of eplontersen and inotersen are different, therefore the structure of the therapeutic moiety is different, and it is concluded that the two active substances do not share the same therapeutic moiety at the site of the biological activity. Eplontersen is thus considered a New Active Substance (NAS) under Indent 1 of Chapter 1 of Volume 2A of the Notice to Applicants.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site. Satisfactory information regarding GMP compliance has been provided.

Eplontersen is a synthetic oligonucleotide that is manufactured in a 9-stage process using commercially available well-defined starting materials with acceptable specifications.

The active substance synthesis begins with repeated cycles of solid-phase synthesis. This is performed on a synthesis column charged with a synthesis resin. Synthesis is followed by cleavage of the oligonucleotide from the synthesis resin, and deprotection of the base protecting groups. The synthesis resin is removed by filtration. Purification steps follow.
The oligonucleotide is then conjugated to THA8, the molecular building block from which the GalNAc (N-Acetylgalactosamine) structures derive. A final freeze-drying step is performed to generate the solid-state form of eplontersen sodium.
Adequate information related to the manufacturing process development and the history of process changes has been provided. The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The synthetic process has not changed during development and changes were made primarily to facilitate equipment and sites changes during development. The provided description of the changes was considered sufficient to conclude comparability or improvement between batches after the reported adjustments.

The proposed in-process controls for the operation of critical steps in the active substance manufacturing process have been described. These could not be accepted initially, however the applicant explained how the process parameters were selected and the experiments performed. Also, the applicability of lab-scale development experiments to the commercial process was properly justified. The approach was considered acceptable, and the MO resolved, concluding that adequate in-process controls are applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents have been presented and considered acceptable.
The starting materials for the manufacture of eplontersen are nine phosphoramidites, and THA8 (5-[[tris(3-(6-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-galactopranosyloxy)hexylamino)-3-oxopropoxymethyl)]methyl]-amino-5-oxopentanoic acid). The choice of starting materials, which are purchased from qualified vendors, is well justified according to the principles outlined in ICH Q11. With respect to the synthetic process employed to manufacture the phosphoramidite starting materials, a general reaction scheme and theoretical discussions on structurally related impurities, stereoisomeric impurities and process-related impurities in the starting materials have been provided. It is considered that starting material impurities are sufficiently well understood, and the approach was considered acceptable.

Impurities of phosphoramidites are classified as non-reactive, reactive/non-critical (result in active substance upon incorporation) or critical (result in non-removable impurities). For non-reactive and reactive/non-critical impurities, structures have been presented. For critical impurities, the possible resulting active substance impurities and their prevalence in the respective starting materials was indicated in addition. Specifications and batch data were presented for each phosphoramidite starting material.

For THA8, non-reactive, reactive/non-critical and critical impurities were described. Specifications and batch data have been provided.

The justifications of specification and applied methods descriptions were considered acceptable for all starting materials.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities are classified into product-related impurities and process-related impurities. The product-related impurities are further classified into those derived from starting materials, those formed during processing and degradation products. These are quantified using ion-pair high performance liquid chromatography with ultraviolet and mass spectrometry detection (IP-LC-UV-MS). As it is not possible to resolve each single impurity, a grouping strategy according to structural characteristics was applied. The product-related impurities have been discussed in sufficient detail and the information was considered acceptable. Overall, it was confirmed that no significant amount of any process-related impurities was found in the active substance. In order to confirm the drug substance manufacturing process is under control, however, the drug substance specification includes a test for the final solvent used in the process.

Potential mutagenic impurities were assessed according to ICH M7. Predicted purge factors demonstrated that no testing in the active substance is required.

A risk assessment for potential sources of nitrosamines in the active substance manufacturing process was performed. Further information about the risk factors considered was provided following a request from CHMP. No potential risk of nitrosamines in the active substance has been identified.

The active substance packaging complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (mass confirmation: IP-LC-UV-MS; sequence confirmation: T_m, IP-LC-MS; and sodium counterion: ICP-OES), assay (IP-LC-UV-MS), purity (IP-LC-UV-MS), oligonucleotide impurities (IP-LC-UV-MS), residual solvents (GC), bacterial endotoxins (Ph. Eur.), microbiological quality (Ph. Eur.) and water content (KF).

The proposed active substance specification is acceptable and appropriate limits were set. Three orthogonal methods were applied to determine identity. An OC was raised to request inclusion of a specific sequencing method for unambiguous identification of the active substance. As a consequence, the applicant included Failure Sequence Analysis as an additional specification test and the OC was considered resolved.

Potential impurities in the product originating from the synthesis and degradation of the active substance have been outlined, and the limits for the relevant impurities sufficiently justified. The thresholds proposed for identification and qualification of impurities in the specifications are suitably justified for this oligonucleotide active substance. Toxicologically, the limits proposed for oligonucleotide impurities are considered acceptable based on the non-clinical studies performed. The

rationale for grouping of impurities as proposed in the specification has been justified and was considered acceptable. Omission of testing for most process-related impurities was sufficiently justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, assay, purity and impurities testing has been presented.

Batch analysis data from 10 batches of the active substance are provided, including 6 batches at the proposed commercial scale. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in a package equivalent to the commercial one for up to 24 months under long term conditions (-20 °C / ambient RH) and for up to 6 months under accelerated conditions (5 °C / ambient RH) according to the ICH guidelines were provided. Additionally, data from 3 months at 30 °C/65% RH have been provided.

The parameters tested are the same as for release, with the exception of the omission of testing for identification and residual solvents. The analytical methods used were the same as for release and were stability indicating.

At long term and accelerated conditions, all tested parameters were within the specifications and no significant trends were observed.

Photostability testing revealed some minor degradation associated with minor increases in certain oligonucleotide degradation products. The levels of these degradants remained within specification, and it was observed that the photodegradation is slow. The active substance is therefore not considered to be sensitive to light and therefore no special precautions for protection from light are needed for the active substance.

Forced degradation studies were also performed to determine degradation pathways, structures of degradation products and the intrinsic stability of eplontersen sodium. Results on stress conditions of increased thermal, acid & base exposure, oxidation and photolytic conditions were also provided on one batch. Significant degradation was shown at all conditions with decreases in assay values and corresponding increases in degradation products.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at -20 °C ± 5 °C in the proposed container.

A post-approval stability protocol was submitted. Stability studies are still ongoing and will continue up to 60 months for the long-term storage condition.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a solution for injection in a pre-filled pen. Each pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 mL of solution. The solution is a clear, colourless to yellow

solution and contains 56 mg/mL eplontersen (59 mg/mL eplontersen sodium) in 10 mM phosphate buffer, at pH 7.4 and with osmolality 250 to 330 mOsm/kg.

The composition of the finished product is presented in section 2.4.1 of this report.

The finished product is filled into a 1 mL Long (1 mL L) borosilicate siliconised clear glass syringe with a staked needle and closed with a siliconised chlorobutyl elastomeric plunger stopper. The filled primary container is assembled into a pre-filled pen (autoinjector) for the final finished product presentation.

The pharmaceutical development for the finished product was based on a Quality by Design approach. The formulation and the manufacturing process were developed based on the Critical Quality Attributes (CQAs) required for a sterile solution in a syringe assembled into an autoinjector. A comprehensive Quality Target Product Profile (QTPP) has been established.

Eplontersen sodium is freely soluble in water and phosphate buffered saline (PBS) pH 7.4. It is also an amorphous solid for which no polymorphic form is reported. Since amorphous powders are generally susceptible to humidity this aspect is considered during the compounding step, by performing an IPC test to determine the content of the active substance in the concentrated bulk solution before final dilution. The result of this test is used to calculate the quantity of vehicle to be added to reach the final active substance concentration (final dilution). The physical characteristics of the active substance are therefore not expected to impact the finished product manufacturing.

All excipients are well known pharmaceutical ingredients, which are common for injectable finished products and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is presented in section 2.4.1 of this report and in section 6.1 of the SmPC.

The finished product presentation for clinical studies was eplontersen sodium solution for injection, 150 mg/mL, filled into vials and administered subcutaneously by using a syringe with a needle. For the commercial formulation, an autoinjector formulation is proposed to administer the relevant dose. In the development of the product for the autoinjector, eplontersen concentration was reduced from 150 to 56 mg/mL, the tonicity was adjusted accordingly, and sodium dihydrogen phosphate was included to minimise pH changes during manufacture. To support that the cumulative adjustments would not impact the in-vivo performance of the product, a bioequivalence study was performed to compare the clinical solution for injection in vials to the formulation considered for commercial use in autoinjector. The bioequivalence study was found acceptable.

The manufacturing process is a common process for aqueous sterile finished products, which cannot be subjected to terminal sterilisation. It consists of buffer formulation and filtration, finished product formulation and first filtration, on-line sterile filtration and filling, plunger insertion and visual inspection. The syringe is finally assembled into the autoinjector.

Following a risk-based approach, manufacturing process development studies were performed to evaluate compounding, filtration, filling and processing conditions, hold times, device assembly, and product contact material compatibility. Critical process parameters and the overall control strategy were defined based on the results from these studies. Sufficiently detailed lists of critical and non-critical process parameters as well as in-process controls with limits and ranges were provided.

The choice of sterile filtration with aseptic filling has been adequately justified, in accordance with the guideline on sterilisation EMA/CHMP/CVMP/QWP/850374/2015. Moist heat sterilisation applying a cycle with $F_0 \geq 8$ minutes leads to significant decrease of purity. Buffer optimisation and pH were taken into account in this investigation. It has therefore been suitably demonstrated that terminal sterilisation conditions affect the stability of this oligonucleotide formulation. Following the identification of the appropriate method of sterilisation, a method of manufacture based on sterile filtration and aseptic

filling was developed. The method involved commonly employed steps for this type of manufacturing process and built on the methods commonly applied for other oligonucleotides manufactured at the site. An overview of batches manufactured during the development was provided, including information of batches manufactured at a scale greater than intended for commercial manufacturing. This information was used to determine the relevant process parameters and critical manufacturing steps, such as the critical steps related to sterile filtration and filter integrity testing.

The integral medicinal finished product contains a medical device part, i.e. the autoinjector. Therefore, a Notified Body Opinion (NBO) has been provided, as required, confirming requirements with the relevant medical devices legislation. In addition, the NBO covers the design changes made from the clinical to the commercial version of the autoinjector.

The finished product is designed to deliver a 0.8 mL dose volume. In order to meet the deliverable volume requirement, the finished product has an overfill to account for filling process capability. Suitable dose accuracy has been demonstrated.

The primary packaging is type I glass syringe with a staked stainless-steel needle, rigid needle shield, and siliconized chlorobutyl elastomer stopper. The material complies with Ph. Eur. requirements. The primary packaging is contained within an autoinjector (pre-filled pen). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. AstraZeneca AB, Gärtunavägen, 152 57 Södertälje, Sweden is responsible for batch release in the EU/EEA. Satisfactory information regarding GMP compliance has been provided.

The manufacturing process consists of the following main steps: compounding of the phosphate buffered saline vehicle, bioburden reduction filtration of the vehicle, compounding of the bulk solution, bioburden reduction filtration of the bulk solution, in-line sterile filtration and aseptic filling, visual inspection, autoinjector assembly, labelling and packaging. The process is considered to be a non-standard manufacturing process due to the use of sterile filtration and aseptic filling.

The manufacturing process of the finished product has been sufficiently described including critical and non-critical process parameters and IPCs, as well as processing and hold times.

The information regarding the process validation conducted could not initially be accepted as a number of deficiencies were noted. It was considered that there was insufficient assurance that the manufacturing site could manufacture the product in the manner intended for commercial use, and a MO was raised. The applicant resolved this MO by justifying the validation strategy. Process validation studies on three batches were provided. A bracketing approach for different batch sizes of the primary filled containers (syringes) was followed for the validation of the manufacturing process until primary filled container stage. In addition, it was claimed that the autoinjector assembly is a scale independent process. Following resolution of this MO, it was concluded that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Results of media fill studies have been provided in support of the proposed sterile filtration and aseptic handling process. The product contact components of the primary packaging are supplied pre-sterilised, these are sterilised by ethylene oxide, gamma irradiation, or steam sterilisation depending on individual component and suitable information regarding this has been provided.

The impact of shipping and distribution on the critical quality attributes of the finished product has been sufficiently discussed.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), degree of colouration (Ph. Eur.), clarity and opalescence (Ph. Eur.), identification-sequence confirmation (T_m, identification-mass confirmation IP-LC-UV-MS), assay (IP-LC-UV-MS), degradation products (IP-LC-UV-MS), pH (Ph. Eur.), osmolality (vapour pressure), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur. or bioluminescence), activation force and injection time (in-house) and delivered volume (Ph. Eur.).

The finished product specification is acceptable and appropriate limits have been set based on the active substance specification, available toxicological data, finished product batch data and compendial requirements for an injectable sterile product. The specification is aligned with the principles in ICH Q6A Specifications and Q3B Impurities in New Drug Products and confirm the quality of the medicinal product.

A justification for not including purity testing in the release and shelf-life specification has been provided. This was based on the fact that no change in purity or impurities levels was observed at long-term, accelerated and stress condition stability studies on active substance, nor at long-term and accelerated conditions on finished product. Since assay and degradation products are controlled as part of the finished product specification, the justification was considered acceptable.

The finished product assay limits initially proposed by the applicant were not considered acceptable and have been tightened following an OC from CHMP. The limit proposed for the control of bacterial endotoxins is appropriately determined.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or in the related finished product. Therefore, no specific control measures are deemed necessary.

Sufficient specifications for the glass syringe, the plunger stopper and the medical device part of the finished product have been provided.

The applicant adequately justified the approach to perform the release testing of the finished product on the primary filled containers and not on the fully assembled autoinjectors, except for the tests specific to the autoinjectors.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Sufficient test procedure descriptions and validation results have

been presented for the non-compendial test methods on identification by duplex melting temperature and on identification, assay and degradation products by IP-LC-UV-MS, as well as the test procedure for sterility by bioluminescence. In addition, verification data have been provided for the Ph. Eur. tests on sterility and endotoxins.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for a number of clinical and process validation batches including 6 batches at the proposed commercial batch size, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 30 months under long term conditions (2 °C – 8 °C/ ambient RH) and for up to 6 months under accelerated conditions (25 °C ± 2 °C / 60% RH) according to the ICH guidelines were provided. During long term stability testing the samples stored at long-term conditions were further transitioned at 30 °C/75% RH (for 6 weeks prior to a timepoint) to further investigate potential conditions under which the product may be stored by patients outside refrigeration. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the release and shelf-life specification presented above. In addition, testing for deamination products (IP-LC-TOF-MS) and container closure integrity (dye ingress) was performed during stability testing. The tests on deamination products and container closure integrity are part of the stability protocol but are not included in the shelf-life specification. This was appropriately justified. The analytical procedures used are stability indicating.

At long term and accelerated conditions no significant changes or trends were observed in any of the parameters tested. The values for the tested parameters consistently show very little change during the studies. This was also the case for the 6 week storage period at 30 °C/75% RH.

In addition, one commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. While this study did not reveal a photosensitivity, photolytic degradation of the active substance in solution had been observed during forced stability testing (see active substance stability section). For this reason, an instruction to protect the product from light is included in the SmPC.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 3 years and storage conditions to store in a refrigerator (2 °C – 8 °C), do not freeze, store in the original package in order to protect from light, as stated in the SmPC (sections 6.3 and 6.4) are acceptable. In addition, as described in the SmPC the product may be stored in original carton unrefrigerated for up to 6 weeks below 30 °C, after which it should be discarded.

2.4.3.5. Adventitious agents

A material of animal origin is used in the production of one of the active substance starting materials. The material complies with the requirements of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

Two quality MOs have been raised: one MO related to the active substance manufacturing process control strategy and the other MO related to the finished product manufacturing process validation. In addition, a multidisciplinary MO has been raised regarding the NAS claim. The applicant in their response provided additional information and clarifications, and all MOs were resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.4.6. Recommendation(s) for future quality development

N.A.

2.5. Non-clinical aspects

2.5.1. Introduction

The development of eplontersen grounds on previous experience gained with inotersen. The target sequence of eplontersen and inotersen is 100 % complementary to human and Cynomolgus monkey TTR mRNA, whereas 8 mismatches in mice and rats preclude effective hybridisation and, hence, pharmacological activity in these animals. Therefore, monkeys are the most relevant species in terms of clinical safety. Nevertheless, a mouse-specific TTR analogue ASO harbouring the same GalNAc conjugate and mixed phosphorothioate and phosphodiester backbone (ION-1184986) like eplontersen was included in the chronic repeat-dose toxicity as well as the combined fertility and embryonic development studies in mice to distinguish toxicities related to TTR inhibition from non-specific effects associated with the backbone chemistry of the ASO.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Eplontersen was profiled against inotersen in primary pharmacodynamic studies. In co-cultures of human hepatocytes with mouse stromal cells *in vitro*, improved hepatocellular uptake of eplontersen led to 51-fold more potent inhibition of hTTR mRNA expression than observed with inotersen.

In transgenic mice overexpressing mutant human TTR variant known to cause familial amyloid polyneuropathy in humans, eplontersen and inotersen dose-dependently reduced hTTR mRNA with ED_{50} of 0.5 and 13.9 mg/kg/week, whereas TTR protein was decreased with ED_{50} of 1.5 and 22.9 mg/kg/week, respectively. The maximum 85 % reduction of TTR expression was measured at the respective high doses of 6 mg/kg/week eplontersen and 60 mg/kg/week inotersen. Accordingly, eplontersen and inotersen lowered TTR protein plasma levels with ED_{50} of each 1.5 and 22.9 mg/kg/week. Thus, eplontersen 28- and 15-fold more potently reduced hTTR mRNA and TTR protein in these transgenic mice than inotersen.

Eplontersen also dose- and time-dependently diminished TTR mRNA expression by up to 62 % following multiple s.c. injections of up to 24 mg/kg/week for 13 weeks or up to 25 mg/kg/month for 9 months in healthy monkeys. In these toxicity studies, plasma TTR protein was reduced up to 69 % or 52 %, respectively. TTR mRNA and TTR protein declines tended to recover upon termination of eplontersen, which was more prominent in the 9 months toxicity study.

As TTR is a carrier protein for the RBP4-retinol complex, eplontersen doses ≥6 mg/kg/week decreased RBP4 plasma levels by 60 %, which persisted upon treatment cessation for 3 months. In contrast, the RBP4 decline was less pronounced in the 39 weeks toxicity study of eplontersen with 29 % reduction in the 25 mg/kg/month high dose group, which completely reversed in the recovery period in line with the normalization of TTR protein amounts.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic investigations were conducted for eplontersen, which was justified by the high sequence specificity that rendered any interaction with off-targets unlikely. In addition, the target sequence in human TTR mRNA lacks significant sequence polymorphisms.

2.5.2.3. Safety pharmacology programme

Potential effects of eplontersen on cardiovascular, respiratory and CNS function were investigated in the *"core battery"* of safety pharmacological investigations in accordance with ICH S7A and B recommendations (CPMP/ICH/539/00; CPMP/ICH/423/02) and GLP.

Eplontersen did not inhibit rapidly delayed rectifier potassium (I_{kr}-, hERG-) currents up to the highest concentration of 300 µM. In Cynomolgus monkeys, eplontersen did not significantly prolong the QT_c-interval or affect other cardiovascular (arterial blood pressure, heart rate, ECG), respiratory (respiratory rate, blood gases), functional CNS parameters or body temperature in a combined study with s.c. injections up to 24 mg/kg leading to plasma levels of 34.9 µg/ml. The lack of any impact of eplontersen on cardiovascular, respiratory and CNS function is further supported by the absence of such effects in the 13 weeks and 39 weeks repeat-dose toxicity studies in monkeys.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed with eplontersen, because its specificity for human TTR mRNA renders the interference with the expression of other transcripts unlikely.

2.5.3. Pharmacokinetics

The pharmacokinetic properties of eplontersen were studied after single and repeat-dose administrations in toxicity studies for up to 26 or 39 weeks in mice and monkeys, whereas single-dose absorption, distribution, metabolism and excretion including mass balance evaluation were performed

in rats. The metabolism of eplontersen was investigated for both oligonucleotide-related and THA-linker-related moieties in plasma, tissues, urine, and/or faeces samples of mice, rats, monkeys and humans following single or multiple s.c. injections.

A variety of bioanalytical methods was used to investigate the pharmacokinetic properties of eplontersen. In monkey plasma, eplontersen was determined by an enzyme-linked immunosorbent assay (ELISA), which did not discriminate between full-length GalNAc conjugated, partially conjugated and non-conjugated compound. Qualified high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) served to distinguish between eplontersen and its shortmer metabolites in monkey plasma, whereas non-validated HPLC with ultraviolet detection and mass spectrometry (HPLC-UV-MS) was used to profile metabolites (N-1 to N-15) with respect to full-length ASO in monkey plasma, mouse and monkey tissues. Non-conjugated eplontersen was also quantified by qualified HPLC-MS/MS in rat tissues. In addition, unconjugated eplontersen was quantified in tissues of mice and monkeys by HPLC-UV. The shortmer metabolites of eplontersen were determined in urine of mice, rats, monkeys and humans by non-validated HPLC with high-resolution time-of-flight mass spectrometry and HPLC/HRMS, while THA-linker metabolites M4 to M14 were quantified in plasma and urine of mice, rats, monkeys and humans by qualified HPLC-MS/MS. Other qualified analytical methodologies comprised the detection of ^{3}H-labelled eplontersen in animal samples by liquid scintillation counting and quantitative whole body autoradiography as well as the measurement of full-length eplontersen by an electrochemiluminescence assay. Moreover, the formation of anti-eplontersen antibodies was evaluated by a validated ELISA.

Eplontersen was rapidly absorbed into the systemic circulation after single s.c. in rats and following weekly or monthly s.c. injections in the 13 weeks and 39 weeks repeat-dose toxicity studies in male and female monkeys. Following t_{max} of 0.5 to 1 h in rats and 1 to 2 h in monkeys, eplontersen exposure declined biphasically in rats or multimodally in monkeys with a MRT0-48h of 2 to 6 hours, which reflected the subsequent tissue distribution. The terminal plasma half-life was 4.5 days in rats but clearly prolonged in monkeys (2 to 4 weeks). The peak plasma concentrations of eplontersen increased dose-proportionally in monkeys, whereas AUC increased greater than dose-proportionally. Accordingly, the apparent plasma clearance ($CL_{0\text{-}48h}/F$) was dose-dependently reduced. There were no gross differences between both sexes of monkeys and eplontersen did not accumulate in plasma.

Full-length eplontersen preferentially partitioned into plasma and revealed extensive protein binding of >97 % in plasma of mice, monkeys and humans. Eplontersen predominantly distributed into liver and kidneys of rats, which was confirmed for mice and monkeys in toxicity studies. When eplontersen containing the radiolabel in the THA-linker was administered to rats, GalNAc-linker associated radioactivity was additionally found in the small and large intestine.

Eplontersen did not distribute into the placenta in relevant amounts and, hence, did not reach the foetuses of pregnant mice.

The metabolism of eplontersen was evaluated across species by determination of oligonucleotide-related and GalNAc-THA-linker-related metabolites. Within 2 h after s.c. injection, intact eplontersen accounted for 96 % of the total full-length ASO detected in plasma, whereas partially conjugated eplontersen (with 1, 2 or 3 GalNAc sugar deletions) and unconjugated eplontersen each remained below 2 % of the total ASO. Minimal levels of four GalNAc-THA-linker-related metabolites (M5, M7, M8 and M12) were consistently determined in plasma at 2 h post dose in rats, monkeys and humans (<2 % of the eplontersen concentration), which were subsequently cleared from plasma leading to 2- to 20-fold decreases by 24 h.

Contrary to plasma, no intact or partially conjugated eplontersen was confirmed in kidneys and livers of mice and monkeys after 24 h, but unconjugated eplontersen represented about 94 % and 79 % or 85 % and 95 % of the total ASO in kidneys and liver of both species, respectively, compared to low

levels of shortmer oligonucleotide metabolites (<2 % to <6 %). The major GalNAc-THA-linker-related metabolites in kidney and liver of rats were M5 and M8 at 2 h and 24 h post dose. M8 was also the main metabolite in rat liver after 2 h, but no linker-related metabolites were detectable by 24 h.

Following repeated s.c. administration of high doses in toxicity studies in mice, rats and monkeys, unchanged eplontersen and unconjugated eplontersen as well as 3'- and 5'-terminal exonucleolytic shortmers were mainly excreted via urine. In human urine 5'-deletion derivatives of eplontersen were predominantly recovered compared to minimal levels of intact eplontersen. In contrast to the principal urinary elimination of oligonucleotide metabolites, the majority of the THA-linker associated fragments was rapidly excreted by faeces within 24 h compared to less than 10 % in urine.

Eplontersen did not induce or interfere with cytochrome P450 enzyme activities and did not serve as substrate or inhibitor of human drug transporters when evaluated in accordance with European recommendations (CPMP/EWP/560/95/Rev.1 Corr.2). In addition, eplontersen did not displace other drugs from plasma protein binding.

2.5.4. Toxicology

The toxicity of eplontersen was investigated with different s.c. administration regimen (weekly, biweekly, monthly) for up to 26 weeks in mice, 14 weeks in rats and up to 39 weeks in monkeys. Moreover, eplontersen was tested in a standard battery of genotoxicity investigations, a 26 weeks carcinogenicity study in Tg.rasH2 mice, in a combined fertility and embryo-foetal development study in mice and its immunogenic potential was evaluated as part of the 39 weeks repeat-dose toxicity study in monkeys. The eplontersen drug substance batches used in GLP compliant toxicology studies were manufactured under GMP and, hence, comparable to the lots produced for clinical trials and marketing.

2.5.4.1. Single dose toxicity

No single dose toxicity studies have been conducted with eplontersen, which is agreed in line with prevailing ICH M3(R2) and European recommendations (EMA/CPMP/ICH/286/1995; EMA/CHMP/SWP/81714/2010). Nonetheless, the toxicities of large s.c. eplontersen doses up to 1000 mg/kg biweekly were evaluated in the 18 weeks MTD study in mice and up to two 2000 mg/kg s.c. doses were tested in the *in vivo* micronucleus study in mice (see below).

2.5.4.2. Repeat dose toxicity

Repeated s.c. eplontersen injections for 13 or 39 weeks in monkeys dose-dependently reduced hepatic TTR mRNA levels in monkeys by up to ~62 %, while the mouse-specific GalNAc-conjugated analogue ION-1184986 decreased TTR mRNA by 82 % in the 26 weeks in toxicity study in mice. Consequently, TTR and RBP4 plasma protein levels were diminished in monkeys by up to 68 % and 60 % after weekly and by about 52 % and up to 29 % following monthly administrations, respectively. Nevertheless, no toxicological findings related to TTR inhibition and vitamin A deficiency by eplontersen or ION-1184986 including ophthalmological and histological examinations of the eyes were noticed.

Eplontersen dose-dependently accumulated as minimal/mild basophilic granules within cytoplasmic vacuoles of macrophages and/or monocytes at injection sites and in lymph nodes as well as in proximal tubular kidney epithelia, hypertrophied hepatocytes and hepatic Kupffer cells in mice, rats and monkeys. This accumulation was comparably noticed for the mouse-specific analogue ION-1184986. Following more frequent biweekly injections of ≥50 mg/kg eplontersen for 26 weeks in mice, vacuolated granular macrophages were also found in testes, whereas more often weekly administrations of ≥25 mg/kg eplontersen for 13 weeks in mice resulted in sporadic occurrence in

reproductive organs and less commonly in choroid plexus of the brain, heart, tibial-femoral joint, glandular stomach, caecum, lung, pancreas, pituitary gland and/or *biceps femoris* muscle. Furthermore, a high biweekly s.c. dose of 1000 mg/kg eplontersen increased the cellularity of germinal centres in the spleen of mice.

In rats, biweekly s.c. doses of 25 mg/kg eplontersen slightly increased liver and spleen. The reduced thymus weights determined after biweekly injections of 100 mg/kg coincided with lymphocyte depletion. Except minor increases of IL-4 and IL-6 at this dose in rats or of slight elevations of MCP-1 and TNFα after biweekly injections of ≥600 mg/kg in mice and a decreased albumin/globulin ratio in a single monkey administered 5 mg/kg/month, no other pro-inflammatory cytokines and chemokines were induced or changed by eplontersen in any animal species.

In addition, eplontersen did not influence specific subsets of white blood cells (monocytes, granulocytes, T- or B-lymphocytes, natural killer cells) in monkeys. The mild ~2-fold reduction of IgG following biweekly injection of 150 mg/kg in the chronic toxicity study in mice and the dose-related 1.5- to 3-fold increased IgM after biweekly injections of ≥25 mg/kg eplontersen in rats are regarded clinically irrelevant given that IgM and IgG subsets remained unchanged in monkeys, which also developed a normal T-cell dependent immune response against keyhole limpet hemocyanin.

In a single female out of 12 monkeys of the 24 mg/kg/week eplontersen high dose group of the 13 weeks toxicity study, platelet counts were severely decreased to 4×10^9/L from day 73, which was accompanied by spontaneous haemorrhage, haematoma and petechiae. This adverse platelet decline was preceded by an acute 4-fold increase of complement split product Bb at 4 h post first dose, which subsequently normalised within 24 h and did not rise again in week 13. However, complement factor C3 remained unchanged in this female monkey, indicating limited transient activation of the alternative complement pathway. The severe thrombocytopenia improved in the female monkey upon termination of eplontersen dosing in combination with glucocorticoid treatment and fully recovered until the end of the treatment-fee period. No similar platelet reductions were observed in any other animal of this or other toxicity studies of eplontersen, albeit complement split product Bb showed a transient 2.8-fold increase in three other female monkeys of the same eplontersen high dose group of the 13 weeks toxicity study and a 2-fold elevation in male monkeys administered 25 mg/kg/month eplontersen in the 39 weeks toxicity study. Again, split product Bb did not change in the course of both toxicity studies and complement factor C3, the bone marrow cellularity or coagulation parameters were not affected in these primates.

At end of the respective recovery phases of subchronic and chronic toxicity studies in mice and monkeys, basophilic granules remained detectable with clearly reduced incidence in hepatic Kupffer cells, renal tubular epithelia, injection sites, epididymal and testicular interstitium in mice that had received 75 mg/kg/week eplontersen for 13 weeks. Similarly, basophilic granules partially recovered upon treatment cessation in monkeys, but were still found in hepatocytes and macrophages within lymph nodes after eplontersen doses of 24 mg/kg/week for 13 weeks or in axillary lymph nodes and injection sites following 25 mg/kg/months for 39 weeks. Additionally, minimal perivascular and mural infiltrates of lymphohistiocytic inflammatory cells primarily in the *tunica adventitia* of small to medium calibre vessels as well as minimal to slight medial and intimal hyperplasia in arterioles of liver, gallbladder, kidney, heart, colon, pancreas and seminal vesicles and periportal inflammation in the liver were evident in a single monkey of the 25 mg/kg/month group upon termination of the recovery period. Accordingly, liver enzymes were also elevated in this animal.

In view of these findings, NOAELs of 6 mg/kg/week and 25 mg/kg/month were established for eplontersen in the 13 and 39 weeks toxicity in monkeys, which translate into more than 70-fold AUC-related safety margins with respect to human exposure at the recommended therapeutic dose. In

rodents, no NOAELs were defined, although this would have been also permitted by the observed non-adverse effects.

2.5.4.3. Genotoxicity

In an ICH S2(R1) and GLP compliant standard battery of investigations (EMA/CHMP/ICH/126642/2008), eplontersen was not mutagenic in a bacterial Ames test at concentrations up to 5000 µg/plate and did not induce chromosome aberrations at concentrations up to 500 µg/ml in Chinese hamster lung cells *in vitro*, both in the presence and absence of metabolic activation. *In vivo*, two s.c. injections of up to 2000 mg/kg eplontersen did not induce micronuclei in the bone marrow of mice.

2.5.4.4. Carcinogenicity

Eplontersen was not tumorigenic following s.c. injections up to 1500 mg/kg/month in a GLP-compliant 26 weeks carcinogenicity study in transgenic Tg.rasH2 mice. Non-neoplastic findings were restricted to microscopic changes in kidney and liver and basophilic granules in macrophages in epididymis, heart and pancreas indicative of uptake and accumulation of eplontersen.

2.5.4.5. Reproductive and developmental toxicity

In a combined fertility and embryonic development study in mice, s.c. eplontersen doses up to 75 mg/kg/week did not adversely affect fertility or embryogenesis. Hence, the no observed adverse effect level (NOAEL) for fertility, maternal toxicity, and foetal developmental effects of eplontersen was 75 mg/kg/week. In a separate group of mice, a 25 mg/kg/week dose of the mouse-specific analogue ION-1184986 reduced liver TTR mRNA levels by on average 93 or 97% for males or females, respectively, but also did not produce any effects on fertility or embryo-foetal development.

Potential effect of eplontersen on embryo-foetal development in a second species, pre- and post-natal development or juvenile toxicity were not investigated.

2.5.4.6. Toxicokinetic data

The toxicokinetic plasma exposure of eplontersen was only confirmed in the 13 weeks and 39 weeks repeat-dose toxicity studies in monkeys. In view of the primary distribution of eplontersen into liver and kidneys, the dose-dependently but less than dose-proportionally increased exposure of unconjugated eplontersen in both organs was determined in toxicity studies in mice, rats and monkeys instead.

The eplontersen exposure in the kidneys of rats was substantially higher than in the liver and a trend for this difference was also apparent in mice. Of note, female rats were exposed to about 10-fold higher kidney and liver concentrations compared to males, whereas kidney levels were approximately 2-fold higher in female than in male mice. In contrast, eplontersen levels in liver and kidneys were comparable between the two sexes of monkeys. The eplontersen concentrations in both tissues were similar in subchronic and chronic toxicity studies and were 5- to 10-fold higher than those determined at equivalent doses in mice, which was likely related to the longer terminal plasma half-life of eplontersen in monkeys compared to rodents (28 to 32 days in monkeys vs. 4.5 days in rats).

2.5.4.7. Local Tolerance

The s.c. injection sites of eplontersen were evaluated in multiple dose toxicity studies in mice and monkeys in line with ICH M3(R2) recommendations (EMA/CPMP/ICH/286/1995) and revealed the expected accumulation of the ASO within macrophages or monocytes.

2.5.4.8. Other toxicity studies

Antigenicity

Anti-eplontersen antibodies (ADAs) were confirmed in the course of the chronic toxicity study in monkeys. Although no clear dose-relationship was apparent, ADAs emerged earlier (from day 57) and slightly more frequent in the high dose animals. ADAs also remained detectable in one high dose monkey at the end of the recovery period.

Across test groups, ADAs increased the median plasma trough concentrations of eplontersen, which was most prominent in the high dose group. Nevertheless, parameters of plasma or tissue exposure (C_{max} and $AUC_{0\text{-}48h}$) and clearance ($Cl_{0\text{-}48h}$ and $MRT_{0\text{-}48h}$) as well as pharmacological activity (inhibition of hepatic TTR mRNA and plasma TTR protein) or toxicities were comparable between ADA-positive and –negative monkeys. Thus, these ADAs represent binding antibodies without neutralising capacity.

Impurities

Eplontersen-related impurities were adequately qualified up to the specified levels in the 13 weeks and 9 months s.c. toxicity studies in monkeys and in a dedicated 13 weeks s.c. study in mice.

2.5.5. Ecotoxicity/environmental risk assessment

Eplontersen itself is not naturally occurring and the conjugated GalNAc moiety is synthetic, but the major constituents are natural components (nucleotides, amino sugars) to which eplontersen will be metabolised within the body. Therefore, the use of eplontersen will not alter the concentration or distribution of its components in the environment. Eplontersen is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Eplontersen is a mixed phosphorothioate and phosphodiester ASO that harbours the identical sequence of the earlier approved ASO inotersen, which solely consists of phosphorothioate linkages in the backbone (*"Tegsedi"*). Importantly, the 5'-terminus of eplontersen is covalently bound to a THA-C6 linker with triantennary GalNAc residues to facilitate the specific intracellular uptake of the ASO via ASGPR receptors at the principal site of TTR production in the liver. This ASGPR receptor-mediated endocytosis followed by cleavage of the GalNAc-conjugate, cytoplasmic release of the oligonucleotide and recycling of the ASGPR on the hepatocyte cell surface was previously demonstrated (Prakash *et al*., 2014; givosiran, EMEA/H/C/4775; lumasiran, EMEA/H/C/5040; inclisiran EMEA/H/(C/5333; vutrisiran, EMEA/H/C/5852).

The specificity of inotersen for the 3'-UTR of the human TTR mRNA, which leads to RNase H1-mediated degradation of the TTR mRNA, has been earlier established and potential off-target hybridisations were excluded (see EPAR of *"Tegsedi"*). The binding sequence of eplontersen and inotersen lacks significant polymorphisms and amyloid mutations, so both oligonucleotides inhibit the expression of wildtype and

all known mutant variants of the TTR gene. This target sequence is completely conserved between humans and monkeys, while it contains eight mismatches in rodents (EPAR of *"Tegsedi"*). Consequently, eplontersen and inotersen are only pharmacologically active in humans and monkeys, but not in mice and rats.

Inotersen did not suppress any potential off-target transcript with a contiguous match ≥10 nucleotides *in vitro*, which would be required for effective hybridisation. As eplontersen harbours the same nucleotide sequence, the lack of relevant off-target interactions is also applicable for eplontersen. This is supported by a more favourable toxicological profile of eplontersen compared to inotersen (see below). Hence, further secondary pharmacodynamic investigation are not required for eplontersen.

The more specific GalNAc-mediated liver targeting of eplontersen resulted in a 51-fold more potent inhibition of TTR mRNA expression than inotersen *in vitro*. The pharmacological *in vivo* activity of eplontersen was investigated in comparison to inotersen in transgenic mice overexpressing a mutant human TTR variant known to cause familial amyloid polyneuropathy in humans (hTTR I84S; Benson *et al.*, 2006). As these transgenic mice do not develop the cardiac, neuronal or renal symptoms of the human disease, only the suppression of hTTR mRNA translation could be evaluated. Eplontersen 28- and 15-fold more effectively inhibited hepatic hTTR mRNA and plasma TTR protein levels in hTTR transgenic mice than inotersen (ED_{50} of 1.5 and 22.9 mg/kg/week, respectively), which coincides with the potency of another GalNAc-conjugated compared to non-conjugated ASOs (Prakash *et al*., 2014).

In healthy monkeys of the subchronic and chronic toxicity studies, eplontersen also dose- and time-dependently diminished TTR mRNA expression with a maximum decrease of 62 % following multiple s.c. injections of up to 24 mg/kg/week for 13 weeks or up to 25 mg/kg/month for 9 months. Concomitantly, TTR plasma protein was differently reduced by 69 % and 52 % in the two toxicity studies, which might be attributed to the weekly and monthly administration schedules and/or divergent baseline levels used for the respective determinations. Both TTR mRNA and TTR protein tended to recover upon termination of eplontersen dosing, which was more prominent in the 9 months toxicity study.

The TTR protein normally interacts with the RBP4-retinol complex to prevent its renal clearance, while enabling the recycling of RBP4 after intracellular retinol release (Li *et al.*, 2014). Accordingly, eplontersen doses ≥6 mg/kg/week for 13 weeks also decreased RBP4 plasma levels by 60 % in monkeys, which persisted upon treatment cessation for 3 months. In contrast, the RBP4 decline was less pronounced in the 9 months toxicity study with a maximum reduction of 29 % in the 25 mg/kg/month eplontersen high dose group, which completely reversed in the recovery period in line with TTR protein normalisations.

Overall, the reductions in TTR mRNA expression and plasma TTR protein observed with eplontersen in monkeys were in the same range as earlier reported for the more often administered inotersen (cf. EPAR of *"Tegsedi"*). The RBP4 decrease noticed in the 13 weeks toxicity of eplontersen was also similar to that determined in repeat-dose toxicity studies at higher and more frequent doses of inotersen (see EPAR of *"Tegsedi"*), whereas monthly s.c. injections of eplontersen in the 9 months toxicity study produced less pronounced and reversible RBP4 reductions.

Safety pharmacological effects of eplontersen on cardiovascular, respiratory and CNS function were investigated in the *"core battery"* of investigations in accordance with GLP, ICH S7A and ICH S7B guidelines (CPMP/ICH/539/00; CPMP/ICH/423/02). Eplontersen concentrations up to 300 µM did not inhibit hERG-currents *in vitro*. In monkeys, no changes of cardiovascular, respiratory or CNS parameters were noticed at s.c. eplontersen doses of 24 mg/kg leading to plasma levels of 34.9 µg/ml, which is further supported by the outcome of the 13 weeks and 39 weeks repeat-dose toxicity studies in monkeys. Moreover, no safety pharmacological abnormalities were observed with other GalNAc-conjugated or non-conjugated 2'-MOE ASOs in animals or healthy human subjects including inotersen

(Kim *et al*., 2014; Yu *et al.*, 2017; Zanardi *et al*., 2021; EPAR of *"Tegsedi"*). It can be assumed that the large molecular size of oligonucleotide therapeutics likely precludes their interaction with the pore of cardiac ion channels and their permeation across the blood-brain-barrier, respectively (Berman *et al*., 2014).

In view of the known specificity of inotersen, dedicated evaluations of pharmacodynamic interactions are not necessary for eplontersen.

Pharmacokinetics

The pharmacokinetic properties of eplontersen were studied *in vitro* and after single or multiple s.c. administrations in toxicity studies for up to 26 or 39 weeks in mice and monkeys, whereas mass balance evaluations were performed in rats. The metabolism of eplontersen was investigated for both oligonucleotide-related and THA-linker-related moieties in plasma, tissues and excreta of mice, rats, monkeys and humans. The employed bioanalytical methodologies are regarded established for the respective analytical purposes.

The quantification of eplontersen in monkey plasma by ELISA and in monkey tissue by HPLC-UV was performed by a GLP accredited contract laboratory in line with the validation principles of the ICH M10 guideline (EMA/CHMP/ICH/172948/2019).. Nevertheless, subsequent toxicokinetic determinations using these methods by another contract laboratory complied with GLP regulations. The considerable safety margins based on the plasma AUC at the respective NOAELs in both monkey toxicity studies with respect to human exposure at the recommended therapeutic dose is therefore considered reliable.

Eplontersen was rapidly absorbed after s.c. injection reaching dose-dependently increased peak plasma concentrations between 0.5 to 1 h in rats and 1 to 2 h in monkeys. Eplontersen showed comparably extensive plasma protein binding of >97-98 % across species including humans and preferentially partitioned into plasma. Subsequently, plasma levels declined in monkeys with a MRT0-48h of 2 to 6 hours post dose, which reflected the tissue distribution of eplontersen, predominantly into liver and kidneys of mice, rats and monkeys as known from inotersen and other GalNAc-conjugated or non-conjugated ASOs (Geary, 2009; Yu *et al*., 2016a and b; EPAR of *"Tegsedi"*). The more than dose-proportionally increased plasma AUC in monkeys suggests saturation of ASGPR-mediated hepatic uptake, which is also indicated by the less than dose-proportionally increased kidney and liver concentrations of unconjugated eplontersen in mice, rats and monkeys. Comparable findings were observed with another GalNAc-conjugated 2'-MOE ASO and the GalNAc-conjugated siRNA vutrisiran (Zanardi *et al*., 2021; EPAR of *"Amvuttra"*, EMEA/H/C/5852). No significant plasma accumulation or sex difference was noted upon repeated once monthly s.c. injections in monkeys, which was to be expected from the specific GalNAc-mediated liver-targeting approach and previous experience with inotersen (see EPAR of *"Tegsedi"*).

Eplontersen did not distribute into the placenta in relevant amounts and, hence, did not reach the foetuses of pregnant mice, which was to be expected from experience gained with non-conjugated ASOs in mice and rabbits (Henry *et al.*, 2004a and b). Similarly, a significant systemic eplontersen exposure of nursing pups seems unlikely given the minimal milk secretion observed with inotersen or the lack of milk transfer reported for another ASO (Henry *et al.*, 2004a; EPAR of *"Tegsedi"*). The macromolecular size and hydrophilicity of ASOs likely interfere with their passage across the placental barrier and into milk.

Intact eplontersen accounted for 96 % of the administered s.c. dose in monkey plasma, whereas partially conjugated compound (with 1, 2 or 3 GalNAc sugar deletions) or unconjugated eplontersen each constituted <2 % and no shortmer metabolites were identified. In contrast, no intact or partially conjugated eplontersen was detected in kidneys and livers of mice and monkeys. Instead, unconjugated eplontersen represented about 94 % and 79 % of the total ASO in kidneys as well as

85 % and 95 % in liver of mice and monkeys, respectively, while shortmer metabolites summed up to <2 % to <6 %. The predominance of intact eplontersen and the absence of shortmer oligonucleotide metabolites in plasma reflects the stability of eplontersen in the circulation and the ASGPR-mediated endocytosis of the intact compound leading to intracellular cleavage of the GalNAc-THA-linker (reviewed by Crooke *et al*., 2021). The observed more rapid intracellular metabolism of the GalNAc-THA-linker of eplontersen and main excretion of resulting metabolites via faeces with minor contribution of the renal route coincides with detailed reports for another GalNAc-conjugated ASO containing the same THA-C6-linker chemistry (Yu *et al*., 2016a and b; Shemesh *et al*., 2016). On the contrary, the initial endonuclease-mediated cleavage of unconjugated eplontersen followed by exonucleolytic degradation from the respective 5'- and 3'-termini proceeded much slower as indicated by high amounts of N-7 to N-10 oligonucleotide metabolites compared to other shortmers in kidney and liver. These oligonucleotide-related fragments can be reliably expected to form thermodynamically even less stable hybrids with potential off-targets than the full-length parent molecule. Chain-shortened oligonucleotide metabolites were primarily eliminated by the renal route as established for inotersen or other 2'-MOE-ASOs with and without GalNAc-conjugate (Geary, 2009; Shemesh *et al*., 2016; Crooke *et al*., 2021; EPAR of *"Tegsedi"*).

Eplontersen did not induce or interfere with cytochrome P450 enzyme activities and did not serve as substrate or inhibitor of human drug transporters when evaluated in accordance with European recommendations and those for oligonucleotide drugs (CPMP/EWP/560/95/Rev.1 Corr.2; Berman *et al*., 2023). Despite its extensive plasma protein binding capacity, eplontersen did not displace other highly bound drugs. Hence, eplontersen lacks a significant potential for pharmacokinetic interactions, which has been adequately addressed in section 4.5 of the proposed SmPC and coincides with the therapeutic experience gained with other phosporothioate ASOs including inotersen (Geary, 2009; EPAR of *"Tegsedi"*).

Repeat-dose toxicity

The repeat-dose toxicity of eplontersen was investigated following weekly, biweekly or monthly s.c. administration for up to 26 weeks in mice, 14 weeks in rats and up to 39 weeks in monkeys. All pivotal subchronic and chronic toxicity studies in mice and monkeys complied with GLP and prevailing ICH requirements. The tested eplontersen batches were comparable to the lots produced for clinical development and future marketing. As the TTR mRNA target sequence of eplontersen is only conserved between primates and humans, monkeys were selected as pharmacologically responsive species, while mice and rats served to unravel possible off-target effects. Nevertheless, a mouse-specific TTR analogue ASO containing the same GalNAc-conjugate and chemical modifications like eplontersen was tested in a satellite group of mice in the 26 weeks toxicity study to distinguish toxicities related to TTR inhibition from non-specific effects related to the backbone chemistry of the ASO. At the NOAELs determined in the 13 and 39 weeks toxicity studies in monkeys (6 mg/kg/week and 25 mg/kg/month), cumulative plasma AUC translated into more than 70-fold safety margins with respect to human exposure at the recommended therapeutic dose of 45 mg/month.

Eplontersen induced the envisaged dose-dependent reductions of hepatic TTR mRNA by up to ~62 % at 24 mg/kg/week or 25 mg/kg/month in monkeys, whereas biweekly 10 mg/kg doses of the mouse-specific analogue ASO decreased TTR mRNA by 82 % in mice. Consequently, TTR and RBP4 plasma protein levels were diminished in monkeys by up to 68 % and 60 % after weekly and by about 52 % and up to 29 % following monthly administrations, respectively. Nevertheless, no eplontersen-related ophthalmological abnormalities were identified in mice or monkeys.

In all repeat-dose toxicity studies, no clinical signs or changes of body weights, coagulation and most clinical chemistry parameters were evident. A relationship of the low mortality incidences in mice with eplontersen treatment could either be excluded or rated improbable.

Contrary to the clear stimulation of inflammatory events by inotersen in animals (EPAR of *"Tegsedi"*), eplontersen did not significantly impact on various pro-inflammatory and anti-inflammatory cytokines and chemokines in mice, rats and monkeys.

The widely observed non-adverse histological changes in the liver, kidneys, lymphoid tissues and injection sites of mice, rats and monkeys reflect the principal sites of uptake, distribution and accumulation of eplontersen that were impacted by the respective frequency of the s.c. dosing regimen. The microscopic alterations included dose-dependently enriched minimal/mild basophilic granules within cytoplasmic vacuoles of macrophages and/or monocytes at injection sites, in lymph nodes, proximal tubular kidney epithelia, hypertrophied hepatocytes and in hepatic Kupffer cells of mice, rats and monkeys, which was comparably evident for the mouse-specific analogue ASO. More frequent s.c. eplontersen injections ≥25 mg/kg/week or ≥50 mg/kg every other week resulted in the sporadic occurrence of vacuolated granular macrophages in reproductive organs and less commonly in a variety of other tissues. Upon cessation of eplontersen treatment, basophilic granules were still detected with noticeably reduced incidence in Kupffer cells, renal tubular epithelia, injection sites, epididymal and testicular interstitium of mice. Similarly, basophilic granules were identified upon termination of the recovery period in hepatocytes, lymph nodes and injection sites of monkeys. These histological findings have been earlier described for inotersen, other non-conjugated phosphorothioate 2'-MOE ASOs as well as the more recent GalNAc-conjugated successors and are characteristic for the pharmaceutical class of oligonucleotides (Frazier, 2015; Crooke *et al*., 2021; Zanardi *et al*., 2021; EPAR of *"Tegsedi"*).

At the end of the recovery period, one monkey administered previously the 25 mg/kg/month eplontersen high dose for 39 weeks revealed minimal perivascular and mural inflammatory cell infiltrates in small to medium calibre vessels as well as minimal to slight medial and intimal hyperplasia in arterioles of liver, gallbladder, kidney, heart, colon, pancreas and seminal vesicles and periportal inflammation in the liver along with elevated liver enzymes. These perivascular inflammations were more common with inotersen or other unconjugated 2'-MOE ASOs in monkeys and have been related to the ASO-mediated activation of the complement system, for which monkeys are more sensitive than humans (Engelhardt *et al*., 2015). Thus, these vascular inflammatory events do not raise particular concerns in terms of human safety, which is supported by the clinical experience gained since licensing of inotersen.

The most prominent adverse event was severe thrombocytopenia (platelet count of 4×10^9/L) that developed in a single female out of 12 monkeys of the 24 mg/kg/week eplontersen high dose group from day 73 of the 13 weeks toxicity study. The platelet decline was accompanied by spontaneous haemorrhage, which presented as haematoma and petechiae. This monkey fully recovered upon termination of eplontersen dosing in combination with glucocorticoid treatment. Of note, the female monkey had shown an acute 4-fold increase of complement split product Bb at 4 h post first dose, which subsequently normalised within 24 h and did not reoccur in week 13. The apparent limited activation of the alternative complement pathway in this monkey was confirmed by individual transient 2.8-fold increases of complement split product Bb in three other females of the same eplontersen high dose group of the 13 weeks toxicity study and in male monkeys administered 25 mg/kg/month eplontersen in the 39 weeks toxicity study (2-fold). However, no further platelet declines or changes of complement factor C3, bone marrow cellularity or coagulation parameters were detected in any monkey or rodent treated with eplontersen.

Pronounced platelet decreases have been occasionally observed in monkeys administered specific unconjugated 2'-MOE phosphorothioate ASOs with considerable variability of incidence and severity even within the same dose group (Henry *et al*. 2017). The pronounced sensitivity of monkeys to complement system activation by 2'-MOE phosphorothioate ASOs has been linked to the approximately 3-fold higher inhibition of monkey complement factor H compared to humans (Shen *et al*., 2014).

Inotersen also lowered platelet counts across species including human patients leading to a warning of thrombocytopenia and regarding the cautious use of concomitant anticoagulants in the product information (cf. sections 4.4, 4.5 and 4.8 of the SmPC of *"Tegsedi"*). The high individual susceptibility of certain inotersen-treated monkeys for thrombocytopenia has not been unravelled so far, but has been hypothetically attributed to the augmentation of pre-existing antibodies against various platelet surface epitopes, which in particular combinations could increase platelet clearance (see EPAR of *"Tegsedi"*). As inotersen and eplontersen share the identical sequence, the severe thrombocytopenia seen in the single monkey of the eplontersen high dose group in the 13 weeks toxicity study is regarded treatment-related. However, the more efficient hepatic uptake and lower systemic bioavailability of eplontersen apparently lowers the thrombocytopenic hazard, which is supported by less marked platelet reductions in monkeys administered GalNAc-conjugated ASOs (Zanardi *et al*., 2021) and in patients who received eplontersen. Given the very low incidence of thrombocytopenia in just one eplontersen-treated monkey, further non-clinical clarification of the possible human risk for thrombocytopenia associated with eplontersen is considered impossible and cannot be justified with respect to European principles concerning animal welfare (Dir. 2010/63/EU; EMA/CHMP/CVMP/JEG-3Rs/450091/2012; see clinical AR for further evaluation).

Eplontersen induced minimal to mild signs of anaemia in the female monkey with thrombocytopenia administered the 24 mg/kg/week high dose for 13 weeks and in another female monkey injected the 5 mg/kg/month low dose for 39 weeks. Signs of anaemia were more prominent in inotersen-treated animals (see EPAR of *"Tegsedi"*), but were not observed during therapeutic administration of eplontersen in patients. Hence, the two cases of mildly altered red blood cell counts in monkeys are regarded clinically irrelevant.

ADAs were confirmed in the chronic toxicity study in monkeys that were identified as binding antibodies without neutralising capacity. These ADAs increased median plasma trough concentrations of eplontersen, but the antigenicity of eplontersen following long-term treatment of monkeys was lower than previously reported for inotersen. In addition, ADAs did not impact on the efficacy and toxicity of eplontersen, which coincides with earlier experience from ADA development against inotersen and other oligonucleotides (Yu *et al.*, 2020; Henry *et al.*, 2022; Berman *et al.*, 2023). In monkeys, eplontersen did not affect specific subsets of white blood cells (monocytes, granulocytes, T- or B-lymphocytes, natural killer cells), which therefore mounted a normal T-cell dependent immune response (TDAR). It should be also noted that inotersen did not induce immunosuppression or immunotoxicity in the influenza host-resistance model in mice (see EPAR of *"Tegsedi"*) and that a normal TDAR was observed in monkeys administered another GalNAc-conjugated 2'-MOE ASO (Zanardi *et al*., 2021). In accordance with the weight-of-evidence approach of the ICH S8 guideline (CHMP/167235/2004), further immunotoxicity testing of eplontersen is therefore not required.

Genotoxicity and carcinogenicity

Eplontersen did not exert any genotoxic potential in a standard battery of *in vitro* and *in vivo* studies, which complied with ICH S2(R1) and GLP regulations (EMA/CHMP/ICH/126642/2008).

In a GLP-compliant 26 weeks carcinogenicity study in Tg.rasH2 mice, s.c. eplontersen injections of up to 1500 mg/kg/month did not induce tumorigenic effects. Non-neoplastic microscopic changes in kidneys, liver and basophilic granules in macrophages in epididymis, heart and pancreas reflected the uptake and accumulation of eplontersen as seen in repeat-dose toxicity studies. Based on the negative outcome of this investigation in Tg.rasH2 mice, the lack of genotoxicity, immunosuppressive or proliferative findings in other toxicity studies, as well as the similarity of eplontersen and inotersen, which was not carcinogenic in rats, the lack of a 2 years rat carcinogenicity study is acceptable and eplontersen is not considered to be carcinogenic.

Reproductive and developmental toxicity

Eplontersen doses up to 75 mg/kg/week did not affect fertility and embryonic development in a combined study in mice, which coincides with the lack of relevant distribution to placenta and foetal tissues and earlier observations with inotersen or other 2'-MOE ASOs (see EPAR of *"Tegsedi"*; Henry *et al.*, 2004a and b). The no observed adverse effect level (NOAEL) for fertility, maternal toxicity, and foetal development of eplontersen was therefore 75 mg/kg/week. As eplontersen harbours the identical sequence of inotersen, which had been also tested with respect to embryo-foetal development in rabbits and in a pre-/postnatal development study in mice (see EPAR of *"Tegsedi"*, the previous CHMP advice is confirmed that further reproduction and developmental toxicity studies are not required for eplontersen.

The mouse-specific TTR analogue ASO tested at 25 mg/kg/week in a parallel arm of the study reduced liver TTR mRNA levels on average by 93 % and 97 % in males or females, respectively, but also did not produce any effects on fertility or embryo-foetal development in mice.

However, TTR in complex with RBP4 plays an important role as major carrier for retinoids in humans (~95 %; Li *et al*., 2014). Balanced levels of retinoids are crucial for normal embryonic development, because their deficiency as well as their excess may cause teratogenicity (reviewed by Zile MH, 1998; Collins MD and Mao GE, 1999; Ross SA *et al*., 2000). Moreover, TTR is synthesised, secreted and taken up by the human placenta, influences human receptivity and normal pregnancy (Landers *et al*. 2013; Wang *et al*. 2016). There may be additionally different species sensitivities towards retinoids because of altered pharmacokinetics in humans and monkeys compared to rodents and rabbits (Nau H, 2001). Except one dose group administered the TTR analogue ASO in mice, the pharmacological effects of eplontersen could not be captured in the embryo-foetal development study. Since the envisaged patient population of eplontersen includes women of child-bearing potential, the adequate warnings for vitamin A supplementation and instructions to prevent pregnancies have been implemented in sections 4.4 and 4.6 of the SmPC and corresponding sections of the PL.

No other toxicity studies were conducted or are deemed necessary. Eplontersen is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Eplontersen revealed improved inhibition of TTR mRNA and TTR protein in human transgenic mice and healthy monkeys compared to that observed after higher doses or more frequent administrations of inotersen.

The pharmacokinetic and toxicological properties of eplontersen have been sufficiently characterised in accordance with prevailing ICH and GLP requirements and coincide with existing experience from other oligonucleotide drugs including those with GalNAc-conjugate. Adequate warnings for vitamin A supplementation and instructions to prevent pregnancies were implemented in the SmPC and corresponding sections of the PL.

Thus, marketing authorisation can be recommended from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
ION-682884-CS3 (NEURO-TTRansform)	Ongoing Interim analysis (Week 35) data cut-off date: 18-Apr-2022 (efficacy) and 19-Jul-2022 (safety) Week 66 Analysis (Week 65/66) and Week 85 Analysis data cut-off date: 07-Apr-2023 Eplontersen: n = **144** randomized; n = 135 completed Week 66 Concurrent Inotersen: n = **24** randomized; n = 20 completed Week 66 External placebo (from Study ISIS 420915-CS2): n = **60** randomized; n = 52 completed Week 66 Historical Inotersen (from Study ISIS 420915-CS2): n = 113 randomized; n = 87 completed Week 66	Phase 3 randomized, open-label study with external placebo group to assess efficacy and safety of eplontersen 84 weeks treatment duration	<u>Eplontersen group</u> Eplontersen: 45 mg q4w (s.c.) <u>Inotersen-eplontersen group</u> Inotersen sodium (for first 34 weeks): 300 mg q1w (s.c.) Eplontersen (from Week 37): 45 mg q4w (s.c.) <u>Historical Inotersen group (from Study ISIS 420915-CS2):</u> 300 mg q1w	Male and female patients not of childbearing potential (post-menopausal and/or surgically sterile) aged 18 to 82 years with ATTRv-PN stage 1 or stage 2 according to the Familial Amyloid Polyneuropathy or Coutinho Stage, with documented genetic mutation in the TTR gene, and symptoms consistent with neuropathy associated with TTR mediated amyloidosis, including Neuropathy Impairment Score ≥ 10 and ≤ 130. Willingness to take to vitamin A supplements.
ION-682884-CS13	Ongoing Interim 1 CSR data cut-off date: 19-Jul-2022 Interim 2 CSR data cut-off date: 07-Apr-2023 Enrolment: Eplontersen 165 (planned) **108** patients treated up to the data cut-off (DCO) date	Phase 3 open-label, extension study to assess long-term safety and tolerability Up to 3 yrs treatment duration	Eplontersen (s.c.) 45 mg q4w	Completion of ION-682884-CS3 OR diagnosis of ATTRv-PN and satisfactory completion of either study ISIS 420915-CS101 (Investigator-Sponsored study with inotersen). Male and female patients not of childbearing potential (post-menopausal and/ or surgically sterile). Willingness to take to vitamin A supplements.

ION-682884-CS1	Completed Eplontersen: 39 Placebo: 8	Phase 1/2 study to evaluate safety, tolerability, PK, PD of single and multiple doses of eplontersen [a]	<u>Multiple dose:</u> 45, 60, and 90 mg eplontersen (s.c.) or placebo q4w (total of 4 doses) for 13 weeks <u>Single dose:</u> 120 mg eplontersen (s.c.) or placebo	Healthy volunteers (Cohorts A, B, C and E): Male and female volunteers of non-childbearing potential (post-menopausal and/ or surgically sterile), 18 to 65 years of age of Japanese descent. Willingness to take to vitamin A supplements. ATTRv patients (Cohort D): Male and female patients not of childbearing potential (post-menopausal and/or surgically sterile) aged 18 to 82 years with ATTRv-PN stage 1-3, with documented genetic mutation in the TTR gene, and symptoms consistent with polyneuropathy as measured by including NIS score ≥ 10. Willingness to take to vitamin A supplements.
ION-682884-CS20	Completed Eplontersen: 18 Placebo: 6	Phase 1, randomized, double-blinded, placebo-controlled study to evaluate safety, tolerability, PK, and PD of single doses of eplontersen treatment	<u>Single dose:</u> 45, 60, and 90 mg eplontersen (s.c.) or placebo	Healthy, male and female volunteers of non-childbearing potential (post-menopausal and/or surgically sterile), 20 to 65 years of age of Japanese descent. Willingness to take to vitamin A supplements.
ION-682884-CS21	Completed Eplontersen: 57	Phase 1, randomized, open-label, 3-period, crossover, bioequivalence study comparing three s.c. formulations: sealed glass vials, prefilled syringe with safety device, and autoinjector Single dose per period	Periods 1, 2, and 3 Eplontersen 45 mg (s.c.) with a 4-week (28 days) washout between study periods	Healthy, male and female volunteers of non-childbearing potential (post-menopausal and/ or surgically sterile), 18 to 64 years of age. Willingness to take to vitamin A supplements.

[a] As noted in the study title, study ION-682884-CS1 was originally planned to include an ATTR patient cohort (Cohort D); however, the study was ultimately completed without the patient cohort being implemented. Accordingly, no ATTR patient data are available from ION-682884-CS1, and the study is referred to as 'Phase 1' throughout this document.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology of eplontersen was investigated in three healthy volunteer studies and two studies in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy (ATTRv-PN). Additional supportive data were derived from in-vitro studies using human biomaterial.

In healthy volunteers, single doses of 45, 60, 90 and 120 mg eplontersen were investigated as well as multiple doses of 45, 60, and 90 mg eplontersen every four weeks for up to a total of four doses. Additional studies in healthy volunteers included the investigation of single doses of 45, 60 and 90 mg eplontersen in subjects of Japanese descent and of the bioequivalence of three different SC drug product presentations (vial and syringe, PFS with safety device, and autoinjector) at the 45 mg dose in a cross-over design with a 28 days washout between study periods.

Data in patients were collected in the pivotal Phase 3 study ION-682884-CS3 as well as the corresponding open-label extension study ION-682884-CS13.

Bioanalytical methods

Bioanalytical methods for quantification of drug concentrations, serum TTR concentrations, serum RBP4 concentrations and detection of ADAs were developed and validated to fit the intended use of the data generated. Validation reports for the measurement of pharmacokinetics parameters (eplontersen in plasma and urine, eplontersen metabolites in plasma, inotersen in plasma), pharmacodynamics parameters (TTR in serum) and immunogenicity parameters (anti-eplontersen antibodies and anti-inotersen antibodies) were provided. The validations appear to be generally in line with the requirements as provided in the appropriate European guidelines.

Absorption, distribution, metabolism and excretion

Eplontersen is administered by subcutaneous (SC) injection. Following SC administration, eplontersen was rapidly absorbed into the systemic circulation, with peak plasma levels achieved approximately 2 hours post-dose. Time to steady-state observed in patients with ATTRv-PN appeared to be reached by Day 169, consistent with the apparent terminal elimination half-life of 3 to 4 weeks in plasma observed in healthy volunteers.

Eplontersen is highly (> 98%) bound to plasma proteins, with little change over a clinically relevant range of 0.1 to 5 µg/mL. After reaching C_{max}, plasma concentrations of eplontersen declined in a biphasic fashion with an initial, relatively fast disposition phase that dominated the plasma clearance followed by a much slower elimination phase. The oligonucleotide in eplontersen is conjugated to GalNAc that binds to asialoglycoprotein receptors expressed abundantly on the hepatocyte cell surface. This allows for hepatocyte-specific targeting and explains the rapid early clearance through distribution into the liver. The plasma concentrations of eplontersen observed in the post-distribution phase (C_{trough}) represent the level that is in equilibrium with target tissue.

The primary route of elimination of eplontersen is initial rapid hydrolysis of GalNAc conjugate following uptake into tissues, where the unconjugated eplontersen is slowly metabolized by endo- and exonucleases, and subsequent rapid excretion of the slowly formed fragmented oligonucleotide metabolites in urine. Meanwhile, the THA-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.

Metabolite profiling of human plasma peak and trough samples at steady-state showed that there was little to no (< 1%) circulating eplontersen metabolites relative to total full-length oligonucleotides. Profiling of length-based oligonucleotide metabolites demonstrated that the most abundant oligonucleotide species detected was intact eplontersen at the 2-hour time point, while trough samples following repeated q4w doses of 90 mg eplontersen for 13 weeks (Day 85) were below the LLOQ. The full-length ASOs accounted for 100% of the total oligonucleotides present, when detected, and no shortmer metabolites of eplontersen were detected in plasma at trough concentrations and two hours post dose. The lack of accumulation of shortmer oligonucleotide metabolites in plasma is consistent with the nuclease-mediated metabolism in tissues being the rate-limiting step, and shortened oligonucleotides were rapidly eliminated in urine once generated.

The apparent terminal eplontersen 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. The long elimination half-life reflects the slow elimination of drug from the liver.

Bioequivalence

Three different drug product presentations for eplontersen have been developed, all use solution for injection but different devices are used for application: vial and syringe, autoinjector, and a prefilled syringe (PFS) with safety device. The vial and syringe presentation was used in the Phase I healthy volunteer studies ION-682884-CS1 and ION-682884-CS20 as well as the patient Phase III study ION-682884-CS3. In the long term extension study ION-682884-CS13 about 10% of participants used the vial and syringe while approximately 90% used the autoinjector, which is also the presentation intended for commercial use. In the clinical development program for ATTRv-PN, the PFS has not been used.

Comparison of PK profiles between the vial or syringe with the autoinjector as well as the PFS respectively showed that $AUC_{0\text{-}168h}$ fulfils the formal BE criteria while the upper limit of C_{max} is slightly above the pre-specified target range for both devices, autoinjector and PFS. Based on the mode-of-action, drug concentrations within the cells will be most relevant for efficacy and this is best represented by AUC in plasma. Slight increases in C_{max} on the other hand would not be expected to have a significant impact as peak plasma concentrations are not representative for the drug's concentration at the target.

Dose proportionality and time dependencies

Following single SC eplontersen doses ranging from 45 to 120 mg, eplontersen exposure (C_{max} and AUC) showed a slightly greater than dose-proportional increase (slope of 1.27 for C_{max} and 1.26 for AUC using linear regression analyses of the log-transformed data). Presence of ADA had no impact on C_{max} or AUC. Following multiple SC eplontersen doses ranging from 45 to 90 mg, C_{trough} also showed a slightly greater than proportional increase in ADA-negative subjects. On Day 113 (at near steady-state), the mean C_{trough} ratio comparing the 60-mg and 90-mg dose to the 45-mg dose was 1.2 and 2.7, respectively. Higher plasma eplontersen C_{trough} levels were observed in both healthy volunteers and patients with ATTRv-PN who had treatment-emergent ADA. The half-life of eplontersen estimated in healthy volunteers after repeated dosing was dose-independent.

Pharmacokinetics in the target population and special populations

In healthy volunteers, slight differences in PK parameters between dosing days or across clinical studies were observed, which can be attributed to differences in intrinsic factors (body weight) and extrinsic factors (injection site, drug product presentations), which are further evaluated in the popPK

analysis. There were no apparent differences in the PK parameters following multiple SC administrations of 45 mg eplontersen q4w between patients with ATTRv-PN and healthy volunteers.

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. Specifically, cases of more severe renal and hepatic impairment have not been sufficiently investigated. In the absence of specific safety signals for hepatotoxicity eplontersen should be used only after a careful, individual risk-benefit assessment in patients with moderate or severe hepatic impairment.

Population PK modelling

Eplontersen PK was adequately described through a 2-compartment disposition model with parallel first-order and a 3-transit absorption model, along with parallel linear and nonlinear Michaelis-Menten elimination analysing data from n=230 patients. The popPK model was further used to simulate different dosing regimens (30 mg, 45 mg, 60 mg or 90 mg q4w or q1m) showed increasing plasma exposure with increasing dose and comparable levels of exposure between q4w and q1m dosing. Therefore, the q1m dosing can be supported through popPK simulations.

Clarification was needed due to the exclusion of ADA positive samples in the analysis. Even though the applicant discussed that the immune response against ASOs typically has no clinically meaningful consequences, the popPK model should be able to describe the effect of ADAs on C_{trough} especially when the effect of ADAs on the C_{trough} of eplontersen is as pronounced as it was shown. Therefore, no conclusions regarding dose adjustments in ADA positive patients can be drawn from the popPK model. The applicant clarified that the M3 method for handling BLQ observations was considered but the BLQ imputation strategy was chosen due to performance issues.

Pharmacokinetic interaction studies

The drug-drug-interaction potential of eplontersen has been investigated in in-vitro studies using human biomaterials. These studies are described in greater detail in the non-clinical assessment report. As is expected for an oligonucleotide eplontersen is not an inhibitor or inducer of metabolising cytochrome enzymes nor an inhibitor or a substrate of common drug transporters.

Eplontersen does also not interact with highly plasma protein-bound drugs. No drug-drug interaction was observed in vitro with regard to plasma protein binding displacement between eplontersen and highly plasma protein-bound drugs, warfarin and ibuprofen.

In conclusion, eplontersen has a very low potential for involvement in plasma protein binding, CYP-mediated, or transporter-mediated drug-drug interactions. Therefore, dedicated clinical drug interaction studies with eplontersen were not deemed necessary and were not conducted.

2.6.2.2. Pharmacodynamics

Mechanism of action

Eplontersen is a triantennary GalNAc-conjugated 2'-MOE-modified chimeric gapmer ASO with a mixed backbone of PS and PO internucleotide linkages. It hybridizes with the 3'-untranslated region of *TTR* mRNA and selectively silences *TTR* mRNA in the liver. It shares this same basic mechanism of action with inotersen. Eplontersen sodium differs chemically from inotersen sodium in that it contains a

mixture of PS and PO internucleotide linkages, whereas inotersen sodium contains only PS diester internucleotide linkages.

Selective delivery to the liver is achieved via conjugation to GalNAc (which is also a difference to inotersen) that binds to asialoglycoprotein receptors expressed abundantly on the hepatocyte cell surface, while binding to *TTR* mRNA is mediated by 20 nucleotides that are complementary to the sequence from position 618 to 638 (using the NM_000371.3 as TTR mRNA reference sequence) within the 3'-untranslated region of the *TTR* mRNA (this sequence is identical to inotersen). Hybridization (binding) of eplontersen to *TTR* mRNA leads to its cleavage by Ribonuclease H1 (a nonspecific endonuclease that catalyses the cleavage of RNA via a hydrolytic mechanism), thus preventing production of TTR protein. By decreasing the amount of liver-derived TTR protein in the circulation, eplontersen treatment decreases the formation of TTR amyloid fibril deposits, and thus slows, halts, and reverses the symptoms of ATTR disease.

Both parts of the MoA, silencing of mRNA and targeted delivery to the liver, are well described in the scientific literature and have been in routine clinical use for several year now. Confirmation of the MoA was provided by demonstrating the primary pharmacodynamic effect, reduction of plasma TTR levels.

Primary and secondary pharmacology

PD data were analysed as change and percent change from baseline in serum TTR concentration and RBP4 concentration following SC administrations of eplontersen.

The administration of single and multiple doses of eplontersen resulted in dose-dependent reductions in serum TTR concentrations and RBP4 concentrations in healthy volunteers. In study ION-682884-CS1, for example, the mean percent change from baseline in serum TTR concentration at Day 29 after a single 45-, 60-, 90-, or 120-mg dose of eplontersen was -59.3%, -77.1%, -82.3%, and -86.7%, respectively.

The mean serum TTR concentration reductions were persistent through and after the treatment. For example, in study ION-682884-CS1 in healthy volunteers, the maximum serum TTR concentration percent change from baseline (-81.3%) following the administration of eplontersen 45 mg q4w was reached 2 weeks after the last dose and remained as high as -55.1% 13 weeks after the last dose.

The mean RBP4 change from baseline in subjects treated with eplontersen 45 mg q4w reached a maximum of -77.8% 4 weeks after the last dose and remained as high as -54.1% 13 weeks after the last dose.

Consistently, following the administration of eplontersen 45 mg q4w in patients with ATTRv-PN in study ION-682884-CS3, the mean percent change from baseline in serum TTR concentration reached -82.13% at Week 35 and was sustained throughout the treatment period (-82.96% at Week 65 and -81.83% at Week 85).

Sustained reductions of serum TTR levels by more than 80% compared to baseline are the intended pharmacodynamics effect for the treatment of patients with hereditary amyloidosis. The efficacy of TTR lowering has previously been demonstrated for similar acting drugs like inotersen or vutrisiran that also specifically target the mRNA. For eplontersen effective lowering of TTR has been convincingly demonstrated in patients and healthy volunteers. The observed primary pharmacodynamic effect therefore provides strong supportive evidence for the efficacy of eplontersen in the treatment of ATTRv-PN.

Immunological events

Immunogenicity of eplontersen was evaluated in healthy volunteers (ION-682884-CS1) and in patients with ATTRv-PN (ION-682884-CS3 and ION-682884-CS13), including analyses of anti-eplontersen antibody positivity on measures of PK, PD, efficacy, and safety.

No impact of immunogenicity on C_{max}, AUC, elimination half-life, or clearance was observed. These plasma PK parameters were similar between the ADA-negative and ADA-positive subjects in both studies. Higher plasma eplontersen C_{trough} levels were observed in both healthy volunteers and patients with ATTRv-PN who had treatment-emergent ADA compared with subjects with treatment-unaffected ADA or ADA-negative subjects.

ADA positivity did not have any effect on serum TTR concentration reduction in eplontersen-treated healthy volunteers or patients with ATTRv-PN at any timepoint. Following the administration of 45-mg eplontersen q4w, the mean serum TTR concentration percent change from baseline at Week 85 in patients with ATTRv-PN with treatment-emergent ADA (-81.69%) was similar to that in patients with treatment-unaffected ADA (-80.12%) and ADA-negative patients (-82.04%).

Dose justification

The summary of clinical pharmacology data demonstrates that a single fixed dose of 45 mg eplontersen once per month is able to achieve a TTR reduction >80% in patients with amyloidosis independent from the investigated covariates. Higher doses would allow even higher TTR reductions, however clinical experience with similar therapeutic approaches shows that further reduction does not lead to further relevant clinical improvement. The rational was therefore to choose a dose that was able to achieve the required TTR reduction and was the lowest possible dose to minimise any dose dependent adverse events.

Eplontersen was specifically designed to be rapidly distributed in the liver where it acts intracellularly with a half-life of 3-4 weeks, which allows for long dosing intervals. While the clinical development program investigated subcutaneous injections once every four weeks popPK and popPKPD models indicate comparable PK and PD parameters for once monthly dosing. Once monthly injections could help to further improve patient adherence, as the drug can then be applied on a “fixed” date.

Overall, the applicant has provided a robust clinical pharmacology package that adequately justifies the proposed dosing regimen.

2.6.3. Discussion on clinical pharmacology

The applicant has provided a rather comprehensive data package for clinical pharmacology. Therapeutic oligonucleotides have a very well defined target and mechanism of action. In the case of eplontersen there is also a clearly defined biomarker to indicate target engagement in the form of TTR.

Bioanalytical validation reports were provided for all relevant analytes. Standard analytical methods were employed for sample analysis. The applicant provided results for incurred sample reanalysis (PK) and long term storage up to 24 months (PK and TTR) with 4 year results becoming available in October 2025 (TTR).

Eplontersen, a ligand-conjugated antisense oligonucleotide (ASO), is a triantennary GalNAc designed for receptor-mediated hepatocyte uptake. It shares a base sequence with inotersen sodium, allowing hybridization with the 3'-untranslated region of transthyretin (TTR) mRNA.

Single and multiple dose PK has been investigated in healthy volunteers and patients. However, as eplontersen is rapidly distributed into the liver, plasma concentration-time profiles do not really represent the drug's effect. While eplontersen concentrations in plasma rapidly reach trough concentrations an extended pharmacodynamics effect is found that corresponds to the long half-life of 3-4 weeks within hepatocytes, where eplontersen is slowly metabolised through nucleases. The sustained reduction of TTR of more than 80% compared to baseline provides strong supportive evidence for the drug's efficacy.

The application relies on Phase III pivotal data from ION-682884-CS3, supported by other studies in the eplontersen clinical development program: ION-682884-CS21 (bioequivalence of subcutaneous formulations), ION-682884-CS20 (single-dose PK and PD in Japanese subjects), and ION-682884-CS1 (ascending dose PK and PD in healthy adults). Modeling using data from these studies comprehensively explores the pharmacokinetics (PK), pharmacodynamics (PD), and exposure-effect relationships of eplontersen.

Pharmacokinetic data underwent standard analysis, with a PopPK model developed based on studies involving healthy volunteers and patients with ATTRv-PN. The final PK model identified covariates like body weight, race, baseline eGFR, drug product presentation, and injection site as statistically significant, impacting various PK parameters.

According to the PopPK analysis presented by the applicant, the injection site serves as a statistically significant covariate on the absorption rates, with injections in the arm resulting in a 23% lower mean $C_{max,ss}$ compared with the abdomen or thigh. Despite the arm being deemed an acceptable injection site in the pivotal study, considering the observed differences in C_{max}, it is recommended that the SmPC should specify the abdomen and thigh as the preferred sites for injections. This adjustment could align with the observed pharmacokinetic variations and ensure consistency with the findings from the PopPK analysis. The SmPC recommends using the drug at monthly intervals. However, in the pivotal study (ION-682884-CS3), the dosing interval applied was every 4 weeks. Although modelling showed a minor impact on PK parameters with such a change, C_{trough} was lower when the drug was administered at monthly intervals. The lower C_{trough} translated into minimal effect on TTR reduction (<0.1%) according to PopPKPD analysis.

In the assessment of the impact of body weight on PK parameters, the most significant changes were observed, such as a 46% decrease in C_{max} for high body weight (92 kg) compared to reference body weight (70 kg) or a 23% reduction in C_{max} when administered in the arm compared to when administered in abdomen or thigh Based on PopPKPD analysis and exposure-response analyses on serum TTR reduction, efficacy and safety, the impact of body weight was not considered clinically meaningful and the applicant does not recommend dosage adjustment. In a worst-case scenario, considering administration in the arm and patients with the highest body weight, a significant reduction in drug exposure is expected, with significantly higher exposure in the case of low body weight and administration in the thigh.

Eplontersen is rapidly absorbed into the circulation (with median T_{max} values ranging from 1 to 6 hours across dosage regimens), and its exposure is dose-dependent. After reaching peak plasma levels, eplontersen decreases in a multiphasic fashion, with a dominant disposition over plasma clearance. The ION-682884-CS21 study aimed to assess the bioequivalence between prefilled syringe with safety device or prefilled syringe with autoinjector versus vial and syringe in healthy subjects. The bioequivalence study results indicated a lack of fulfilment of bioequivalence criteria between the analysed forms of eplontersen for C_{max}. Both prefilled syringe forms showed an exceedance of the upper confidence interval limit for C_{max}. Additionally, although the bioequivalence criterion for AUC is formally met, there is a tendency for greater exposure in both cases when eplontersen is administered using prefilled syringes.

Eplontersen is highly bound to plasma proteins (> 98% bound), which limits glomerular filtration and urinary excretion. The primary route of elimination of eplontersen is initial rapid hydrolysis of the GalNAc conjugate following uptake into tissues. Unconjugated eplontersen is cut by endo- and exo-nucleases to short oligonucleotides and is excreted in urine. Oligonucleotide therapeutics, including eplontersen, are not metabolized by CYP enzymes. The most abundant full-length oligonucleotide was ION-682884 (99.1%). Minimal detection was observed for the metabolite with one deletion of sugar (0.898%). According to preclinical studies, eplontersen, after subcutaneous administration, primarily distributes to the liver and kidney. The modelled volume of distribution for the central compartment was 12.9 L.

Exposure of ION-682884 after subcutaneous administration increased with dose. Greater than dose-proportional increase in ION-682884 C_{max} and AUC was shown following single-dose administration (1 to 2.7). Likewise, C_{trough} after multiple doses of ION-682884 increased in a greater than dose-proportional manner.

The pivotal efficacy study ION-682884-CS3 aimed to assess efficacy and safety parameters as well as PK characteristics in the target population. No accumulation was observed during eplontersen treatment, as measured by C_{max} and $AUC_{0\text{-}6h}$ after 45 mg every 4 weeks. C_{max} and $AUC_{0\text{-}6}$ were comparable in ADA negative and positive patients; however, ADA positive subjects had a higher C_{trough} of eplontersen.

PopPK analysis in special populations, especially those with impaired renal function, identified statistically significant impact on steady-state exposure. The popPK analysis revealed that moderate renal impairment (eGFR 45 ml/min) was associated with a 24% increase in C_{max}, 38% in C_{trough}, and 30% in $AUC_{0\text{-}t}$. The difference may be attributable to differences in body weight between the normal, mild renal impairment and moderate renal impairment group. Race emerged as a significant covariate, and age was not found to be significant. In vitro studies indicated no impact on CYP enzymes or transporters, and clinical drug-drug interaction studies were deemed unnecessary.

According to *in vitro* studies using human biomaterials, eplontersen is not an inhibitor or inducer of CYP enzymes nor a substrate or inhibitor of transporters. Clinical drug-drug interaction studies deemed to be not necessary and were not conducted.

Age was determined not to be a significant covariate of eplontersen pharmacokinetics. The range of the age of patients participating in the clinical studies spanned from 23 to 82 years. The applicant provided the table with PK trials with participation of older population at age ranges: 65-74, 75-84, and 85+.

Pharmacodynamic data were analysed as changes and percent changes from baseline in serum TTR concentration (in studies ION-682884-CS1, ION-682884-CS20, ION-682884-CS21, and ION-682884-CS3) and RBP4 concentration (in studies ION-682884-CS1 and ION-682884-CS20) following subcutaneous administrations of eplontersen. The reduction in the PD biomarker, starting at Day 8 after the initiation of eplontersen administration (the first post-dose measurement of serum TTR concentration), was observed across all studies and remained substantial up to the last day of each study (up to 3 months after the last dose).

The analysis of popPKPD did not encompass individuals treated with placebo; thus, it was impossible to characterise the placebo response in TTR concentration. The popPKPD model delineated the serum TTR concentration in both healthy volunteers and patients with ATTRv-PN, utilizing an indirect response model with a zero-order production rate and a first-order elimination rate for TTR. Within the model, the eplontersen plasma concentration inhibits the TTR production rate. A range of covariates was scrutinized for potential effects on the PD response, including body weight, age, sex, race, disease status (healthy volunteer vs. patient with ATTRv-PN), disease stage, and Val30Met mutation. The

population PKPD analysis identified body weight, sex, race, disease status, and Val30Met mutation as statistically significant covariates affecting PD model parameters. Conversely, other covariates evaluated, such as age and disease stage (1 vs. 2), did not exhibit a statistically significant impact on the dynamics of serum TTR concentration.

Body weight was identified as a statistically significant covariate on baseline serum TTR concentrations and on the maximum inhibition of TTR production (Imax). Higher baseline serum TTR concentrations, as well as a higher maximum inhibition, were observed in individuals with higher body weight. Sex was identified as a statistically significant covariate on IC_{50}, with females having lower values than males. ADA positivity did not have any effect on serum TTR concentration reduction in eplontersen-treated healthy volunteers or patients with ATTRv-PN at any timepoint. Following the administration of 45 mg eplontersen every 4 weeks, the mean serum TTR concentration percent change from baseline at Week 85 in patients with ATTRv-PN with treatment-emergent ADA (-81.69%) was similar to that in patients with treatment-unaffected ADA (-80.12%) and ADA-negative patients (-82.04%). These results were consistent with time-matched, ADA status-stratified serum TTR concentration levels over time in patients with ATTRv-PN. Serum TTR reductions among different peak ADA titer level quartiles were similar. Likewise, in patients with ATTRv-PN, ADA positivity and peak titre quartiles had no impact on change from baseline at Week 85 in clinical efficacy endpoints mNIS+7 composite score and Norfolk QoL-DN total score.

The lack of QT risk and/or effect with eplontersen is supported by *in vitro*, preclinical, and clinical studies. Eplontersen cardiac safety assessment suggested that there was no correlation between plasma concentration and placebo-adjusted, change-from-baseline QTcF across a wide dose range (including a supratherapeutic 120 mg dose tested in a Phase I study, which is 2.7-fold higher than the clinical dose of 45 mg evaluated in Phase III studies). Thus, a thorough QTc study has not been conducted.

Oligonucleotides are known for their very limited potential for drug-drug-interactions. No dedicated clinical drug-drug-interaction studies had to be conducted. There was also no necessity for a TQT study. Eplontersen was not investigated in patients with severe stages of organ impairment and use in these patients should be restricted.

Anti-drug antibodies have been identified and seem to have an effect on plasma trough levels. This is however insufficiently addressed in the popPK model. No covariate with significant effects on PK and PD was identified. Overall data support use of a single fixed dose in all patients.

2.6.4. Conclusions on clinical pharmacology

The clinical PK/PD programme seems acceptable and no major issues with the clinical pharmacology data were identified. All outstanding issues have been resolved.

2.6.5. Clinical efficacy

Table 1: Phase II/III and III studies contributing to evaluation of efficacy

Study ID	**ISIS 420915-CS2 (external placebo)**	**ION-682884-CS3 (eplontersen and concurrent inotersen)**
Study phase	Phase II/III	Phase III
Protocol title	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (NEURO-TTR Study)	A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Eplontersen in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (NEURO-TTRansform Study)

Table 1: Phase II/III and III studies contributing to evaluation of efficacy

Study ID	ISIS 420915-CS2 (external placebo)	ION-682884-CS3 (eplontersen and concurrent inotersen)
Primary efficacy objective	Efficacy of inotersen, based on the change from baseline to Week 66 in mNIS+7 composite score and Norfolk QoL-DN total score in patients with ATTRv-PN, as compared with a concurrent placebo group.	To evaluate efficacy of eplontersen after administration for 65 weeks, based on the change from baseline in serum TTR concentration, mNIS+7 composite score, and Norfolk QoL-DN total score, compared to the placebo arm in ISIS 420915-CS2.
Critical design features	Multicenter, double-blind, randomized (2:1), placebo-controlled, stratified.	Multicenter, open-label, randomized, externally controlled, eligible patients randomized 6:1 to eplontersen or inotersen-eplontersen treatment group
Study population	Patients with Stage 1 or Stage 2 ATTRv-PN with documented genetic mutation in the TTR gene and NIS ≥ 10 and ≤ 130 at baseline.	Patients with Stage 1 or Stage 2 ATTRv-PN with documented genetic mutation in the TTR gene and NIS ≥ 10 and ≤ 130 at baseline.
Treatment regimen	Placebo arm: Placebo SC 3 times on alternate days in the first week and then q1w for 64 weeks Inotersen treatment arm: 300 mg inotersen SC 3 times on alternate days in the first week and then q1w for 64 weeks	Eplontersen treatment arm: 45 mg SC eplontersen q4wk through Week 81 Inotersen treatment arm (ie, the concurrent inotersen group): 300 mg SC inotersen sodium q1wk through Week 34, then 45 mg eplontersen SC q4w from Week 37 through Week 81
Number of patients planned	Approximately 135	Approximately 140
Number of patients randomized	173 Placebo: 60 Inotersen:113	168 Eplontersen: 144 Inotersen-eplontersen: 24
Number of patients dosed	172 Placebo: 60 Inotersen: 112	168 Eplontersen: 144 Inotersen-eplontersen: 24
Number of patients who completed study treatment	Inotersen: 87 Placebo: 52	Eplontersen: 130 Inotersen-eplontersen: Inotersen treatment (Week 1 through Week 34): 20 Eplontersen treatment (from Week 37): 19
Study centers (location)	United States, France, Germany, Italy, Portugal, Spain, United Kingdom, Argentina, Brazil, and New Zealand	United States, Canada, Cyprus, France, Germany, Italy, Portugal, Spain, Sweden, Turkey, Argentina, Australia, Brazil, New Zealand, and Taiwan
Study start Study end Study status	15 March 2013 28 March 2017 Completed	11 December 2019 Not applicable Ongoing
Module location	Module 5.3.5.1	Module 5.3.5.1

2.6.5.1. Dose response studies

The selection of the dosing regimen for eplontersen was supported by TTR reduction data from the Phase 1 Study ION-682884-CS1 in healthy subjects. In this study, multiple doses of eplontersen were evaluated in cohorts at doses of 45, 60, or 90 mg q4w. The observed mean serum TTR concentration reductions by Day 99 (after approximately 13 weeks treatment period and 2 weeks after the last dose) were 81.3%, 90.8%, and 93.3%, respectively. Eplontersen was well-tolerated across all dose cohorts. Although not clinically meaningful, a dose-dependent, reversible elevation of ALT levels was noted in the 60 mg and 90 mg dose cohorts. This elevation occurred in a small number of healthy volunteers with no concurrent elevations in bilirubin levels or international normalized ratio (for further details on ION-682884-CS1).

The therapeutic goal of eplontersen is to maximally reduce serum TTR concentrations, while maintaining a favourable benefit-risk profile. A serum TTR concentration reduction (PD effect) of

approximately 80% has been shown to lead to meaningful clinical benefit as demonstrated by mNIS+7 and Norfolk QoL-DN in patients with ATTRv-PN (AMVUTTRA™ 2022, ONPATTRO™ 2018, TEGSEDI™ 2018).

An eplontersen dose of 45 mg q4w was determined by the applicant as the optimal dose to evaluate in the Phase III clinical program based on the achieved reduction in serum TTR concentration and acceptable safety profile in the Phase I study ION-682884-CS1 in healthy volunteers.

A dose lower than 45mg every 4 weeks has not been investigated. However, the 45mg q4w achieved an approximate 80% serum TTR concentration reduction, which is expected to show a clinical effect as well in patients with ATTRv-PN. As it is well known by now, there is a direct pharmacodynamic relationship between TTR reduction and clinical benefit. The higher doses of eplontersen (60mg and 90mg) presented with ALT levels elevation. The justification provided by the Phase 1 Study CS1 is sufficient. The 45mg q4w may not be the optimal dose, but it has been shown as a dose with acceptable efficacy and safety.

2.6.5.2. Main study

Efficacy evaluation for eplontersen is based on data from the ongoing pivotal Phase 3 ION-682884-CS3 study, which is described below.

Table 2: ION-682884-CS3 (NEURO-TTRansform)

Study code	ION-682884-CS3
EU CT number	2019-001698-10
NCT number	NCT04136184
ISRCT number	---
Other identifier(s)	NEURO_TTransform
Location in eCTD	5.3.5.1. Study reports of controlled clinical studies pertinent to the claimed indication

ION-682884-CS3 (NEURO-TTransform) - A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Methods

ION-682884-CS3 is an ongoing open-label, externally controlled, randomized (6:1 eplontersen:concurrent inotersen) phase 3 study to evaluate the efficacy of SC administered eplontersen 45 mg q4w (hereafter referred to as the eplontersen group) versus the external placebo group from ISIS 420915-CS2 (hereafter referred to as the external placebo group) in slowing disease progression in a broad range of patients with Stage 1 or 2 ATTRv-PN disease with documented genetic mutation in the TTR gene.

Patients were randomized 6:1 to eplontersen (eplontersen SC 45 mg q4w) or inotersen-eplontersen (inotersen SC 300 mg q1w until Week 34, then switched to eplontersen SC 45 mg q4w from Week 37). An interim analysis was conducted after all patients in ION-682884-CS3 had the opportunity to complete 35 weeks of treatment. The final placebo-controlled analysis was conducted at Week 66 since there was no external placebo data beyond this timepoint.

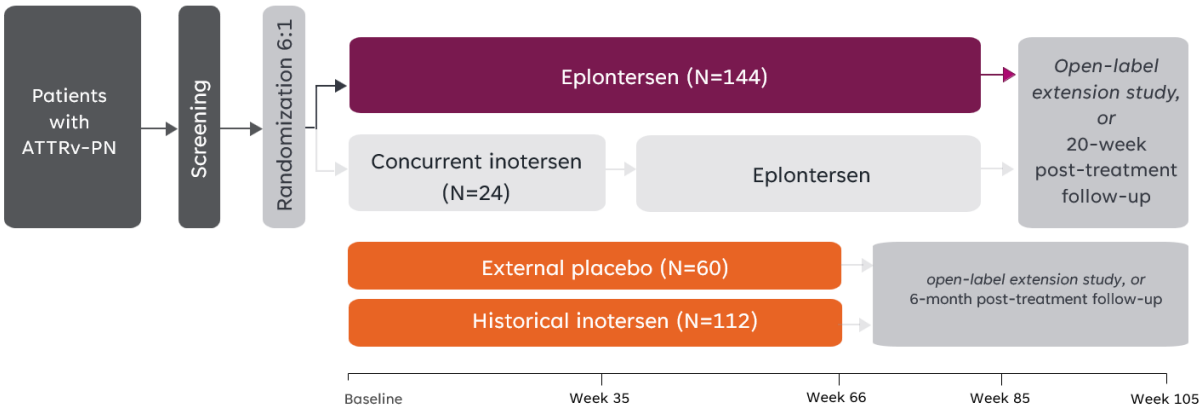
The study consisted of a ≤ 10-week screening period, an 84-week treatment period (last dose administered at Week 81), and a 20 week post-treatment evaluation period or enrolment into the long-term extension study ION-682884-CS13.

Eplontersen is a follow-up product of inotersen and was developed with the use of indirect comparisons to the inotersen development programme. A similar approach was taken in the clinical development program of Amvuttra (vutrisiran) for adult patients with ATTRv (previously known as hATTR) amyloidosis with polyneuropathy, performing the main comparison versus an external placebo group from patisiran study ALN-TTR02-004 (APOLLO), which is a completed, multicenter, multinational, randomized, double-bind, placebo-controlled Phase 3 study in the same indication. An active comparator was used in both clinical programs. Patisiran was included in the Amvuttra pivotal study (HELIOS-A) and inotersen in the eplontersen pivotal study CS3 (NEURO-TTransform).

Treatment groups and comparator

According to the applicant, since ATTRv-PN is a rare disease, active comparator designs for superiority or non-inferiority testing were considered unfeasible due to the large sample size requirements. Given the life-threatening nature of ATTRv-PN and the existence of approved therapies, a concurrent placebo control group would have been unethical. Therefore, an external placebo group from ISIS 420915-CS2 was used instead. Both studies enrolled patients using the same eligibility criteria and the majority of the ION-682884-CS3 study sites were also used in ISIS 420915-CS2. To perform the comparison between studies, the primary analysis was based on propensity score re-weighting to adjust baseline characteristics of the external placebo control to match baseline characteristics of the eplontersen group.

Figure 2: Study ION-682884-CS3 [CS3 study] schema



ATTR-PN, transthyretin-mediated amyloidosis with polyneuropathy; N = number of patients in treatment group.
Source: Figure 1, ION-682884-CS3 CSR, Module 5.3.5.1.

In the pivotal study ION-682884-CS3 [CS3 study] for eplontersen, the applicant has chosen an open label design with a small inotersen group as the active comparator within CS3. This small concurrent inotersen group was descriptively compared to the historical inotersen group from the pivotal study Neuro TTR/ISIS 420915-CS2 [CS2 study] from the inotersen development to ensure comparability between the populations included in the CS3 and CS2 trials. The main comparison was between eplontersen and the external placebo group from this CS2 study.

CS2 was a well-conducted Phase 2/3 multicenter, double-blind, randomized, stratified, placebo-controlled study of inotersen in stage 1 and stage 2 subjects with ATTRv-PN (previously known as hATTR-PN) with a Neuropathy Impairment Score (NIS) ≥10 and ≤130. Approximately 135 subjects were planned to be randomized 2:1 to 300 mg inotersen or placebo. The ratio for eplontersen vs external placebo is also 2:1.

Study Participants

ION-682884-CS3 included 168 randomized patients, all of whom received at least one dose of study drug. Of the 144 patients randomized to eplontersen, 140 (97.2%), 135 (93.8%) and 130 (90.3%) patients completed study treatment through Week 35, Week 66, and Week 85, respectively.

Of the 24 patients randomized to the concurrent inotersen group, 20 (83.3 %) completed the 35 weeks inotersen treatment, all of whom switched to eplontersen treatment from Week 37 and completed treatment through Week 66.

The external placebo group from study ISIS 420915-CS2 included 60 patients all of whom received at least one dose of study treatment. Of the 60 patients, 57 (95.0%) and 52 (86.7%) patients completed 35 and 65 weeks of treatment, respectively.

Inclusion criteria

Key inclusion criteria were the following:

1. Aged 18 to 82 years at the time of IC.
2. ATTRv-PN as defined by meeting all 3 of the following criteria:
    - 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.
    - Symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including NIS $\geq$ 10 and $\leq$ 130
    - Willingness to adhere to vitamin A supplementation per protocol

Exclusion criteria

Key exclusion criteria included:

- Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
- Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
    1. Urine protein/creatinine ratio (UPCR) $\geq$ 1000 mg/g. Renal insufficiency as defined by estimated glomerular filtration rate (eGFRcreat-cys) < 45 mL/min/1.73 m2 at Screening.
    2. Positive test (including trace) for blood on urinalysis.
    3. Alanine aminotransferase/ aspartate aminotransferase (ALT/AST) > 2 × upper limit of normal (ULN)
    4. Bilirubin $\geq$ 1.5 $\times$ ULN (patients with bilirubin $\geq$ 1.5 $\times$ ULN may be allowed on study if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert's disease)
    5. Platelets < 125 × 109/L
    6. HbA1C $\geq$ 7%

7. Abnormal thyroid function tests with clinical significance per Investigator judgement in consultation with the Sponsor Medical Monitor
8. Serum vitamin A / retinol level at Screening < LLN. For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and vitamin A / retinol < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as dry eye, Bitots' spot observed in the ophthalmology exam, that in the opinion of the ophthalmologist is consistent with vitamin A deficiency)

- Uncontrolled hypertension (BP > 160/100 mm Hg)
- Current treatment with any approved drug for hereditary TTR amyloidosis such as Vyndaqel® / Vyndamax™ (tafamidis), Tegsedi™ (inotersen), Onpattro™ (patisiran), off-label use of diflunisal or doxycycline, and tauroursodeoxycholic acid (TUDCA). If previously treated with Vyndaqel® / Vyndamax™, diflunisal or doxycycline, and TUDCA, must have discontinued treatment for 2 weeks prior to Study Day 1
- Previous treatment with Tegsedi™ (inotersen) or Onpattro™ (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA)
- Treatment with another investigational drug, biological agent, or device within 3 months of screening, or 5 half-lives of study agent, whichever is longer History of bleeding, diathesis or coagulopathy
- Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, diabetic neuropathy)
- New York Heart Association (NYHA) functional classification of ≥ 3
- Anticipated survival less than 2 years

Treatments

Eplontersen was supplied as 150 mg/mL solution in a 2-mL glass vial containing 1.05-mL solution and was to be administered SC as a 45-mg (as eplontersen free acid) dose in a single 0.3-mL injection once every 4 weeks from Week 1 through Week 81. Inotersen was to be administered SC as a 300-mg (as inotersen sodium salt) dose in a single 1.5-mL pre-filled syringe injection once weekly from Week 1 through Week 34, after which subjects switched to eplontersen at Week 37.

In addition to Study Drug, all subjects were required to take daily oral supplemental doses of the recommended dietary allowance of vitamin A (approximately 3000 IU of vitamin A or the closest approximate dose as available in the region in which the subject resides). Commercially available vitamin A as a single supplement or as part of a multivitamin are to be taken by the subject, in accordance with local regulatory requirements and availability.

Concomitant and rescue therapies

Any medications deemed necessary by the Investigator were allowed except those listed as disallowed concomitant therapy. Concomitant therapy with the following medications were not allowed: Vyndaqel/ Vyndamax (tafamidis), Tegsedi (inotersen), Onpattro (patisiran), or off-label use of diflunisal. Short term use (< 15 days) of doxycycline to treat an infection is allowed.

All patients were required to take daily oral supplemental doses of the recommended daily allowance of vitamin A during the treatment and post-treatment evaluation periods.

Objectives

The primary objective was to evaluate the efficacy of eplontersen, compared with external placebo, with regards to serum TTR concentration, mNIS+7 composite score, and Norfolk QoL-DN total score over 65 weeks of treatment. The primary objective was evaluated at 2 timepoints: in an interim analysis when all patients reached at least Week 35 and in the Week 66 final analysis performed after all patients reached at least Week 66. In the Week 35 interim analysis, the 2 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 35 and change in mNIS+7composite score from baseline to Week 35) and the key secondary endpoint (change in Norfolk QoL-DN from baseline to Week 35) were analysed. In the Week 66 final analysis, the 3 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 65, change in mNIS+7 composite score from baseline to Week 66, and change in Norfolk QoL-DN total score from baseline to Week 66) were analysed.

Estimand

No estimand was specified for the primary efficacy objectives/endpoints and relevant intercurrent events were not discussed; neither at week 35 nor 66.

Secondary and exploratory objectives

A number of secondary and exploratory objectives have been set for this study.

Secondary objectives:

To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in:

- Neuropathy Symptom and Change (NCS) score
- Physical Component Summary (PCS) score of 36-Item Short Form Survey (SF-36)
- Polyneuropathy disability (PND) score
- Modified body mass index (mBMI)

Additional/Exploratory Objectives

To evaluate the efficacy of ION-682884 in mNIS+7 at Week 85, compared to Baseline.

To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm in the ALN-TTR02-004 trial (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) in:

- Change from Baseline in Norfolk QOL-DN at Week 85
- Change from Baseline in 10MWT
- Change from Baseline in Rasch-built Overall Disability Score (R-ODS)

The applicant has clarified that for some exploratory endpoints and/or timepoints (Norfolk QoL-DN at Week 85, 10-Meter Walk Test, Rasch-built Overall Disability Score, Composite Autonomic Symptom Score-31 and 5-level EQ-5D version) that were not evaluated in ISIS 420915-CS2, external placebo data from ALN TTR02 004 (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) were used for comparisons between eplontersen and placebo.

To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, in:

- Change from Baseline in the SF-36
- Frequency of all-cause hospitalizations (in all patients and in patients with cardiac involvement)

- Change from Baseline in transthoracic echocardiogram (ECHO) parameters including left ventricular (LV) mass, LV wall thickness, intraventricular septum (IVS) thickness, global longitudinal strain (GLS), in patients with cardiac involvement
- Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with cardiac involvement

To evaluate the plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, and to evaluate plasma pharmacokinetic (PK) parameters in a subset of patients.

Safety objective

To evaluate safety and tolerability of ION-682884 in ATTRv-PN (previously known as hATTR-PN) patients, in the following measures: change from Baseline in platelet count and renal function, adverse events, vital signs and weight, physical examination findings, clinical laboratory tests, electrocardiogram (ECG) parameters, use of concomitant medication, ophthalmology examination, thyroid panel tests, inflammatory panel tests, coagulation tests, complement and immunogenicity tests.

If the primary objective was met all secondary objectives were to be evaluated in the Week 66 final analysis to provide additional support for the treatment effect of eplontersen on halting progression of symptom severity (NSC) and improving physical symptoms (SF-36 PCS), nutritional status (mBMI), and PN disability (PND).

Exploratory endpoints were evaluated from Week 37 up to Week 85.

Outcomes/endpoints

Efficacy assessments

The final analysis co-primary efficacy endpoints were the percent change from baseline in serum TTR concentration at Week 66, the change from baseline in mNIS+7 at Week 66, and the change from baseline in Norfolk QOL-DN at Week 66.

The final analysis secondary endpoints were the change from baseline in NSC at Weeks 35 and 66, the change from baseline in the PCS score of SF-36 at Week 65, the change from baseline in PND score at Week 65, and the change from baseline in mBMI at Week 65.

The interim analysis co-primary efficacy endpoints at Week 35 were the percent change from baseline in serum TTR concentration at Week 35, and the change from baseline in mNIS+7 at Week 35.

The interim analysis key secondary efficacy endpoint at Week 35 was the change from baseline in Norfolk QOL-DN at Week 35.

Additional/exploratory endpoints

Exploratory endpoints included the change from baseline in mNIS+7 at Week 85, change from baseline in Norfolk QOL-DN at Week 85, change from baseline in 10MWT at Week 81, change from baseline in R-ODS at Week 81, change from baseline in the SF-36 components at Weeks 35, frequency of all cause hospitalizations in all patients and in patients with cardiac involvement by Week 66, change from baseline in transthoracic ECHO parameters, including LV mass, LV wall thickness, IVS thickness, and GLS, in patients with cardiac involvement at Week 65, and change from baseline in NT-proBNP in patients with cardiac involvement at Week 65.

Safety Assessments

Safety endpoints included the change from baseline in platelet count during the treatment period, the change from baseline in renal function during the treatment period, adverse events, vital signs and weight, physical examination, clinical laboratory tests, electrocardiogram (ECG), use of concomitant medication, ophthalmology examination, thyroid panel, inflammatory panel, coagulation, complement, and immunogenicity.

Pharmacokinetic Assessments

PL assessments were conducted on the treated subjects. Plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, area under the curve (AUC), C_{max}, and t_{max} in a subset of patients, and $t_{½\lambda z}$ for patients who did not roll over to the open-label extension (OLE) study.

Sample size

The sample size for this study was estimated based on the data from the NEURO-TTR clinical trial.

With 140 patients (120 of them dosed with ION-682884) and assuming a 10% dropout rate, there would be 108 evaluable patients treated with ION-682884. In the NEURO-TTR trial, there are 52 evaluable placebo patients.

It is observed that the NEURO-TTR placebo group had a 23.8 point increase in the mNIS+7 score from Baseline to Week 66. It is estimated that the ION-682884 group will have a 4.2 point increase in mNIS+7. The SD of the change from Baseline is estimated to be 20. There would be at least 90% power to detect a 19.6 point difference in the change from Baseline of the mNIS+7 score between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

For the Norfolk QOL-DN, it is observed that the NEURO-TTR placebo group had 10.7 points change from Baseline to Week 66. It is estimated that the ION-682884-treated group will have a 0 point change from Baseline. The SD is estimated to be 20. There would be at least 80% power to detect a 10.7 points difference in the change from Baseline of the Norfolk QOL-DN between ION- 682884 treated patients and the NEURO-TTR placebo patients, with a 2-sided alpha level of 0.025.

For the TTR percent change from Baseline, it is observed that the NEURO-TTR placebo group had 9.7% reduction from Baseline to Week 65. It is estimated that the ION-682884-treated group will have at least 80% reduction from Baseline. The SD is estimated to be 13%. There would be at least 95% power to detect a 70.3% difference in the percent change from Baseline between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

Randomisation and blinding (masking)

A total of 168 patients were randomized 6:1 to receive eplontersen (144) or inotersen (24) using an interactive voice/web response system and all received treatment.

This is an open-label study; Investigators and patients were unblinded to Study Drug identity. However, the Sponsor team responsible for oversight of the study was insulated from knowledge of the mNIS+7 and Norfolk QOL-DN endpoint results, the mNIS+7 assessors at the study sites were blinded to the patient's general study procedures and other study data (e.g., any AEs), and the mNIS+7 central reader (the Peripheral Nerve Research Laboratory) was blinded to treatment allocation.

Statistical methods

Planned analyses

Analysis sets

The population definitions that will be used in this study are provided below and are the same or historical control patients from NEURO-TTR trial.

- **Full analysis Set (FAS):** All randomized patients who received at least 1 injection of ION-682884 or inotersen and who have a Baseline and at least 1 post-Baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score.
- **Per Protocol Set (PPS):** A subset of FAS who received at least 80% of the prescribed doses of ION-682884 or inotersen and that have no significant protocol deviations that would be expected to affect efficacy assessments.
- **Safety Set (SS):** All patients who are randomized and receive at least 1 dose of ION-682884 or inotersen.
- **Pharmacokinetic Set (PK Set):** All patients who are randomized and receive at least 1 dose of ION-682884 or inotersen and have at least 1 evaluable PK sample.

The FAS will be the primary analysis population. Furthermore, for primary analyses only on-treatment data (i.e. data collected up until 52 after the last dose of medication) will be included.

Primary analysis at interim analysis

The percent change in serum TTR from Baseline to Week 35 will be analysed using the MMRM model adjusted by propensity score weights based on on-treatment data. The MMRM model will also include the effects of treatment (ION-682884 or NEURO-TTR placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score will be calculated for each NEURO-TTR placebo or ION-682884 patient using a logistic regression model with covariates including disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment (Yes/No).

In this model, missing data are not explicitly imputed. Instead, all available post-baseline assessments up to the Week 35 endpoint during the treatment period and via modelling of the within subject correlation structure, the endpoint treatment differences are derived assuming data to be missing at random.

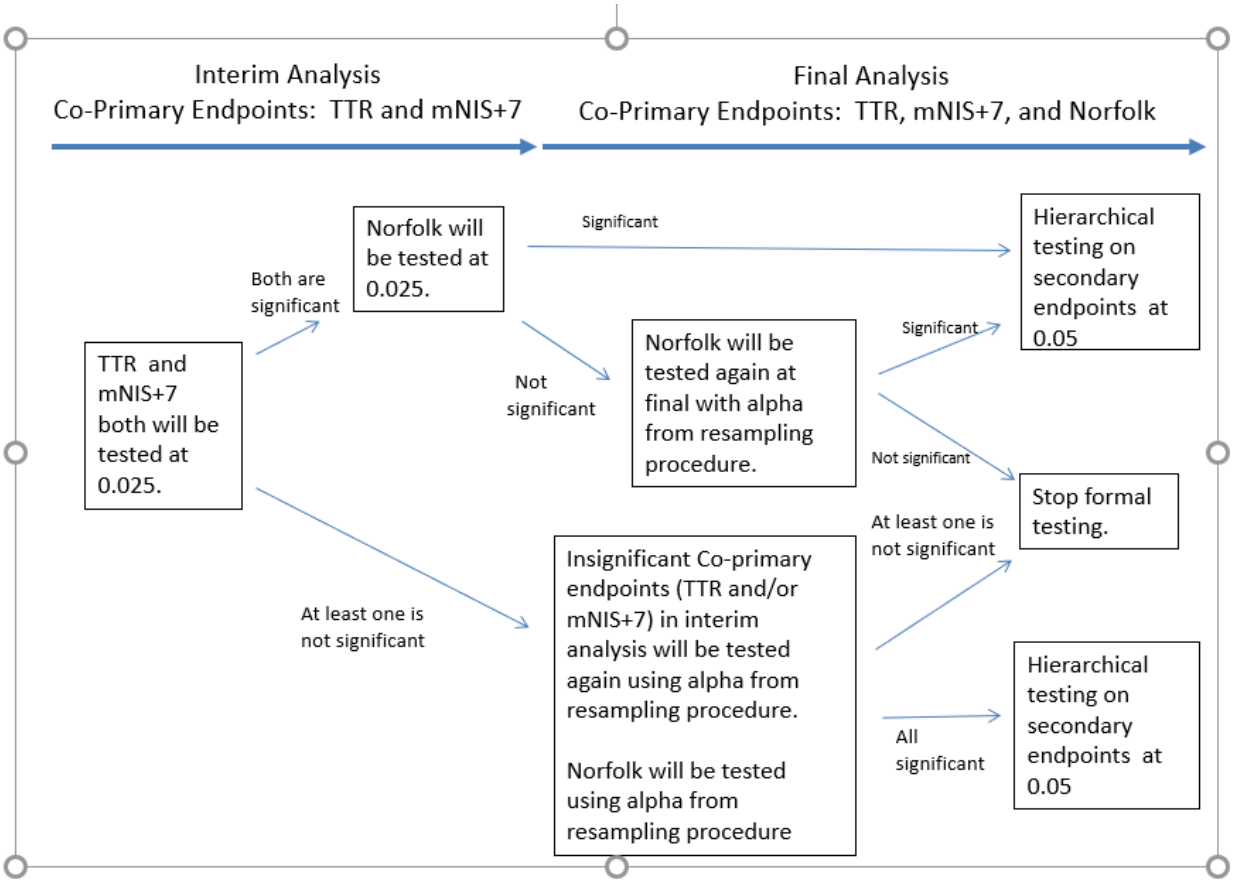
The mNIS+7as well as Norfolk are scheduled to be assessed at Week 35, Week 66, and Week 85. Because only 1 post-Baseline assessment (Week 35) is available at Week 35 Interim Analysis, the treatment comparison at Week 35 will be based on the analysis of covariance (ANCOVA) model adjusted by propensity score. The Analysis of covariance (ANCOVA) model will also include the effects of treatment (ION-682884 or NEURO-TTR placebo), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment (Yes/No), and the baseline value of the endpoint. Patients with a missing mNIS+7 at Week 35 will have value multiply imputed using an imputation model that contains the following variables: disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment (Yes/No), and the Baseline value of the endpoint and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999).

Primary analysis at week 66 final analysis

For percent change from Baseline of TTR at Week 65, change from Baseline of mNIS+7 at Week 66, and change from Baseline of Norfolk QOL-DN at Week 66, MMRM model adjusted by propensity score weights will be used. Similar to interim analysis for TTR, the MMRM model will include the effects of treatment (ION-682884 or NEURO-TTR placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score will be calculated using the same logistic regression model as described above in the primary analysis at week 35.

Multiplicity control

The following multiplicity control strategy was applied:



If both co-primary endpoints of interim analysis (TTR and mNIS+7, see above) are significant at alpha level of 0.025, then the secondary endpoint (Norfolk) below will be tested at the interim analysis at alpha level of 0.025.

In the Week 66 Final Analysis, for those statistically significant endpoints at Week 35 interim analysis, their corresponding tests at the Week 66 final analysis will not be conducted. The insignificant endpoint(s) (serum TTR and/or mNIS+7) and the co-primary endpoint Norfolk will be tested at the final analysis. The alpha level of the final analysis for each endpoint will be determined by the resampling procedure (Westfall and Young 1993).

Sensitivity analyses

In addition to the primary efficacy analysis performed in either interim analysis or final analysis, the following sensitivity analyses will be conducted on the FAS and for each endpoint (TTR, mNIS+7, Norfolk) performed in the Week 35 interim analysis and Week 66 final analyses except where noted:

- **Sensitivity analysis 1**: non-parametric stratified Wilcoxon rank sum test adjusted by stratified propensity score weights
- **Sensitivity analyses 2-4** investigating the impact of alternative missing data handling and including data even if collected more than 52 days after last dose (On-Study analysis; based on safety set):
    - **Sensitivity analysis 2:** Multiple imputation assuming Missing at Random (MAR)
    - **Sensitivity analysis 3:** Multiple imputation assuming Copy Increments from Reference (CIR)
    - **Sensitivity analysis 4:** Multiple Imputation assuming Jump to Reference (J2R)
- **Sensitivity analysis 5:** primary analysis will be repeated on the per-protocol population
- **Sensitivity analysis 6:** responder analysis
- **Sensitivity analysis 7:** primary analysis repeated with propensity scores estimated taking three additional covariates into account (gender, modified BMI and region)
- **Sensitivity analysis 8:** The same ANCOVA in the primary analysis will be performed based on observed data for mNIS+7 and NORFOLK for Week 35 Interim analysis.

Analysis of secondary endpoints

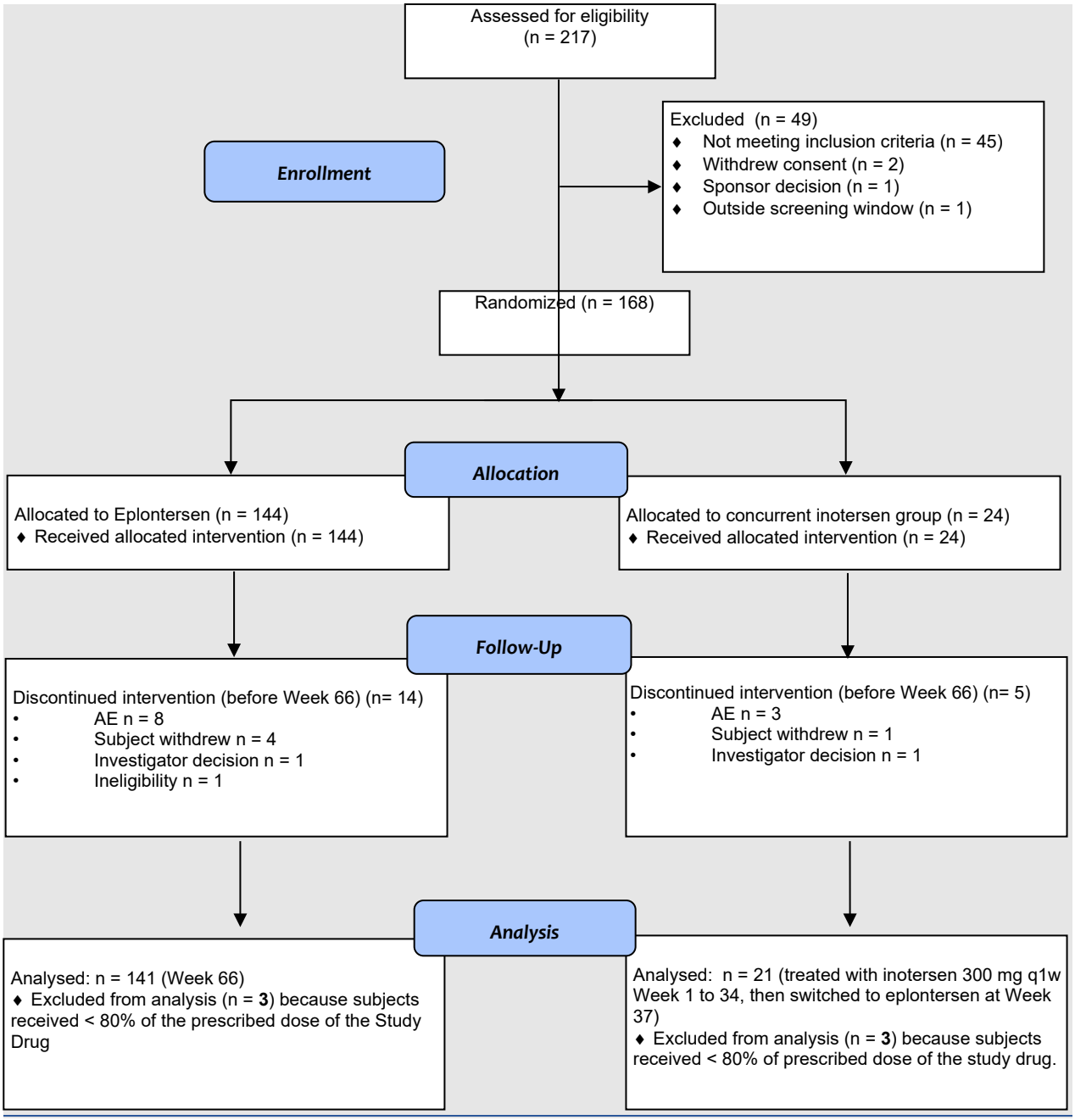
For the secondary endpoints, treatment group differences were evaluated using the same method as the primary efficacy analysis (MMRM described above). These analyses were conducted on both the FAS and the PPS populations. No sensitivity analyses were conducted.

Results

Participant flow

A total of 168 patients were randomized, all of whom received at least one dose of study drug.

Figure 3: Participant flow



Recruitment

First subject enrolled: 11-Dec-2019

Last subject, last visit for the current analysis: 20-Mar-2023 (data cut-off for CSR 7-Apr-2023).

Conduct of the study

No changes were made to the planned analyses in the Study Protocol.

Protocol deviations

The majority of patients had at least one (1) protocol deviation during the study (please see the table below). The incidence of protocol deviations was similar in the 2 treatment groups in the ION-682884-CS3 study.

According to the applicant, none of the major protocol deviations were anticipated to affect the efficacy or safety endpoint analyses or the conclusions of the study. There was one (1) protocol deviation in the eplontersen group that was due to eligibility criteria not being met at Screening. This patient was participating in another trial with eplontersen and did not inform site personnel at Screening.

Table 3: Summary of patients with protocol deviations (randomized set)

	External Placebo (N=60)	**Historical Inotersen (N=113)**	**Concurrent Inotersen (N=24)**	**Eplontersen (N=144)**
Any Protocol Deviations, n (%)	60 (100%)	111 (98.2%)	23 (95.8%)	137 (**95.1%)**
Any Major Protocol Deviation, n (%)	49 (81.7%)	94 (83.2%)	21 (87.5%)	120 (**83.3%**)
Study Procedure	40 (66.7%)	76 (67.3%)	19 (79.2%)	108 (75.0%)
Drug Error	21 (35.0%)	38 (33.6%)	14 (58.3%)	61 (**42.4%**)
Improper Informed Consent Procedures	4 (6.7%)	9 (8.0%)	6 (25.0%)	33 (22.9%)
Visit Out of Window	8 (13.3%)	14 (12.4%)	2 (8.3%)	9 (6.3%)
Eligibility Criteria	1 (1.7%)	4 (3.5%)	0	1 (0.7%)
Missed Visit	0	9 (8.0%)	2 (8.3%)	1 (0.7%)
Restricted Concomitant Meds	3 (5.0%)	0	0	1 (0.7%)
Other	11 (18.3%)	27 (23.9%)	0	0
Any Minor Protocol Deviation, n (%)	60 (100%)	108 (95.6%)	21 (87.5%)	125 (86.8%)

The applicant provided additional information and details for the protocol deviations under the term "Drug Error" including the number of missed doses and over/underdosing, the reasons for drug errors and single or multiple events in individual patients. Only a minority of major protocol deviations (13/122, 10.7%) involved missed doses. The majority of the major protocol deviations were due to two reasons:

A) failure to withhold the investigational product, because of the absence of availability of evaluable platelet count or other laboratory parameter and

B) Investigational Product (IP) administration occurring outside the visit window.

Baseline data

The mean age was lower in ION-682884-CS3 than in ISIS 420915-CS2, which is possibly due to early diagnosis becoming more common over time. The percentage of patients < 65 years was also higher in ION-682884-CS3 than in ISIS 420915-CS2. In both studies, patients were predominantly male, White and Not Hispanic or Latino. The percentage of Asian patients was higher in ION-682884-CS3 than in ISIS 420915-CS2, reflecting the fact that only ION-682884-CS3 included sites in Asia (Taiwan). Most

patients in ION-682884-CS3 were enrolled at sites in South America/Australasia/Asia and Europe, whereas most patients in ISIS 420915-CS2 were enrolled at sites in North America and Europe.

At baseline, most patients in both studies had stage 1 disease, an average time since diagnosis of between 3 and 4 years, and more than 50% had received previous treatment for ATTRv-PN. Around one third of patients also had a diagnosis of ATTRv-CM at baseline.

When compared with ISIS 420915-CS2, ION-682884-CS3 had a higher percentage of patients with previous treatment for ATTRv-PN, a lower percentage with stage 2 disease, and a lower percentage with PND scores ≥ IIIa. These differences are likely to reflect a move towards earlier diagnosis and improved availability of treatments in recent years.

A total of 20 different TTR mutations were observed across the 2 studies. The most common TTR mutation was Val30Met, and its prevalence was similar between treatment groups across both studies. However, there was a larger percentage of patients with "Other TTR genotypes" in ION-682884-CS3 compared with ISIS 420915-CS2. The difference is due to a more frequent presence of patients with the Ala97Ser mutation in ION-682884-CS3 (in this study this mutation was only observed in patients from Taiwan) (see Listing 10a, ION-682884-CS3 CSR).

In the eplontersen group, there was a lower percentage of patients with a ATTRv-CM diagnosis than in the other treatment groups. Mean NT-proBNP levels were also numerically lower in ION-682884-CS3 than in ISIS 420915-CS2.

Despite that, the details of the Baseline data are presented in Annex I of this document, some of important baseline characteristics are presented in the table below.

Table 4: Baseline disease characteristics (full analysis set)

Characteristic	ISIS 420915-CS2		ION-682884-CS3	
	Placebo (N = 59)	**Inotersen 300 mg q1w (N = 106)**	**Inotersen-eplontersen[a] (N = 21)**	**Eplontersen 45 mg q4w (N = 141)**
Disease stage, n (%)				
n	59 (100%)	106 (100%)	21 (100%)	141 (100%)
Stage 1	42 (71.2%)	71 (67.0%)	16 (76.2%)	113 (80.1%)
Stage 2	17 (**28.8%**)	35 (33.0%)	5 (**23.8%**)	28 (**19.9%**)
Previous treatment (Vyndaqel or Diflunisal), n (%)				
n	59 (100%)	106 (100%)	21 (100%)	141 (100%)
Yes	35 (59.3%)	62 (58.5%)	12 (57.1%)	99 (70.2%)
No	24 (40.7%)	44 (41.5%)	9 (42.9%)	42 (29.8%)
Serum TTR (g/L)				
n	59	106	21	141
Mean (SD)	**0.15** (0.037)	0.15 (0.052)	**0.21** (0.072)	**0.23** (0.075)
Median (Min, Max)	0.16 (0.1, 0.2)	0.15 (0.1, 0.3)	0.20 (0.1, 0.3)	0.22 (0.1, 0.4)
mNIS+7 composite scores				
n	59	106	21	141
Mean (SD)	**74.12** (39.029)	79.35 (37.524)	**65.41** (35.855)	**79.81** (42.250)
Median (Min, Max)	74.66 (13.2, 156.7)	76.83 (11.2, 174.7)	55.86 (17.0, 130.4)	76.83 (7.9, 205.6)
NIS composite scores				

Characteristic	ISIS 420915-CS2		ION-682884-CS3	
	Placebo (N = 59)	Inotersen 300 mg q1w (N = 106)	Inotersen-eplontersen[a] (N = 21)	Eplontersen 45 mg q4w (N = 141)
n	59	106	21	141
Mean (SD)	**43.40** (24.659)	46.59 (25.714)	**38.20** (25.894)	**45.31** (28.942)
Median (Min, Max)	38.50 (3.5, 88.4)	44.50 (9.5, 114.8)	26.50 (11.5, 86.5)	41.25 (4.0, 127.8)
Modified +7 component score				
n	59	106	21	141
Mean (SD)	**30.73** (18.116)	32.76 (16.597)	**27.22** (15.665)	**34.50** (19.706)
Median (Min, Max)	31.35 (2.7, 85.6)	31.44 (-1.8, 77.2)	32.07 (-0.2, 59.6)	31.13 (-4.1, 88.4)
Norfolk QoL-DN total scores				
n	58	105	21	134
Mean (SD)	**48.60** (26.974)	48.57 (28.184)	**37.97** (21.512)	**43.33** (26.206)
Median (Min, Max)	47.56 (-1.0, 111.0)	47.00 (-2.0, 127.0)	43.00 (1.0, 74.0)	40.00 (1.0, 106.0)
NT-proBNP (pmol/L)				
n	59	102	21	140
Mean (SD)	**82.2** (160.51)	118.8 (260.05)	**34.1** (44.21)	**53.8** (123.75)
Median (Min, Max)	30.0 (2, 872)	41.5 (1, 2252)	16.0 (2, 157)	13.5 (1, 821)
PND score				
n	59 (100%)	106 (100%)	21 (100%)	140 (99.3%)
I	23 (39.0%)	31 (29.2%)	12 (57.1%)	55 (39.3%)
II	19 (32.2%)	40 (37.7%)	6 (28.6%)	60 (42.9%)
IIIa	14 (**23.7%**)	29 (27.4%)	2 (**9.5%**)	15 (**10.7%**)
IIIb	3 (**5.1%**)	6 (5.7%)	1 (**4.8%**)	10 (**7.1%**)
IV	0	0	0	0
NYHA classification, n (%)				
n	59 (100%)	106 (100%)	21 (100%)	141 (100%)
I	40 (67.8%)	68 (64.2%)	15 (71.4%)	102 (72.3%)
II	19 (**32.2%**)	38 (35.8%)	6 (**28.6%**)	39 (**27.7%**)
FAC (ATTRv-CM) clinical diagnosis from CRF, n (%)				
n	59 (100%)	106 (100%)	21 (100%)	141 (100%)
Yes	22 (**37.3%**)	43 (40.6%)	7 (**33.3%**)	38 (**27.0%**)
No	37 (62.7%)	63 (59.4%)	14 (66.7%)	103 (73.0%)

[a]: Treated with inotersen 300 mg q1w Week 1 to 34, then switched to eplontersen 45 mg q4w at Week 37.
Denominator for 'n' is the number of subjects in the analysis set. Denominator for subcategory of each parameter is 'n'.
[b]: A patient could have ATTRv-CM diagnosis based on more than one criterion.
Only years and months were collected for Disease from ATTRv-PN Diagnosis and onset of ATTRv-PN symptoms. Duration was calculated relative to the informed consent date. Only years and months were collected for FAC clinical diagnosis and onset of FAC symptoms. The duration from FAC clinical diagnosis and onset of FAC symptoms was calculated relative to the informed consent date.
PND score is defined as I = sensory disturbances in limbs without motor impairment; II = difficulty walking without the need of a walking aid; IIIa = 1 stick or 1 crutch required for walking; IIIb = 2sticks or 2 crutches needed; IV = wheelchair required, or patient confined to bed.
Val30Met includes the following genotypes: Val30 Met, V50M, V50M MUTATION, VAL50MET, P.VAL50MET. V30 was also written as V50 due to alternative nomenclature used by the testing laboratory
ATTRv-CM diagnosis was based on CRF provided information.

ATTRv-CM = hereditary transthyretin-mediated amyloidosis with cardiomyopathy (used to be called FAC); CM = cardiomyopathy; CRF = case report form; Echo = echocardiogram; FAC = familial amyloid cardiomyopathy; Max = maximum; Min= minimum; mNIS+7 = modified Neuropathy Impairment Score +7; N = number of participants in treatment group; n = number of participants with characteristic; NIS = Neuropathy Impairment Score; Norfolk QoL-DN =Norfolk quality of life-diabetic neuropathy; NSC = neuropathy symptom and change; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PN = polyneuropathy; PND = polyneuropathy disability; q1w = once weekly; q4w = every 4 weeks; SD = standard deviation; SF-36 = 36-item short form survey (version 2); TTR = transthyretin.
Source: ION-682844-CS3 Clinical Study Report

Efforts were made to minimise potential bias and differences in the populations evaluated including using propensity score weight adjusted models, matching inclusion/exclusion criteria, and use of same sites for the open label pivotal study. The applicant justified this approach by stating that the expected large magnitude of effect with the use of eplontersen would overcome any potential bias inherent to the study design.

Numbers analysed

A total of 168 patients were randomized, all of whom received at least one dose of study drug. Of the 144 patients randomized to eplontersen, 140 (97.2%), 135 (93.8%) and 130 (90.3%) patients completed study treatment through Week 35, Week 66, and Week 85, respectively. Fourteen (9.7%) patients in the eplontersen group discontinued treatment during the study period, of whom 9 (6.2%) had discontinued by Week 66. The most common reasons for discontinuation were AEs/SAEs and voluntary withdrawal.

Of the 24 patients randomized to the concurrent inotersen group, 20 (83.3 %) completed the 35 weeks inotersen treatment, all of whom switched to eplontersen treatment from Week 37 and completed treatment through Week 66. In total 19 (79.2%) patients completed the full 84-week treatment period. The most common reason for discontinuation was AEs/SAEs.

In the ISIS 420915-CS2 study, which provided the external placebo group and a historical inotersen group used for safety comparisons, a total of 173 patients (60 patients in the external placebo group and 113 patients in the inotersen group) were randomized. Overall, 86.7% of patients in the external placebo group and 77.0% of patients in the historical inotersen group completed the study. The proportion of patients who discontinued study drug early (before completing the ISIS 420915-CS2 study or before Study Day 456 in the ION-682884-CS3) was higher in the external placebo (8 patients; 13.3%), historical inotersen (26 patients; 23.0%), and concurrent inotersen (4 patients; 16.7%) groups compared to the eplontersen group (8 patients; 5.6%), primarily due to AEs or SAEs in the historical inotersen and concurrent inotersen groups and voluntary withdrawal and disease progression in the external placebo group.

Overall, 130 (90.3%) patients in the eplontersen group and 19 (79.2%) patients in the inotersen-eplontersen switch group completed the ION-682884-CS3 study treatment period through Week 85.

The following analysis populations were evaluated and used for presentation and analysis of the data.

Table 5: Number of participants by analysis set (randomized set)

Analysis Set	ISIS 420915-CS2		ION-682884-CS3	
	Placebo (N = 60)	Inotersen 300 mg q1w (N = 113)	Inotersen-eplontersen a (N = 24)	Eplontersen 45 mg q4w (N = 144)
Safety set	60 (100%)	112 (99.1%)	24 (100%)	144 (100%)
Full analysis set (Week 35 interim analysis)	59 (98.3%)	106 (93.8%)	20 (83.3%)	140 (97.2%)
Full analysis set (Week 66/85 analyses)	59 (98.3%)	106 (93.8%)	21 (87.5%)	141 (97.9%)
Per-protocol analysis set at Week 35 (interim analysis)	52 (86.7%)	84 (74.3%)	15 (62.5%)	138 (95.8%)
Per-protocol analysis set (Week 66/85 analyses)	52 (86.7%)	84 (74.3%)	18 (75.0%)	137 (95.1%)
Pharmacokinetic set	NA	NA	24 (100%)	144 (100%)

[a] Treated with inotersen 300 mg q1w Week 1 to 34, then switched to eplontersen 45 mg q4w at Week 37.
Full Analysis Set is defined as all randomized patients received at least 1 injection of Eplontersen or inotersen and had a Baseline and at least 1 post-baseline efficacy assessment for mNIS+7 composite score or Norfolk QoL-DN questionnaire total score.
For ISIS 420915-CS2, the FAS includes all randomized patients who received at least 1 injection of study drug with a Baseline and at least 1 post-Baseline efficacy assessment for mNIS+7composite score or Norfolk QoL-DN questionnaire total score.
The FAS at Week 66/85 contains one additional patient in the eplontersen group compared to the Week 35 interim analysis FAS. This is because of the definition of the FAS, which requires at least one post-baseline mNIS+7 or Norfolk QoL-DN assessment to be available at the time of the data-cut.
Per Protocol Set is defined as those patients from the FAS who received at least 80% of prescribed injections of eplontersen or inotersen with no significant protocol deviations expected to affect efficacy assessments.
Safety Set is defined as all randomized patients who received at least 1 dose of eplontersen or inotersen. For ISIS 420915-CS2 trial, the Safety Set includes all randomized patients who received at least 1 injection of study drug.
Pharmacokinetic Set is defined as all patients who are randomized and receive at least 1 dose of eplontersen or inotersen with at least 1 evaluable PK sample.
FAS = full analysis set; mNIS+7 = modified Neuropathy Impairment Score +7; NA = not applicable; Norfolk QoL-DN = Norfolk quality of life-diabetic neuropathy; PK = pharmacokinetic; q1w = once weekly; q4w = every 4 weeks.
Source: ION-682884-CS3 interim Clinical Study Report,ION-682884-CS3 Clinical Study Report

Outcomes and estimation

The primary objective was to evaluate the efficacy of eplontersen, compared with external placebo, with regards to serum TTR concentration, mNIS+7 composite score, and Norfolk QoL-DN total score over 65 weeks of treatment. None of the co-primary endpoints in the Week 66 final analysis were formally tested. The applicant justified this approach by stating that all 3 endpoints were statistically significant for change from baseline at Week 35 (interim analysis). The Week 66 final analysis confirmed the Week 35 analysis showing sustained treatment benefits superior to placebo (Table 6 below). At Week 65, the serum TTR concentration reduction was sustained and the results at Week 66 for the mNIS+7 and Norfolk scores were all consistent with the Week 35 results. Eplontersen continued to demonstrate treatment benefits compared to baseline in patients with ATTRv-PN through Week 85.

Table 6: Serum TTR concentration, mNIS+7 composite score, and Norfolk QoL-DN total score at week 35 interim analysis and week 66 final analysis (full analysis set)

	Baseline, mean (SD)		LSM Percent change from baseline, (SE) [95% CI]		Treatment difference (95 % CI)	
Analysis/Endpoint	ISIS 420915-CS2 External Placebo	ION-682844-CS3 Eplontersen 45 mg q4w	ISIS 420915-CS2 External Placebo	ION-682844-CS3 Eplontersen 45 mg q4w	Eplontersen 45 mg q4w minus External Placebo	p-value [a]
Week 35						
Full analysis set	N = 59	N = 140	N = 59	N = 140	NA	NA
Serum TTR, g/L [b] (percent change from baseline)	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 [cd] (change from baseline)	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 [c,d] (change from baseline)	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	NA	NA
Serum TTR, g/L [b] (percent change from baseline)	0.15 (0.038)	0.23 (0.075)	-11.2% (1.91) [-15.06, -7.41]	-81.7% (1.61) [-84.82, -78.48]	**-70.4%** (-75.17, -65.66)	< 0.0001
mNIS+7 composite score [b] (change from baseline)	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 [b] (change from baseline)	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] 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.

[b] 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.

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

[d] Patients with a missing mNIS+7 composite score or Norfolk QoL-DN total score at Week 35 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.

Eplontersen dosing regimen was 45 mg q4w. Analysis of serum TTR based on data collected up to 28 days after last dose of study drug. Analysis of mNIS+7 composite score and Norfolk QoL-DN total score based on data collected up to 52 days after last dose of study drug.

The interim analysis was conducted using the full analysis set with observations up to Week 35 from the interim analysis (DCO 18 April 2022). The Week 66 final analysis was conducted using the full analysis set with observations from up to Week 66 (DCO 07 April 2023). Full analysis set differs between Week 35 interim analysis and Week 66 final analysis due to the requirement to have at least one post-baseline mNIS+ 7 composite score or Norfolk QoL-DN total score assessment.

Source: ION-682884-CS3 interim Clinical Study Report, ION-682884-CS3 Clinical Study Report

In order to be able to contextualise the results, a comparative table of the effects of eplontersen and other approved medications has been constructed by the assessment team with publicly available data (see below).

Table 7: Comparative table

Analysis/endpoint	**Tegsedi - Inotersen 300 mg (N=113) minus Placebo (N=60)**	**Onpattro-Patisiran 0.3 mg/kg patisiran-LNP q3w (N=148) Minus placebo (N=77)**	**Amvuttra-Vutrisiran (N=122) in HELIOS-A minus External Placebo (N=77) APOLLO**	**Treatment difference (95% CI) Eplontersen 45 mg q4w minus External Placebo**
Administration	Subcutaneous injection (SC) Q1W (once every week)	Intravenous (IV) infusion Q3W (once every 3 weeks)	Subcutaneous (SC) injection Q3M (once every 3 months)	Subcutaneous (SC) injection Q4W (once every 4 weeks)#
Full analysis set				
Week 35 (Month 9)				
Serum TTR, g/L [b] (percent change from baseline)	**Diff: -64.35%** 95% CI: -68.70, -59.99 P-value < 0.001 Placebo (N=57) **-9.64%** (16.787) Inotersen (N=93) **-74.03** (13.045)		-78-82%	**-66.64** (95% CI: -71.61, -61.53)
mNIS+7 composite score [c, d] (change from baseline)	**-8.69** (-13.49, -3.90) P=0.0005		**-17.00** (2.44) (-21.78, - 12.22) P=3.542E-12	**-8.8** (95% CI: **-13.21, -4.34)** p< 0.0001
Norfolk QoL-DN total score [c, d] (change from baseline)	**-6.14** (-11.77, - 0.52) P=0.032	**-15.0** (-19.8, -10.2)	**-16.2** (2.8) (-21.7, -10.8) P=5.426E-09	**-11.3** (95% CI: -16.26, -6.30) p< 0.0001
Week 66 (Month 18)				
Serum TTR, g/L [b] (percent change from baseline)	**Diff: -66.41%** 95% CI: -71.41, -61.42 P-value < 0.001 Placebo (N=51) **-5.24%** (18.204) Inotersen (N=84) **-71.09%** (15.097)	**87.8%** Long term dosing with patisiran LNP sustained a mean TTR reduction of approximately **80%** over 2 years of treatment	Vutrisiran (n=120) -**80.99%** (20.96) vs. Patisiran (n=40) **-78.56%** (13.63) in HELIOS-A*	**-70.1%** (95% CI: -75.02, -65.15)[§]

Analysis/endpoint	Tegsedi - Inotersen 300 mg (N=113) minus Placebo (N=60)	Onpattro-Patisiran 0.3 mg/kg patisiran-LNP q3w (N=148) Minus placebo (N=77)	Amvuttra-Vutrisiran (N=122) in HELIOS-A minus External Placebo (N=77) APOLLO	Treatment difference (95% CI) Eplontersen 45 mg q4w minus External Placebo
Administration	Subcutaneous injection (SC) Q1W (once every week)	Intravenous (IV) infusion Q3W (once every 3 weeks)	Subcutaneous (SC) injection Q3M (once every 3 months)	Subcutaneous (SC) injection Q4W (once every 4 weeks)#
mNIS+7 composite score [b] (change from baseline)	**-14.89** (-22.55, -7.22) p< 0.0001	**-33.99 (2.974)** -39.86, -28.13 P=9.262E-24	**-28.55** (2.76) (-34.00, -23.10) P=6.505E-20	**-23.1** (95% CI: -29.26; -17.01)§
Norfolk QoL-DN total score [b] (change from baseline)	**-8.56** (-15.42, -1.71) P=0.015	**-21.3** (-27.2; -15.0) P=1.103 ×10-10	**-21.0** (3.1) (-27.1, -14.9) P=1.844E-10	**-19.3** (95% CI: -24.99, -13.53)§

[b] 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.

[c] 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.

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

Patients with a missing mNIS+7 composite score or Norfolk QoL-DN total score at Week 35 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.

#Eplontersen dosing regimen was 45 mg q4w. Analysis of serum TTR concentration based on data collected up to 28 days after last dose of study drug. Analysis of mNIS+7 composite score and Norfolk QoL-DN total score based on data collected up to 52 days after last dose of study drug.
The interim analysis was conducted using the full analysis set with observations up to Week 35 from the interim analysis (DCO 18 April 2022). The Week 66 final analysis was conducted using the full analysis set with observations from up to Week 66 (DCO 07 April 2023). Full analysis set differs between Week 35 interim analysis and Week 66 final analysis due to the requirement to have at least one post-baseline mNIS+7 composite score or Norfolk QoL-DN total score assessment.
* Percent Reduction from baseline and no difference with placebo. Comparison for non inferiority
§ TTR concentration percent change from baseline, mNIS+7 Composite Score, and Norfolk QoL-DN Total Score change from baseline up to Week 66-Primary calculated using reference based multiple imputation analysis (Copy increments from reference, CIR) in CSR (ION-682884-CS3) with all on-study (ie, both on-treatment and post-treatment) measurements (Full Analysis Set). The results of the CIR analysis were applied to only those missing data following treatment discontinuation (see Table 7 above)

Serum Transthyretin

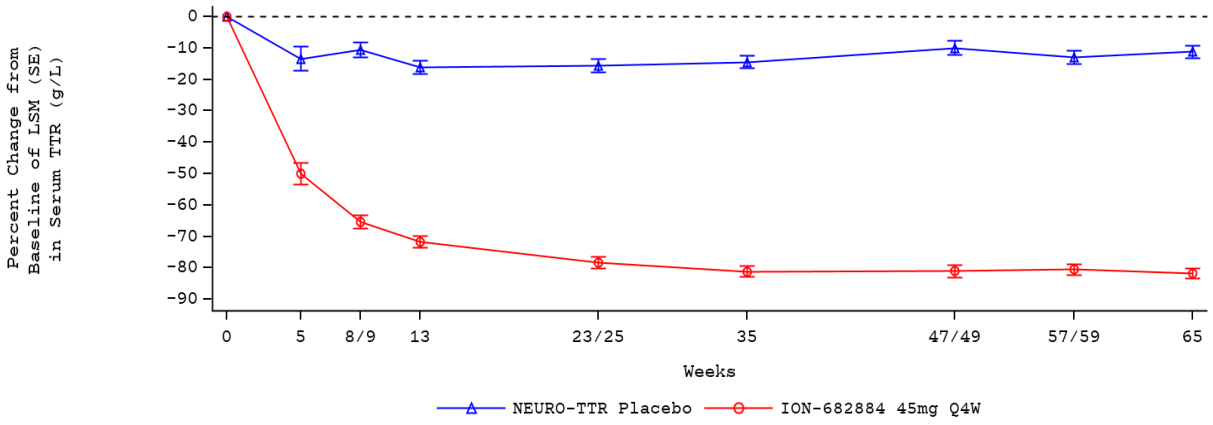
Eplontersen was superior to external placebo for the co-primary endpoint percent change in serum TTR from baseline to Week 35 ($p < 0.0001$), with a sustained reduction at Week 65 (please see Figure 4 below).

At Week 65, the LSM percent reduction from baseline was 81.7% (95% CI: 84.82%, 78.48%) in the eplontersen group and 11.2% (95% CI: 15.06%, 7.41%) in the external placebo group, with an LSM difference between eplontersen and external placebo of 70.4% (95% CI: 75.2%, -65.7%) at Week 65.

In the eplontersen group, the serum TTR concentration decreased rapidly (as early as Week 5, which was the first post-baseline evaluation timepoint). The mean percent serum TTR concentration reduction from baseline reached 82.13% at Week 35 and was sustained throughout the treatment period (82.96% at Week 65 and 81.83% at Week 85).

All prespecified sensitivity analyses were consistent with the primary analysis.

Figure 4: LSM (SE) percent change in serum TTR concentration from baseline to week 66 final analysis (on-treatment) (full analysis set)



N of evaluable patients

NEURO-TTR Placebo	59	58	59	59	55	57	53	50	51
ION-682884 45mg Q4W	141	132	136	136	140	139	136	135	135

Analysis based on data collected up to 28 days after last dose of study drug.
LSMs are 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. Only data up to Week 65 are included in the modeling.
ION-682884 = eplontersen; LSM = least squares mean; MMRM = mixed effects model with repeated measures; N = number of patients in treatment group; NEURO-TTR Placebo = external placebo; q4w = once every 4 weeks; SE = standard error; TTR = transthyretin.
Source: ION-682884-CS3 Clinical Study Report

<u>Comparison versus the within study concurrent inotersen group (serum TTR)</u>

At Week 35, the mean percent change in serum TTR was -74.26 following treatment with inotersen (ie, prior to switch to eplontersen) and -82.13 in the eplontersen group. After patients in the concurrent inotersen group switched to eplontersen, the effect on serum TTR was similar for both treatment groups at Week 65 and was maintained through Week 85.

Table 8: Percent change from baseline of serum transthyretin for eplontersen and inotersen-eplontersen over time up to week 85 using day 1 baseline values (on-treatment) (full analysis set)

	Inotersen - Eplontersen (N=21)	Eplontersen (N=141)
Baseline		
n	21	141
Mean (SD, SEM)	0.2139 (0.0718, 0.0157)	0.2272 (0.0754, 0.0063)
Median (P25, P75)	0.1980 (0.1650, 0.2560)	0.2220 (0.1820, 0.2700)
Min, max	0.083, 0.334	0.064, 0.448
Percent Change from Baseline[a]		
Week 35		
n	20	139
Mean (SD, SEM)	**-74.26** (23.281, 5.206)	**-82.13** (11.660, 0.989)
Median (P25, P75)	-82.06 (-91.47, -67.45)	-84.41 (-90.24, -77.45)
Min, max	-96.5, -19.3	-97.2, -33.0
Week 65		
n	20	135
Mean (SD, SEM)	**-79.89** (12.007, 2.685)	**-82.96** (10.374, 0.893)
Median (P25, P75)	-84.02 (-88.78, -71.39)	-85.04 (-91.70, -76.00)
Min, max	-96.0, -51.8	-97.6, -48.8
Week 85[b]		
n	18	129
Mean (SD, SEM)	**-80.61** (11.519, 2.715)	**-81.83** (13.380, 1.178)
Median (P25, P75)	-83.01 (-87.62, -73.02)	-86.18 (-90.82, -75.90)
Min, max	-96.4, -59.7	-98.5, -33.2

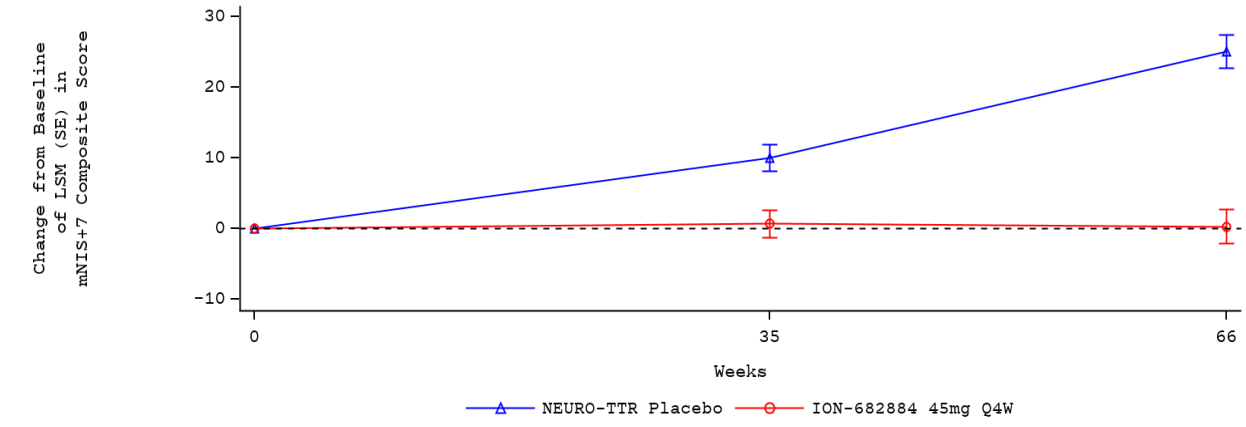
[a] For the concurrent inotersen group, Week 35 results are for treatment with inotersen (prior to switch to eplontersen), and results are for treatment with eplontersen (after switch) at Weeks 66 and 85.
[b] Week 85 is based on the nominal visit. It includes all data collected on Week 85 visit without visit windows implemented.
Analysis is based on data collected up to 28 days after last dose of Study Drug except for Week 85, which includes all Week 85 data regardless of last dose date. Only data up to Week 85 are included in the summary. Baseline is the average of all non-missing pre-dose assessments.
Max, maximum; Min, minimum; P25, 25th percentile; P75, 75th percentile; SD, standard deviation; SEM, standard error of the mean.

Modified Neuropathy Impairment Score+7 Composite Score

Eplontersen was superior to external placebo for the co-primary endpoint mNIS+7 composite score change from baseline at Week 35 ($p < 0.0001$) with a consistent treatment effect at Week 66 (please see Figure 5 below). At Week 66, the LSM change from baseline was 0.3 (95% CI 4.46 to 5.06) in the eplontersen group and 25.1 (95% CI: 20.23 to 29.88) in the external placebo group. The LSM difference between eplontersen and external placebo at Week 66 was -24.8 (95% CI: -30.96 to 18.56) between treatment groups.

The mean change in mNIS+7 composite score remained close to zero, ie, on average no change, through Week 85 in the eplontersen group and suggests stabilization of disease state. In the external placebo group, a gradual increase, ie, worsening, in mean mNIS+7 composite score was observed over the 65-week treatment.

Figure 5: LSM (SE) change from baseline in mNIS+7 composite score over time up to week 66 final analysis (on-treatment) (full analysis set)



Analysis based on data collected up to 52 days after last dose of study drug.
Source: Figure 2.28, ION-682884-CS3 Clinical Study Report, Module 5.3.5.1

Responder analysis

A responder analysis was performed to examine the difference in response between eplontersen and external placebo over a range of cut-points from -2 to 10 points change from baseline. A responder was defined as a patient who had a change from baseline that was less than or equal to the threshold value (ie, < -2, < 0, < 2, < 4, < 6, < 8, < 10 points). A missing value was defined as a non-response. A 2-point change has been established as the minimal clinically detectable difference by a physician for the NIS but a definitive threshold has not been ascertained for mNIS+7.

Across all of the threshold values evaluated in the responder analysis at Week 66, the percentages of responders were higher in the eplontersen group than in the external placebo group (Table 9). In the eplontersen group 48.2% (68/141) of patients had an improvement in mNIS+7 composite score, defined as a decrease in score (ie, < 0 change) from baseline, compared to 16.9% (10/59) in the external placebo group.

Table 9: Modified neuropathy impairment score +7 composite score change from baseline to week 66 (responder analysis) (on-treatment) (full analysis set)

	ISIS 420915-CS2	ION-682884-CS3
Score change	**Placebo (N = 59)**	**Eplontersen 45 mg q4w (N = 141)**
With non-score	52 (88.1%)	128 (90.8%)
With missing score	7 (11.9%)	13 (9.2%)
≤ -2 points increase	8 (13.6%)	61 (43.3%)
< 0 points increase	10 (16.9%)	68 (48.2%)
≤ 0 points increase	10 (16.9%)	68 (48.2%)
< 2 points increase	11 (18.6%)	76 (53.9%)
≤ 2 points increase	11 (18.6%)	76 (53.9%)
< 4 points increase	13 (22.0%)	80 (56.7%)
≤ 4 points increase	13 (22.0%)	80 (56.7%)
< 6 points increase	14 (23.7%)	84 (59.6%)
≤ 6 points increase	14 (23.7%)	84 (59.6%)
< 8 points increase	15 (25.4%)	90 (63.8%)
≤ 8 points increase	15 (25.4%)	90 (63.8%)
< 10 points increase	17 (28.8%)	96 (68.1%)
≤ 10 points increase	17 (28.8%)	96 (68.1%)

Analysis is based on data collected up to 52 days after the last dose of the study drug.
A responder is defined as a patient whose mNIS+7 score change from baseline to Week 66 ≤ the threshold value. Patients that terminate treatment early irrespective of the reason or have missing Week 66 data are considered non-responders. Source: ION-682884-CS3 Clinical Study Report

The components of mNIS+7 were directionally consistent with the overall composite score at both Week 35 and Week 66.

Comparison versus the within study concurrent inotersen group (mNIS+7)

At Week 35, the mean change in mNIS +7 composite score was 4.06 following treatment with inotersen (ie, prior to switch to eplontersen) and -0.04 in the eplontersen group. In the eplontersen group, the effect on mNIS+7 composite score remained stable between Weeks 66 and 85. Given the small sample size of the concurrent inotersen group, the changes in mNIS +7 composite score (after switching to eplontersen) between the 2 time-points was not clinically meaningful.

Table 10: Change from baseline of modified neuropathy impairment score+7 composite score for eplontersen and inotersen-eplontersen over time up to week 85 using day 1 baseline values (on-treatment) (full analysis set)

	Inotersen - Eplontersen (N=21)	Eplontersen (N=141)
Baseline		
n	21	141
Mean (SD, SEM)	65.41 (35.855, 7.824)	79.81 (42.250, 3.558)
Median (P25, P75)	55.86 (30.89, 95.16)	76.83 (43.25, 107.01)
Min, max	17.0, 130.4	7.9, 205.6
Change from Baseline[a]		
Week 35		
n	19	138
Mean (SD, SEM)	**4.06** (13.392, 3.072)	**-0.04** (16.222, 1.381)
Median (P25, P75)	2.86 (-5.24, 10.47)	-0.09 (-6.30, 7.65)
Min, max	-17.7, 43.2	-80.6, 47.4
Week 66		
n	19	128
Mean (SD, SEM)	**3.22** (15.443, 3.543)	**-0.21** (17.620, 1.557)
Median (P25, P75)	5.44 (-7.56, 10.35)	-1.12 (-10.23, 10.56)
Min, max	-19.3, 48.9	-71.2, 46.1
Week 85		
n	18	122
Mean (SD, SEM)	**5.61** (20.627, 4.862)	**-2.86** (20.541, 1.860)
Median (P25, P75)	4.07 (-5.29, 9.74)	-1.85 (-11.34, 8.34)
Min, max	-28.7, 48.2	-79.0, 58.3

[a] For the concurrent inotersen group, Week 35 results are for treatment with inotersen (prior to switch to eplontersen), and results are for treatment with eplontersen (after switch) at Weeks 66 and 85. Analysis is based on data collected up to 52 days after last dose of Study Drug. Only data up to Week 85 are included in the summary. Max, maximum; Min, minimum; P25, 25th percentile; P75, 75th percentile; SD, standard deviation; SEM, standard error of the mean.

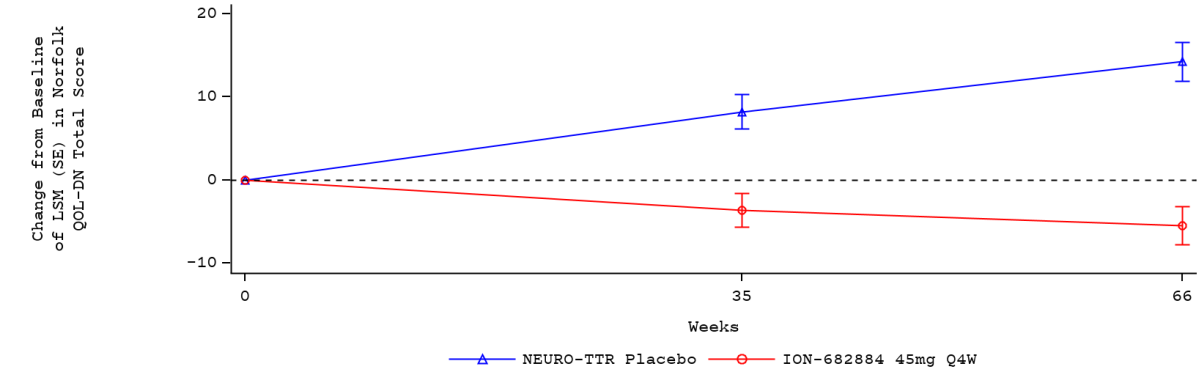
Norfolk Quality of Life – Diabetic Neuropathy Questionnaire Total Score

Eplontersen was superior to external placebo for the endpoint Norfolk QoL DN change from baseline at Week 35 ($p < 0.0001$), with an increased benefit observed at Week 66 (please see Figure 6 below). Change from baseline in Norfolk QoL DN total score was a key secondary endpoint in the Week 35 interim analysis and a co-primary endpoint in the Week 66 analysis.

At Week 66, the LSM change from baseline was -5.5 (95% CI -10.03, -0.96) in the eplontersen group and 14.2 (95% CI 9.51, 18.97) in the external placebo group. The treatment difference between eplontersen and external placebo was -19.7 (95% CI -25.63, -13.84).

The reductions (improvement) in mean Norfolk QoL-DN total score in the eplontersen group were sustained through Week 85, while the increase in mean Norfolk QoL DN total score in the external placebo group through Week 65 suggests worsening of PN.

Figure 6: LSM (SE) change from baseline in Norfolk QoL-DN total score up to week 66 final analysis (on treatment) full analysis set



Analysis based on data collected up to 52 days after last dose of study drug.

Responder Analysis

A responder analysis was performed on the Norfolk QoL-DN data to examine the difference in response between eplontersen and external placebo over a range of cut-points from -2 to 10 points change from baseline. A responder was defined as a patient who had a change from baseline that was less than or equal to the threshold value (ie, from < -2, < 0, < 2, < 4, < 6, < 8, < 10 points). A missing value was defined as a non-response. Patients who withdrew from the study prematurely or had missing data were considered non-responders.

Across all of the threshold values evaluated in the responder analysis, the percentages of responders were higher in the eplontersen group than in the external placebo group. At Week 66, 58.9% (83/141) of patients in the eplontersen group showed improvement in Norfolk QoL-DN total score, defined as a decrease in score (ie, < 0 change) from baseline, compared to 20.3% (12/59) in patients in the external placebo group.

Comparison versus the within study concurrent inotersen group (Norfolk QoL-DN)

At Week 35, the mean change in Norfolk QOL-DN total score was -2.97 following treatment with inotersen (ie, prior to switch to eplontersen) and -4.79 in the eplontersen group. In the eplontersen group, the effect on Norfolk QOL-DN total score remained stable between Weeks 66 and 85. Given the small sample size of the concurrent inotersen group, the changes in Norfolk QOL-DN total score (after switching to eplontersen) between the 2 timepoints was not clinically meaningful.

Table 11: Change from baseline of Norfolk quality of life – diabetic neuropathy total score for eplontersen and inotersen-eplontersen over time up to week 85 using day 1 baseline values (on-treatment) (full analysis set)

	Inotersen - Eplontersen (N=21)	Eplontersen (N=141)
Baseline		
n	21	134
Mean (SD, SEM)	37.97 (21.512, 4.694)	43.33 (26.206, 2.264)
Median (P25, P75)	43.00 (21.00, 55.00)	40.00 (21.00, 61.00)
Min, max	1.0, 74.0	1.0, 106.0
Change from Baseline[a]		
Week 35		
n	20	130
Mean (SD, SEM)	-2.97 (12.094, 2.704)	-4.79 (16.514, 1.448)
Median (P25, P75)	-3.00 (-6.00, 2.50)	-2.50 (-13.00, 2.00)
Min, max	-27.0, 20.0	-65.0, 41.0
Week 66		
n	20	128
Mean (SD, SEM)	**-2.37** (11.704, 2.617)	**-7.24** (18.511, 1.636)
Median (P25, P75)	-3.50 (-9.50, 6.00)	-5.00 (-17.00, 4.00)
Min, max	-23.0, 23.0	-75.0, 35.0
Week 85		
n	18	119
Mean (SD, SEM)	**1.21** (14.029, 3.307)	**-6.23** (18.005, 1.651)
Median (P25, P75)	-1.00 (-7.00, 14.00)	-5.00 (-15.26, 5.00)
Min, max	-23.3, 29.0	-57.0, 58.0

[a] For the concurrent inotersen group, Week 35 results are for treatment with inotersen (prior to switch to eplontersen), and results are for treatment with eplontersen (after switch) at Weeks 66 and 85.
Analysis is based on data collected up to 52 days after last dose of Study Drug. Only data up to Week 85 are included in the summary.
Baseline is the average of all non-missing pre-dose assessments. Max, maximum; Min, minimum; P25, 25th percentile; P75, 75th percentile; SD, standard deviation; SEM, standard error of the mean.

Secondary efficacy variables

The results of the eplontersen treatment show clear and large effects. The protein responsible for the ATTR disease was reduced by a mean of 81% from baseline to week 35 and this effect was sustained up to week 65, with a large reduction observed as early as weeks 8/9. The difference in comparison to external placebo is 66% at week 35 and 70% at week 65. Large differences in favour of eplontersen compared to external placebo were also observed for the mNIS+7 composite score and Norfolk QoL-DN total score.

Ancillary analyses

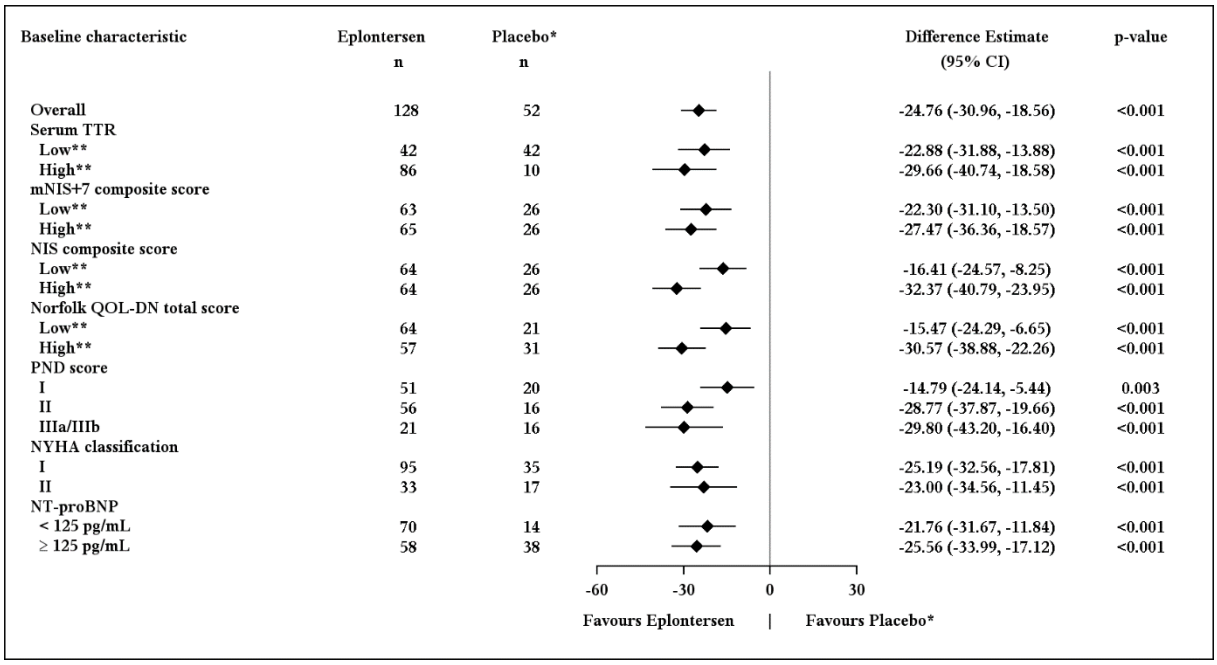
The subgroup analyses supported the results from the primary analyses and provided consistency in the results.

Predefined subgroup analyses of the primary endpoints (i.e. difference in LSM percent change in serum TTR concentration, LSM change in mNIS+7 composite score, and LSM change in Norfolk QoL-DN total score) across all prespecified 9 different demographic and disease baseline characteristics based on sex, race, age, region, CM subgroup, previous treatment, Val30Met TTR mutation, disease stage, and

ATTRv-CM clinical diagnosis showed at week 65 consistent statistically significant efficacy of eplontersen vs placebo.

Consistent efficacy (statistically significant) across all the subgroups analysed was also shown when additional post-hoc subgroup analyses based on additional disease-related baseline characteristics (mNIS+7 composite score, NIS composite score, Norfolk QoL-DN total score, PND score, NYHA classification, and NT-proBNP concentration) was performed.

Figure 7: Forest plot of treatment difference for change from baseline in mNIS+7 composite score at week 66 for selected subgroups based on disease baseline characteristics - on-treatment (full analysis set)



* External placebo group from the ISIS 420915-CS2 study.

** Here, "Low" means strictly less than the observed median at baseline in the Full Analysis Set, and "High" means greater than, or equal to, the same observed median. For serum TTR concentration, the mNIS+7 composite score, the NIS composite score, and the Norfolk QoL-DN total score, the median in question is 0.20 pg/mL, 76.19, 39.25, and 45.50, respectively.

From MMRM adjusted by propensity score weights with categorical effects for treatment, time, treatment-by-time interaction, disease stage, Val30Met mutation, previous treatment, and fixed covariates for baseline and baseline-by-time-interaction. Subgroup models also included treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions.

The Week 66 LSM treatment difference (eplontersen - placebo) with 95% CI (unadjusted) are presented. Data up to Week 66 are included in the model.

CI = confidence interval; LSM = least squares mean; MMRM = mixed effects model for repeated measures; mNIS+7 = Modified Neuropathy Impairment Score +7; n = number of contributing subjects; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; Norfolk QoL-DN = Norfolk Quality of Life – Diabetic Neuropathy; TTR = transthyretin.

The effects of eplontersen and concurrent inotersen at Week 35 on change in serum TTR concentration, mNIS+7 composite score and Norfolk QoL-DN total score were compared using descriptive statistics (Table 12 below). These have already been discussed in the various endpoints sections. As the concurrent inotersen group was small (N = 21) by comparison to the eplontersen group (N = 141), any observed differences should be interpreted with caution.

The mean percent decrease in serum TTR concentration from baseline to Week 35 was numerically larger in the eplontersen group (-82.1%) than in the concurrent inotersen group (-74.3%).

There was very little change in mean mNIS+7 composite score from baseline to Week 35 in the eplontersen group while a small increase (ie, indicating some worsening) was observed in the concurrent inotersen group.

Norfolk QoL-DN total scores were similar in the eplontersen and the concurrent inotersen groups both at baseline and at Week 35.

Table 12: Summary statistics from baseline up to week 35 for serum TTR, mNIS+7 composite score, and Norfolk QoL-DN total score, for eplontersen and concurrent inotersen treatment groups in ION-682884-CS3 (on-treatment) (full analysis set)

	Serum TTR (g/L)		mNIS+7 composite score		Norfolk QoL-DN total score	
Timepoint	Inotersen-eplontersen [a] (N = 21)	Eplontersen 45 mg q4w (N = 141)	Inotersen-eplontersen [a] (N = 21)	Eplontersen 45 mg q4w (N = 141)	Inotersen-eplontersen [a] (N = 21)	Eplontersen 45 mg q4w (N = 141)
Baseline						
n	21	141	21	141	21	134
Mean (SD)	0.21 (0.072)	0.23 (0.075)	65.4 (35.86)	79.8 (42.25)	38.0 (21.51)	43.3 (26.21)
Median	0.20	0.22	55.9	76.8	43.0	40.0
(Min, Max)	(0.1, 0.3)	(0.1, 0.4)	(17, 130)	(8, 206)	(1, 74)	(1, 106)
Week 35						
n	20	139	19	138	20	135
Mean (SD)	0.05 (0.042)	0.04 (0.027)	66.3 (37.49)	79.6 (42.79)	34.3 (21.96)	38.5 (26.81)
Median	0.03	0.03	58.9	78.5	30.0	37.0
(Min, Max)	(0.0, 0.2)	(0.0, 0.1)	(15, 150)	(2, 195)	(0, 79)	(-1, 99)
Percent Change / Change from baseline at Week 35 [b]						
n	20	139	19	138	20	130
Mean (SD)	**-74.3** (23.28)	**-82.1** (11.66)	**4.1** (13.39)	**0.0** (16.22)	**-3.0** (12.09)	**-4.8** (16.51)
Median	-82.1	-84.4	2.9	-0.1	-3.0	-2.5
(Min, Max)	(-97, -19)	(-97, -33)	(-18, 43)	(-81, 47)	(-27, 20)	(-65, 41)

[a] Treated with inotersen 300 mg q1w Week 1 to 34, then switched to eplontersen 45 mg q4w at Week 37.

[b] Serum TTR analysed as percent change. mNIS+7 composite score and Norfolk QoL-DN total score analysed as change from baseline.

Source: ION-682884-CS3 Clinical Study Report.

Sensitivity analyses

A number of sensitivity analyses have been performed as outlined in the protocol. These analyses are included in the ION-682884-CS3 study report Appendix 14.

Table 13: Several sensitivity analyses for mNIS+7 composite score at week 66 final analysis

Statistical Analysis of Change from Baseline
mNIS+7 Composite Score at Week 66 Final Analysis (Sensitivity Analysis 1 - Non-Parametric Analysis) (On-Treatment) Per Protocol Set

	NEURO-TTR Placebo (N=52)	Eplontersen 45mg Q4W (N=137)
Week 35 n (a) Hodges-Lehmann Estimate of Difference (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	51	134 -8.0672 -12.8930, -3.7950 0.00080130
Week 66 n (a) Hodges-Lehmann Estimate of Difference (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	52	127 -21.8034 -29.4777, -14.3688 <0.00000001
mNIS+7 Composite Score at Week 66 Final Analysis (Sensitivity Analysis 2 - Multiple Imputation Assuming Missing at Random) (On-Treatment) Safety Set		
	NEURO-TTR Placebo (N=60)	ION-682884 45mg Q4W (N=144)
Week 35 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo 95% CI P-value	60 9.8361 (1.8731) 6.1649, 13.5074	144 0.4353 (1.8711) -3.2321, 4.1026 -9.4009 -13.8659, -4.9158 0.00003991
Week 66 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	60 26.7347 (2.6584) 21.5238, 31.9455	144 1.7157 (2.5591) -3.3001, 6.7314 -25.0190 -31.3941, -18.6440 <0.00000001
mNIS+7 Composite Score at Week 66 Final Analysis (Sensitivity Analysis 3 - Multiple Imputation Assuming Copy Increments from Reference) (On-Treatment) Safety Set		
	NEURO-TTR Placebo (N=60)	ION-682884 45mg Q4W (N=144)
Week 35 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	60 10.0424 (1.8753) 6.3667, 13.7180	144 1.3122 (1.8441) -2.3022, 4.9265 -8.7302 -13.1898, -4.2706 0.00012468
Week 66 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	60 26.9977 (2.7092) 21.6874, 32.3080	144 4.1891 (2.5643) -0.8369, 9.2151 -22.8086 -29.1532, -16.4640 <0.00000001
mNIS+7 Composite Score at Week 66 Final Analysis (Sensitivity Analysis 4 - Multiple Imputation Assuming Jump to Reference) (On-Treatment) Safety Set		
	NEURO-TTR Placebo (N=60)	ION-682884 45mg Q4W (N=144)

Week 35 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	60 10.0715 (1.8751) 6.3962, 13.7468	144 1.2775 (1.8442) -2.3370, 4.8920 -8.7940 -13.2499, -4.3381 0.00010972
Week 66 (a) n (b) LSM (SE) 95% CI Difference in LSM (ION-682884 45mg Q4W - NEURO-TTR Placebo) 95% CI P-value	60 27.1829 (2.7137) 21.8638, 32.5021	144 5.0845 (2.5729) 0.0418, 10.1272 -22.0985 -28.4528, -15.7441 <0.00000001

A range of relevant sensitivity analyses were conducted covering relevant aspects such as alternative missing data handling and additional covariates to account for the un-randomized comparison. According to the CSR, all these sensitivity analyses yield similar results supporting the primary analysis conducted.

From the applicant's responses to Day 120 LoQ, it is obvious that there are no major differences in the findings between primary analysis and sensitivity analyses CIR and J2R. The applicant further clarified that sensitivity analyses 3 and 4 for mNIS+7 and Norfolk QoL as reported in the CSR were based on on-treatment data only, while all data missing post discontinuation were imputed based on J2R or CIR.

Comparing results of analyses based on on-study and on-treatment data, the following Table 14 was constructed (by the assessment teams) for immediate visual comparison. Overall results of analyses are consistent.

Table 14: Treatment difference in serum TTR concentration percent change from baseline and mNIS+7 composite score, and Norfolk QoL-DN total score change from baseline up to week 66 - primary and sensitivity analyses 3 and 4 in CSR (ION-682884-CS3) with on-treatment measurements and with all on-study (ie, both on-treatment and post-treatment) measurements (full analysis set)

				Treatment Difference (95% CI) [on-treatment measurement]	**Treatment Difference (95% CI)** [all on-study (i.e., both on-treatment and post-treatment) measurements]
Endpoint	**Week**	**Analysis**	**Dataset**	**Eplontersen 45 mg q4w minus External Placebo**	**Eplontersen 45 mg q4w minus External Placebo**
Full Analysis Set			Placebo N=59 Eplontersen N=141		
Safety Set			Placebo N=60 Eplontersen N=144		
Serum TTR concentration, Percent Change from Baseline	Week 35	Primary Analysis	FAS	-66.65 (-71.59, -61.71)	-66.81 (-71.78, -61.84)
		Sensitivity Analysis 3	SS	**-**	**-66.57** (-71.61, -61.53)
		Sensitivity Analysis 4	SS	**-**	**-65.36** (-70.74, -59.99)
	Week 65	Primary Analysis	FAS	-70.42 (-75.17, -65.66)	-70.86 (-75.65, -66.07)
		Sensitivity Analysis 3	SS	**-**	**-70.10** (-75.04, -65.16)
		Sensitivity Analysis 4	SS	**-**	**-65.31** (-71.36, -59.27)
mNIS+7 Composite Score, Change from Baseline	Week 35	Primary Analysis	FAS	-9.3542 (-13.8691, -4.8394)	-9.2506 (-13.7487, -4.7525)
		Sensitivity Analysis 3	SS	**-8.7302** (-13.1898, -4.2706)	**-8.6389** (-13.0685, -4.2094)
		Sensitivity Analysis 4	SS	**-8.7940** (-13.2499, -4.3381)	**-8.6725** (-13.1004, -4.2447)
	Week 66	Primary Analysis	FAS	-24.7593 (-30.9552, -18.5635)	-24.1193 (-30.2157, -18.0230)
		Sensitivity Analysis 3	SS	**-22.8086** (-29.1532, -16.4640)	**-22.1482** (-28.2519, -16.0446)
		Sensitivity Analysis 4	SS	**-22.0985** (-28.4528, -15.7441)	**-21.4181** (-27.5256, -15.3107)
Norfolk QoL-DN Total Score, Change from Baseline	Week 35	Primary Analysis	FAS	-11.8202 (-16.8927, -6.7477)	-11.8166 (-16.8903, -6.7429)
		Sensitivity Analysis 3	SS	**-11.2826** (-16.2862, -6.2790)	**-11.2828** (-16.2607, -6.3048)
		Sensitivity Analysis 4	SS	**-11.5205** (-16.4864, -6.5546)	**-11.5388** (-16.4762, -6.6014)
	Week 66	Primary Analysis	FAS	-19.7352 (-25.6301, -13.8403)	-20.2512 (-26.0378, -14.4646)
		Sensitivity Analysis 3	SS	**-18.4892** (-24.3827, -12.5957)	**-19.1119** (-24.8465, -13.3773)
		Sensitivity Analysis 4	SS	**-18.8054** (-24.6141, -12.9967)	**-19.4530** (-25.0901, -13.8158)

On-Study: Post-baseline assessments include assessments on or after the date of first dose of investigational product.

On-Treatment: Post-baseline assessments include assessments on or after the date of first dose of investigational product up to and including 28 (TTR) or 52 (mNIS+7, Norfolk QoL-DN) days following the date of last investigational product dose.
Primary analysis: MMRM.
Sensitivity analysis 3: MI ANCOVA assuming copy increments from reference.
Sensitivity analysis 4: MI ANCOVA assuming jump to reference.
Analyses included data up to Week 66.
Full details provided in SAPv2.3.
CI = confidence interval; FAS = Full Analysis Set; LSM = least squares mean; MI ANCOVA = multiple imputation analysis of covariance; MMRM = mixed model with repeated measures; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy questionnaire; OS = on-study; q4w = once every 4 weeks; SE = standard error; SS = Safety Set; TTR = transthyretin.

The requested sensitivity analysis accounting for age in the propensity score calculation has been provided for all primary endpoints. The treatment differences with and without including age as a factor in the propensity score model) have been included by the assessment teams in one table for easier use and reference. Results are overall consistent between the two analyses.

Table 15: Least square means estimate for percent change from baseline in serum TTR concentration (g/L) at week 65, in mNIS+7 composite score and in Norfolk QoL-DN total score at week 66 MMRM model with propensity score weighting with and without including age as a factor (full analysis set)

	LSM Estimate for Percent Change From Baseline in Serum TTR Concentration (g/L) at Week 65 Treatment difference Eplontersen – placebo (95 % CI)			LSM Estimate for Percent Change From Baseline in mNIS+7 Composite Score at Week 66 Treatment difference Eplontersen – placebo (95 % CI)			LSM Estimate for Percent Change From Baseline in Norfolk QoL-DN Total Score at Week 66 Treatment difference Eplontersen – placebo (95 % CI)		
Group	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Primary analysis (not including age in propensity score model)									
Eplontersen (N = 141)	-70.42	-75.17, -65.66	< 0.0001	-24.76	-30.96, -18.56	< 0.0001	-19.74	-25.63, -13.84	< 0.0001
Sensitivity analysis with age in propensity score model									
Eplontersen (N = 141)	-71.32	-76.06, -66.58	< 0.0001	-25.34	-31.52, -19.16	< 0.0001	-21.73	-27.48, -15.99	< 0.0001

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. The sensitivity analysis includes age (continuous) as covariate in the MMRM and propensity score models. Only data up to Week 65 are included in the modeling.

CI = confidence interval; MMRM = mixed effects model for repeated measures; TTR = transthyretin.

With the responses to the Day 180 LoOI, the applicant provided argumentation against reporting results of the J2R analysis (sensitivity analysis 4) in the SmPC, which is essentially based on the long half-life and sustained effect of eplontersen on TTR levels supporting a monthly dosing regimen. The J2R approach assumes that the effect of eplontersen is directly lost after discontinuation, which is not biologically plausible. Therefore, the applicant proposed to include the primary analysis (MMRM) for

TTR and a modified Copy Increments from Reference (CIR) analysis (applying CIR imputation only to those patients discontinuing eplontersen prior to week 66) for mNIS+7 and Norfolk QoL.

While the CIR analysis may neither be biologically plausible, as it assumes the effect achieved until treatment discontinuation is maintained, based on the available results of the primary analyses and different placebo-based imputation approaches (see table below), it is apparent that differences in results are only minor and do not impact clinical interpretation. This is supported by the fact that only few patients (n=8) discontinued eplontersen treatment prior to week 66 and had missing week 66 data. Few of these discontinued long before week 66 considering the long-lasting effect of eplontersen: approximately 1 year prior to week 66 (n=3), approximately 6 month prior to week 66 (n=3) and approximately 2/3 months prior to week 66 (n=2).

In conclusion, the argumentation of the applicant can be followed and it can be agreed to report results of the CIR analysis applied to only those missing data following treatment discontinuation for mNIS+7 and Norfolk.

Due to the complexity of the issues with the biological plausibility, the SmPC was updated and mentions only that a reference-based multiple imputation approach for the missing data has been used. This is considered sufficient as all (placebo-based) approaches yield very similar results and differences between results are minor to have any meaningful clinical impact.

To avoid any potential confusions for the prescribers by referring to different approaches for the analyses of the primary endpoints TTR, mNIS+7 and Norfolk QoL-DN, the results of only the CIR approach have been included in the SmPC.

Table 16: Week 65/66 results for serum TTR, mNIS+7 composite score, and Norfolk QoL-DN total score

Analysis	Analysis Set	Serum TTR		nMIS+7		Norfolk	
		Ext. placebo	Eplontersen	Ext. placebo	Eplontersen	Ext. placebo	Eplontersen
Primary analysis	FAS/OT	-11.24	-81.65	25.0557	0.2964	14.2388	-5.4964
		-70.42 [-75.17; -65.66]		**-24.7593** [-30.9552; -18.5635]		**-19.7352** [-25.6301; -13.8403]	
	FAS/OS	-10.88	-81.74	24.3837	0.2643	14.7114	-5.5398
		-70.86 [-75.65; -66.07]		**-24.1193** [-30.2157; -18.0230]		**-20.2512** [-26.0378; -14.4646]	
CIR for those missing after discontinuation	SS/OS	**-70.1%** (95% CI: -75.02, -65.15)		26.3469	3.2145	13.7122	-5.5481
				Difference: -23.1 [-29.26; -17.01]		**Difference: -19.3** [-24.99; -13.53]	
CR for those missing after discontinuation	SS/OS	Not available Difference estimated roughly to be between -70.86 and -68.00		Not available Difference estimated roughly to be between -23.1324 and -22.9387		Not available Difference estimated roughly to be between -19.5069 and -19.2602	
J2R for those missing after discontinuation	SS/OS	Not available Difference estimated roughly to be approx. -68.00		26.4157	3.4770	13.7350	-5.7719
				Difference: -22.9387 [-29.0546; -16.8228]		**Difference: -19.5069** [-25.1482; -13.8656]	

CIR for all missing data	SS/OS	-10.14	-80.24	26.3868	4.2385	13.8277	-5.2842
		Difference: -70.10 [-75.04; -65.16]		**Difference: -22.1482** [-28.2519; -16.0446]		**Difference: -19.1119** [-24.8465; -13.3773]	
J2R for all missing data	SS/OS	-10.58	-75.90	26.5883	5.1702	13.7770	-5.6759
		Difference: -65.31 [-71.36, -59.27]		**Difference: -21.4181** [-27.5256; -15.3107]		**Difference: -19.4530** [-25.0901; -13.8158]	

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy aswell as the benefit risk assessment (see later sections).

Table 17: Summary of efficacy for trial ION-682884-CS3

Title: A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy			
Study identifier	ION-682884-CS3 (study code) 2019-001698-10 (EU CT number) NCT04136184 (NCT number) NEURO_TTRansform (other identifier)		
Design	Global, Phase 3, open-label, external-control, randomized study to assess efficacy and safety of eplontersen in adult patients with ATTRv-PN stage 1 or stage 2 amyloidosis. The placebo group of the inotersen study ISIS 420915-CS2 is used as an external control. Patients were randomized 6:1 to eplontersen (eplontersen SC 45 mg q4w) or inotersen-eplontersen (inotersen SC 300 mg q1w until Week 34, then switched to eplontersen SC 45 mg q4w from Week 37).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		84 weeks not applicable 20 weeks (post-treatment evaluation period)
Hypothesis	Superiority		
Treatments groups	Eplontersen		45 mg eplontersen, SC injection every 4 weeks (q4w) n = 144 (randomized)
	Inotersen-eplontersen		300 mg inotersen for first 34 weeks, SC injection once weekly (q1w) n = 24 (randomized) 45 mg eplontersen from week 37, SC injection q4w
	Historical inotersen (from Study ISIS 420915-CS2)		300 mg inotersen, SC injection n =113 (randomized) Total of 67 doses: Week 1: Days 1, 3 and 5 Weeks 2 to 65: once-weekly
	External Placebo (from Study ISIS 420915-CS2)		placebo, SC injection n= 60 (randomized) Total of 67 doses: Week 1: Days 1, 3 and 5 Weeks 2 to 65: once-weekly
Endpoints and	Co-Primary endpoints	Serum TTR concentration	Percent change from baseline to Week 66

Title: A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy			
Study identifier	ION-682884-CS3 (study code) 2019-001698-10 (EU CT number) NCT04136184 (NCT number) NEURO_TTRansform (other identifier)		
definitions		mNIS+7	Change from baseline to Week 66 in the modified neuropathy impairment score +7 (mNIS+7)
		Norfolk QoL-DN	Change from baseline to Week 66 in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score
	Secondary endpoints	NSC (Week 66)	Change from baseline to Week 66 in the Neuropathy Symptom and Change (NSC) score
		NSC (Week 35)	Change from baseline to Week 35 in the Neuropathy Symptom and Change (NSC) score
		SF-36 PCS	Change from baseline to Week 65 in the Physical Component Summary (PCS) score of the 36-Item Short Form Survey (SF-36)
		PND	Change from baseline to Week 65 in the Polyneuropathy Disability (PND) score
		mBMI	Change from baseline to Week 65 in the modified body mass index (mBMI)
Database lock	Data cut-off: 07-Apr-2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full Analysis Set (FAS)** **Week 66 for Serum TTR, mNIS+7 and Norfolk Qol-DN assessments** **Weeks 35 and 66 for NSC assessment** **Week 65 for SF-36 PCS, PND and mBMI assessments**		
Descriptive statistics and estimate variability	Treatment group	External Placebo	Eplontersen
	Number of subject	59	141
	Serum TTR, g/L (LSM Percent change from baseline)	-11.2%	-81.7%
	Standard Error	1.91	1.61
	mNIS+7 (LSM Percent change from baseline)	25.1	0.3
	Standard Error	2.39	2.41
	Norfolk Qol-DN (LSM Percent change from baseline)	14.2	-5.5
	Standard Error	2.35	2.30
	NSC (Week 66) (LSM Percent change from baseline)	8.2	0.0
	Standard Error	1.0	1.0

Title: A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy			
Study identifier	ION-682884-CS3 (study code) 2019-001698-10 (EU CT number) NCT04136184 (NCT number) NEURO_TTRansform (other identifier)		
	NSC (Week 35) (LSM Percent change from baseline)	4.73	0.79
	Standard Error	0.87	0.87
	SF-36 PCS (LSM Percent change from baseline)	-4.46	0.85
	Standard Error	0.83	0.68
	PND (LSM Percent change from baseline)	0.3	0.1
	Standard Error	0.07	0.07
	mBMI (LSM Percent change from baseline)	-90.8	-8.1
	Standard Error	10.94	10.38
Effect estimate per comparison	**Co-Primary Endpoint: Serum TTR**	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-70.42
		95% CI	-75.17, -65.66
		P-value	<0.00000001
	Co-Primary Endpoint: mNIS+7	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-24.7593
		95% CI	-30.9552, -18.5635
		P-value	<0.00000001
	Co-Primary Endpoint: Norfolk QoI-DN	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-19.7
		95% CI	-25.63, -13.84
		P-value	0.00000001
	Secondary Endpoint: NSC (Week 66)	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-8.21
		95% CI	-10.65, -5.76
		P-value	0.00000001
	Secondary Endpoint: NSC (Week 35)	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-3.94
		95% CI	-6.08, -1.80
		P-value	0.00052447
	Secondary Endpoint: SF-36 PCS	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	5.305
		95% CI	3.195, 7.416
		P-value	0.00000558
	Secondary Endpoint: PND	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	-0.2
		95% CI	-0.4, -0.0
		P-value	0.02407897
	Secondary Endpoint: mBMI	Comparison groups	Eplontersen – external placebo
		Difference in LSMs	82.6991

Title: A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy			
Study identifier	ION-682884-CS3 (study code) 2019-001698-10 (EU CT number) NCT04136184 (NCT number) NEURO_TTRansform (other identifier)		
		95% CI	54.6431, 110.7551
		P-value	0.00000020

2.6.5.3. Clinical studies in special populations

Table 18: Distribution of older subjects enrolled in clinical trials (full analysis set)

Study	**Age 65-74 (Older subjects number/total number)**	**Age 75-84 (Older subjects number/total number)**	**Age 85+ (Older subjects number/total number)**
Placebo-controlled Trials (ISIS 420915-CS2)	16/59 (27.1%) (external placebo) 40/106 (37.7%) (historical inotersen)	9/59 (15.3%) (external placebo) 7/106 (historical inotersen)	0/59 (external placebo) 0/106 (historical inotersen)
Non placebo-controlled trials (ION-682884-CS3)	6/21 (28.6%) (concurrent inotersen) 36/141 (25.5%) (eplontersen)	1/21 (4.8%) (concurrent inotersen) 7/141 (5.0%) (eplontersen)	0/21 (concurrent inotersen) 0/141 (eplontersen)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not Applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant performed analyses across studies ION-682884-CS3 and ISIS 420915-CS2, with the latter serving as the external placebo group of study ION-682884-CS3. The results have been described above in the relevant efficacy section of this assessment report.

In addition the applicant performed, as requested, comparisons between concurrent (from CS3) and historical (from CS2) inotersen.

Table 19: LSM estimates for percent change from baseline in serum TTR concentration, and change from baseline in mNIS+7 composite score and Norfolk QoL-DN total score at week 35 for concurrent inotersen versus historical inotersen: MMRM or MI ANCOVA model with propensity score weighting using on-treatment (full analysis set)

			Comparison of treatment groups				
Group	**n**	**Estimate**	**SE**	**95% CI**	**Estimate**	**95% CI**	**p-value**
Serum TTR concentration (percent change from baseline)							
Concurrent inotersen (N = 21)	20	-69.85	2.757	(-75.31, -64.39)	10.24	(2.89, 17.60)	**0.0068**
Historical inotersen (N = 106)	94	-80.09	2.557	(-85.15, -75.03)			
mNIS+7 composite score (change from baseline)							
Concurrent inotersen (N = 21)	21	4.87	2.088	(0.78, 8.97)	1.11	(-4.41, 6.64)	0.6927
Historical inotersen (N = 106)	106	3.76	2.027	(-0.21, 7.73)			
Norfolk QoL-DN total score (change from baseline)							
Concurrent inotersen (N = 21)	21	-2.64	1.844	(-6.26, 0.97)	-3.12	(-7.91, 1.67)	0.2012
Historical inotersen (N = 106)	105	0.48	1.918	(-3.28, 4.24)			

On-treatment: Post-baseline assessments include assessments on or after the date of first dose of investigational product up to and including 28 (serum TTR concentration) or 52 (mNIS+7 and Norfolk QoL-DN) days following the date of last investigational product dose.

The analysis is performed using MMRM (serum TTR concentration) or MI ANCOVA assuming MAR (mNIS+7 and Norfolk QoL-DN) adjusted by propensity score weights with fixed categorical effects for treatment, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline value.

Only data up to Week 35. Only patients with non-missing covariates are included in the analysis.

The p-value is unadjusted and reflects the 2-sided test of difference in LS means between treatment groups.

CI = confidence interval; MAR = missing at random; MI ANCOVA= multiple imputation analysis of covariance; MMRM = mixed effects model for repeated measures; mNIS+7 = modified Neuropathy Impairment Score +7; N = number of patients in treatment group; n = number of contributing patients; Norfolk QoL-DN = Norfolk Quality of Life – Diabetic Neuropathy; SE = standard error; TTR =transthyretin.

2.6.5.6. Supportive study

Study ION-682884-CS13 is a Phase 3, long-term, open-label extension (OLE) study of ION-682884-CS3 and ISIS 420925-CS101 and therefore does not comprise any control group. The study consists of a ≤ 8-week Screening and Baseline Assessment Period, a 3-year Treatment Period during which all patients receive eplontersen 45 mg once every 4 weeks (Q4W), and a 24-week Post-treatment Evaluation Period.

The primary objective is to evaluate the safety and tolerability of extended dosing with eplontersen in patients with hereditary transthyretin-mediated amyloidosis (ATTRv) with polyneuropathy (ATTRv-PN).

The secondary objective is to evaluate the efficacy of extended dosing with eplontersen.

Patients in ION-682884-CS3 had received either eplontersen or inotersen followed by eplontersen, while patients in ISIS 420915-CS101 had received inotersen. At the time of the 7 April 2023 data cut-off, 108 patients had been enrolled and received Study Drug treatment:

- 91 patients from ION-682884-CS3 who had received eplontersen 45 mg Q4W for the duration of that study ("continuous eplontersen patients")
- 14 patients from ION-682884-CS3 who had received inotersen sodium 300 mg once a week (Q1W) up to and including Week 34 followed by eplontersen 45 mg Q4W from Week 37 ("CS3 switch patients")
- 3 patients from ISIS 420915-CS101 who had received inotersen sodium 300 mg Q1W for 84 months ("prior Investigator Sponsored Inotersen Study [IST] patients")

No analyses of efficacy, PD, or PK were performed for ION-682884-CS13 in data from the 7 April 2023 data cutoff. The study is ongoing.

Summary of results

Eplontersen administration

Most doses of eplontersen (89.2%) were administered using a PFS in autoinjector, while the remaining doses were administered using vial and syringe. No patients used a PFS with a safety device.

Immunogenicity

A total of 10/108 (9.3%) patients were eplontersen ADA positive at Baseline (where Baseline is defined as last assessment prior to first dose of Study Drug in index study ION-682884-CS3 or, for prior IST patients, last nonmissing assessment prior to first dose in ION-682884-CS13). At Baseline for ION-682884-CS13, a total of 40/101 (39.6%) patients were eplontersen ADA positive.

As of the 7 April 2023 data cut-off, the percentage of patients in the continuous eplontersen group (91/108 patients) with eplontersen ADA was 44.0% (40/91) and the percentage of patients with treatment-emergent (from ION-682884-CS3 Baseline) eplontersen ADA was 41.8% (38/91). The median time to onset of treatment-emergent eplontersen ADA in the continuous eplontersen group was 225 days (range 24 to 654) with a median peak titer of 200 (range 50 to 25600). There was no clinically meaningful impact of ADA positivity.

According to the applicant, these results are consistent with index study ION-682884-CS3.

2.6.6. Discussion on clinical efficacy

ATTRv is a rare and rapidly progressing condition and patients ideally should not be left without treatment. In ATTRv amyloidosis, abnormal transthyretin proteins misfold and aggregate into amyloid deposits in peripheral and autonomic nerves and other major organs (e.g., heart, gastrointestinal tract, kidneys, eyes), resulting in progressive dysfunction with declines in quality of life (QoL). Death from complications of amyloid cardiomyopathy or cachexia typically occurs within 3 to 12 years after onset of symptoms, with cardiac involvement associated with particularly poor survival prognosis. Patients with ATTRv-PN have a median life expectancy of 5 to 15 years after diagnosis.

Eplontersen has been developed as a ligand-conjugated ASO, a TTR silencing agent, which degrades hepatic *TTR* mRNA and inhibits human TTR protein synthesis in the liver with the same mechanism of action as inotersen.

The proposed indication for eplontersen is for the treatment of adult patients with PN associated with ATTRv and the proposed dosing regimen is 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) administered by SC injection with an autoinjector monthly.

Design and conduct of clinical studies

The clinical program for eplontersen consisted of one ongoing Phase 3 pivotal study (ION-682884-CS3) and one ongoing Phase 3 Long Term Extension study (ION-682884-CS13), supported by 2 completed Phase I ascending dose studies (ION-682884-CS1 and ION-682884-CS20), and 1 completed Phase I bioequivalence study (ION-682884-CS21).

The Phase 3 pivotal study, ION-682884-CS3 (NEURO-TTRansform, hereafter referred to as CS3 study), is an open-label, externally controlled, randomized (6:1 eplontersen:concurrent inotersen) study, evaluating the efficacy of SC administered eplontersen 45 mg q4w (eplontersen group) versus the external placebo group from the inotersen pivotal study ISIS 420915-CS2 (NEURO-TTR, hereafter referred to as CS2 study) at weeks 35 and 65/66.

The study consisted of a ≤ 10-week screening period and a treatment period of up to 81 weeks. Patients enrolled to the eplontersen group were treated with 45 mg eplontersen subcutaneously (SC) once every 4 weeks (Q4W) up to and including Week 81. Patients in the inotersen group were treated with 300 mg inotersen SC once a week up to and including Week 34 and were then switched to 45 mg eplontersen SC Q4W from Week 37 to Week 81. In addition, all patients were treated with daily supplemental doses of vitamin A. To be eligible to the study, subjects must have been between 18 to 82 years of age with genetically confirmed mutation in the TTR gene, stage 1 or stage 2 symptomatic ATTRv-PN, and with a Neuropathy Impairment Score of 10 to 130. Patients with diabetes mellitus were excluded as diabetic neuropathy may confound the results of ATTRv-PN. The Inclusion and exclusion criteria are supported.

Patients who have completed the study could be enrolled (after EOT assessment at Week 85) in a long-term extension (LTE) study (ION-682884-CS13) and continue to receive eplontersen Q4W. Patients who did not enrol into the LTE study entered a 20-week post-treatment evaluation period for safety monitoring.

CS2 was a well conducted study and it was used as pivotal study for the inotersen application procedure. The use of data from the CS2 study for comparison is considered reasonable considering that treating ATTRv-PN patients with placebo can nowadays be considered unethical. However, some additional information is required. According to the protocol *„the concurrent inotersen reference arm is intended to ensure that no meaningful differences in patient response exist between NEURO-TTR and the current study*" and a descriptive comparison is planned. In order to fully contextualise the results of the CS3 study, it is important to see a comparison between the groups who were administered inotersen in the two studies (CS2 and CS3). The applicant provided a comparison of treatment response between the concurrent inotersen arm and the historical inotersen arm from CS2. Concurrent and historical inotersen presented similar effects regarding the change from baseline at week 35 for important neuropathy measurements (PD: reduction of serum TTR, functional: mNIS+7 composite score and QoL: Norfolk QoL-DN score). The only statistical significant difference (p=0.0068) is in the percent change from baseline in the reduction of serum TTR concentration. However, the lower results in the reduction of serum TTR observed with the concurrent inotersen group (within CS3) should be interpreted with caution due to its small sample size (N=21). The minor differences observed between the two inotersen groups cannot be expected to have any influence on the interpretation of the results and the outcome of the CS3 study and the external comparison. Hence, the same placebo group can be used for the comparisons: inotersen and placebo within CS2 and eplontersen from CS3 and external placebo from CS2.

To address the concern that the open-label design of study CS3 may introduce bias, several measures, esp. blinded assessment of study endpoints were implemented. SAWP recommended conducting a double blind placebo controlled study, an open-label design with a historical placebo group was not

supported. The applicant made efforts to minimize potential bias and differences in the populations included in the pivotal study and a historical control using propensity score weight adjusted models, matching inclusion/exclusion criteria and using the same sites of the study which were used during the study ION-682884-CS2. The applicant's justification for conducting an open label study based on feasibility is acknowledged.

In the case of some exploratory endpoints at Week 85 of the long-term extension study CS13, the external placebo data from the APOLLO study with patisiran were used to perform comparisons between eplontersen and placebo.

No dedicated dose response studies in patients have been conducted. The applicant evaluated 45 mg q4w based on the results of study ION-682884-CS1 in healthy volunteers which showed that administration of 45, 60, or 90 mg q4w resulted in mean serum TTR concentration reductions by Day 99 (2 weeks after the last dose) of 81.3%, 90.8%, and 93.3%, respectively.

Similarities to Amvuttra (vutrisiran) clinical program

A very similar clinical development program, using an external placebo control group from a previous study, was followed for the approval of Amvuttra (vutrisiran), setting a regulatory precedent.

Results on vutrisiran in the pivotal HELIOS-A trial were compared to the placebo group of the APOLLO study that was the pivotal study for patisiran and was conducted in a comparable patient population. A concurrent internal patisiran control arm was included in HELIOS-A for contextualisation of results.

Similarly, in the CS3 study, the main comparison was between eplontersen and the external placebo group from the CS2 study with inotersen. The final placebo-controlled analysis was conducted at Week 66 since there was no external placebo data beyond this timepoint and since it was also recommended during Scientific Advice. A comparison at week 35 only was not recommended by CHMP.

As mentioned above, a comparison of eplontersen with the concurrent active comparator inotersen (within CS3 study) was conducted descriptively after all patients had completed 35 weeks of treatment. In the Week 35 interim analysis, the 2 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 35 and change in mNIS+7composite score from baseline to Week 35) and the key secondary endpoint (change in Norfolk QoL-DN from baseline to Week 35) were analysed.

As stated by the applicant, efforts were made to minimise potential bias and differences in the populations evaluated including using propensity score weight adjusted models, matching inclusion/exclusion criteria, and use of same sites. The applicant justifies this approach by stating that the expected large magnitude of effect with the use of eplontersen would overcome any potential bias inherent to the study design. Furthermore, the inclusion of a concurrent inotersen helped to contextualise the results.

Primary analysis and endpoints

As CHMP has clearly stated during scientific advice that for approval week 66 endpoints are most relevant, change from baseline to week 65/66 in TTR, mNIS+7 and Norfolk QOL-DN are considered pivotal/primary for the current MAA.

For interim and final analysis two different sets of co-primary endpoints were defined:

- interim analysis: percent change from baseline to week 35 in serum TTR concentration and change from baseline to week 35 in mNIS+7 composite score). Additionally, change from baseline to week 35 in Norfolk QoL-DN was tested as a key secondary endpoint.

- final analysis: percent change from baseline to week 65/66 in serum TTR concentration, change from baseline to week 65/66 in mNIS+7 composite score, and change from baseline to week 65/66 in Norfolk QoL-DN total score

Secondary endpoints included assessment of symptom severity (NSC), physical symptoms (SF-36 PCS), nutritional status (mBMI), and PN severity (PND). The secondary and the exploratory endpoints chosen are commonly used in ATTRv-PN patients and meaningful.

Multiplicity control

While the applied multiplicity control strategy may control the type 1 error, the procedure is based on the idea that, from a clinical perspective, it would be sufficient to establish an effect for week 35 endpoints ("week 66 endpoints are not tested when week 35 endpoints are significant"). However, given the results (overall and also for week 65/66 endpoints) and the large effects observed, the study has also established significance for week 66 endpoints across different relevant multiplicity control strategies.

Efficacy data and additional analyses

Inclusion and exclusion criteria and baseline characteristics

A sample size of 140 patients enrolled in CS3 compared to 52 evaluable placebo patients from the inotersen pivotal trial CS2, providing sufficient power to detect treatment differences between eplontersen and external placebo. There was at least 90% power to detect a 19.6-point difference in the change from baseline of the mNIS+7 between eplontersen-treated patients and the ISIS 420915-CS2 placebo patients, with a 2-sided alpha level of 0.025. There was at least 80% power to detect a 10.7-point difference in the change from baseline of the Norfolk QOL-DN between eplontersen-treated patients and the ISIS 420915-CS2 placebo patients, with a 2-sided alpha level of 0.025. A randomisation eplontersen:inotersen of 6:1 with a total of 168 patients was performed. Only a few numbers of patients were excluded from the analysis for the valid reason of not receiving 80% or more of their prescribed doses.

In total 168 patients (144 in the eplontersen group and 24 in the concurrent inotersen [inotersen-eplontersen switch] group) were randomized and received study treatment in ION-682884-CS3 study. 93.8% in the eplontersen group and 83.3% in the concurrent inotersen [inotersen-eplontersen switch] group completed study treatment through Week 66.

A total of 90.3% patients in the eplontersen group and 79.2% patients in the inotersen/eplontersen switch group completed the study treatment period through Week 85. Of note, of the 5 patients who discontinued from inotersen/eplontersen group, 4 discontinued from inotersen treatment and one discontinued from eplontersen treatment. The most frequent reason for discontinuation was AEs or SAEs (12.5% and 5.6% patients in the concurrent inotersen and eplontersen groups, respectively). The vast majority (97%) of the patients included in the study were included in the full analysis set for both analyses at week 35 and week 65/66. This is reassuring.

In general, the population included in the clinical studies is considered representative of the target population with ATTRv-PN based on demographics and baseline disease characteristics. The mean age was 51.4 in the concurrent inotersen group and 52.9 in the eplontersen group with only 8 patients older than 75 years. The age range in the CS2 study was higher with a mean age of 59.4 in the external placebo group and 59.6 in the historical inotersen group.

However, some other baseline imbalances between the eplontersen group in CS3 and the external placebo in CS2 require additional justification. In the ISIS 420915-CS2 study, the majority of patients were enrolled at sites in North America (47.7%) and Europe (34.9%), with the remainder (17.4%)

enrolled in South America/Australasia/Asia. In the ION-682884-CS3 study, the majority of patients were enrolled at sites in South America/Australasia/Asia (46.4%) and Europe (38.1%), with the remainder (15.5%) enrolled in North America. Most of the included subjects were White (78.3% to 93.8% across groups), and approximately 69% were male. With respect to age, all groups in both studies were generally well balanced. The highest proportion of subject included in the eplontersen group was previously treated (with Vyndaqel or diflunisal) – 69.4%, followed by concurrent inotersen group (62.5%), external placebo (60%) and historical inotersen (56.3%). The applicant clarified that due to short half-life of Vyndaqel and Diflunisal, no residual effect should be expected in the study population.

Moreover, there were differences between groups and studies in the proportion of subjects with stage 1 and stage 2. The highest proportion of subjects with stage 1 disease was in the eplontersen group (79.9%), followed by concurrent inotersen (75%), external placebo (70%) and historical inotersen (66.1%). In the eplontersen group, a lower percentage of patients had disease stage 2 (20%) vs 29% for external placebo and the mean Norfolk QoL-DN total score was lower 43.33 (indicating better condition) compared to the external placebo group (48.60). Similarly when looking at the distribution of the PND score, approximately 19% in the eplontersen group corresponded to PND score IIIa and IIIb, whilst this percentage was ~29% of the patients in the external placebo group. With respect to the cardiac involvement, 27% of the patients in the eplontersen group had a clinical diagnosis of FAC (ATTRv-CM = hereditary transthyretin-mediated amyloidosis with cardiomyopathy) whilst more (37.3%) were in the placebo group. Along the same path, the mean level of N-terminal pro b-type natriuretic peptide (NT-proBNP) was approximately 54 pmol/L in the eplontersen group and ~82 pmol/L in the external placebo group, indicating worse heart condition for the patients in the placebo group.

On the other hand, in the eplontersen group the patients appear to be in a worse condition based on serum TTR levels which were higher (0.23g/L) vs external placebo (0.15g/L) and the mNIS+7 and NIS composites scores which were also higher (79.81 and 45.31, respectively) compared to the external placebo (74.12 and 43.40 respectively).

The applicant discussed in their responses the potential impact of these baseline differences, especially in relation to the neurological indices, from the efficacy perspective.

The applicant discussed and concluded that these baseline imbalances do not have an effect on the robustness of the conclusions from study CS3. Some of the baseline values indicate worse heart condition and worse quality of life measurements in the external placebo group, whilst the neurological indices suggest a better condition in comparison to the eplontersen group. Predefined subgroup analyses of the primary endpoints (i.e. difference in LSM percent change in serum TTR concentration, LSM change in mNIS+7 composite score, and LSM change in Norfolk QoL-DN total score) across all prespecified 9 different demographic and disease baseline characteristics based on sex, race, age, region, CM subgroup, previous treatment, Val30Met TTR mutation, disease stage, and ATTRv-CM clinical diagnosis showed consistent statistically significant efficacy of eplontersen vs placebo at week 65.

Consistent efficacy (statistically significant) across all the subgroups analysed was also shown when additional post-hoc subgroup analyses based on additional disease-related baseline characteristics (mNIS+7 composite score, NIS composite score, Norfolk QoL-DN total score, PND score, NYHA classification, and NT-proBNP concentration) was performed.

From the analyses provided, it can be agreed that the baseline differences do not meaningfully impact the overall conclusions on the efficacy of eplontersen and the magnitude of treatment effect is considered large comparatively to potential biases associated with differences in baseline characteristics.

There were also baseline imbalances in the disease characteristics of concurrent inotersen in study CS3 which showed that these patients were in a clearly better condition compared to the eplontersen group. Specifically the patients who received concurrent inotersen had at baseline: a mean serum TTR of 0.21 g/L, a mean mNIS+7 composite score of 65.41, a mean Norfolk QoL-DN total score of 37.97 and 14.3% of them had a PND score of IIIa or IIIb. The respective baseline values for eplontersen were a mean serum TTR of 0.23 g/L, a mean mNIS+7 composite score of 79.81, a mean Norfolk QoL-DN total score of 43.33 and 17.8% of them had a PND score of IIIa or IIIb. However, since these differences were not in favour of eplontersen there is no issue identified for the comparison of concurrent inotersen and eplontersen.

Endpoints, efficacy data and statistical methods

The main comparison in the clinical program was between eplontersen in CS3 study and external placebo group from CS2 study.

In the Week 66 final analysis, the 3 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 65, change in mNIS+7 composite score from baseline to Week 66, and change in Norfolk QoL-DN total score from baseline to Week 66) were analysed. It is noted that serum TTR concentration is not a validated surrogate endpoint for clinical outcomes. Nevertheless, since co-PEP included evaluation of clinical outcomes, the PEPs are supported.

Efficacy results

Primary analysis

Eplontersen was found superior to external placebo for all primary efficacy endpoints in the Week 35 interim analysis, with sustained effects observed in the Week 66 final analysis:

- Percentage change in serum TTR concentration:
    - At Week 35: -66.64% (95% CI: -71.61, -61.53)
    - At Week 65: -70.14% (95% CI: -75.02, 65.15)
- Change in mNIS+7 composite score:
    - At Week 35: -8.8 (95% CI: -13.21, -4.34)
    - At Week 66: -23.1 (95% CI: -29.26, -17.01)
- Change in Norfolk QoL-DN total score:
    - At Week 35: -11.3 (95% CI; -16.26, -6.30)
    - At Week 66: -19.3 (95% CI; -24.99, -13.53)

It is acknowledged that the treatment effects of eplontersen observed for all three primary endpoints (pharmacodynamic, functional and QoL) in study ION-682884-CS3 are large.

At the Week 35 Interim Analysis co-primary endpoints were met. However, since all 3 corresponding endpoints were statistically significant (p-value < 0.025) at the interim analysis (at Week 35), the applicant did not conduct a formal statistical testing within the prespecified testing strategy at Week 66. The efficacy results obtained for all three co-primary endpoints at week 65/66 were in favour of eplontersen treatment with clear and large differences compared to the external placebo group. Similarly the effect observed with the two co-primary and one secondary endpoints at week 35 was large. At Week 65, the LSM percent change from baseline in serum TTR concentration was -81.7% in the eplontersen group and -11.2% in the external placebo group, with an LSM difference (eplontersen – external placebo) of -70.4%. At Week 66, the LSM change from baseline was 0.3 in the eplontersen

group and 25.1 in the external placebo group, with an LSM difference (eplontersen – external placebo) of -24.8.

Superiority of eplontersen to external placebo was shown for the the co-primary endpoint change in Norfolk QOL-DN total score from baseline to Week 35 ($p < 0.001$), with an increased benefit relative to external placebo at Week 66 and effect maintained through Week 85. At Week 66, the LSM change from baseline was -5.5 in the eplontersen group and 14.2 in the external placebo group, with an LSM difference (eplontersen – external placebo) of -19.7.

In a responder analysis conducted to examine the difference in response between the 2 treatment groups over a range of thresholds from -2 to 10 points, the response rate in the eplontersen group was consistently higher than that of the placebo group over all thresholds evaluated (-2 to 10-point increase), with an approximate 2.4 to 3.2-fold difference observed between the eplontersen and placebo groups at each threshold. Of note, 47.2% of eplontersen-treated patients showed improvement in neuropathy, as measured by mNIS+7 compared with 16.7% of placebo-treated patients.

The observed large effects together with the mechanism of action, the target engagement and a clear and large pharmacodynamic effect on the TTR levels are quite reassuring for the efficacy of eplontersen in patients with stage 1 or stage 2 ATTRv-PN, as this was measured by mNIS+7 composite score and in Norfolk QoL-DN total score. However, the population studied in the pivotal CS3 study does not correspond to the proposed broad indication initially applied for. The applicant argued that, while the pivotal study (CS3) only included patients with stage 1 and stage 2, there is no apparent biological rationale for why patients with more severe disease (ie, stage 3 - bedridden or wheelchair bound) would not benefit from the eplontersen mechanism of action as seen by the consistency of the serum TTR concentration reductions and clinical benefits across various levels of severity. Based on the mechanism of action, it can be agreed that there is biological plausibility that patients with stage 3 could benefit from the reduction of TTR and amyloid deposition. The unmet medical need for patients with ATTRv and stage 3 polyneuropathy can definitely be acknowledged. The argumentation of the applicant in their responses can be followed and efficacy could be extrapolated to patients with stage 3 polyneuropathy. However, there were no FAP stage 3 patients recruited and any potential benefit in these bedridden or wheelchair bound patients has not been evaluated up to now.

The applicant clarified that there are currently data only from 3 patients who were included in the epolontersen arm and received 45mg Q4W and progressed to stage 3 (PND score IV) polyneuropathy during the course of the study ION-682884-CS3. The fact that 2 out of 3 patients who progressed to stage 3 disease, improved again is acknowledged. It is welcomed that the applicant is committed to collect data in stage 1 to 3 polyneuropathy patients through an ongoing registry study (MaesTTRo).

Despite that the data from the applicant and relevant publications are very limited (Ungerer et al, 2020 and Dohrn et al, 2021), the mechanism of action and the target engagement of eplontersen could justify extrapolation from stage 1 or 2 patients to stage 3. Furthermore patients who progress to stage 3 should be allowed to receive treatment.

The applicant also committed to collect data in Stage 1 to 3 polyneuropathy patients through an ongoing registry study (MaesTTRo).

MaesTTRo is an ongoing, prospective, international, longitudinal, non-interventional study of adult patients with ATTR. The study aims to enroll a global cohort of patients with ATTR to longitudinally observe the natural course of the disease and describe real-world treatment patterns and outcomes. In addition, the study will examine effectiveness and collect all SAEs regardless of ATTR treatment including eplontersen. The study plans to enrol a minimum of 1,600 patients with ATTR, including a minimum of 1,500 patients with ATTRv-CM, and a minimum of 100 patients with ATTRv-PN. The

enrolment period is expected to last approximately 4 years, with a follow-up duration of at least 3 years and up to 7 years depending on the enrolment date of each patient. Participating countries include Canada, Germany, Spain, United Kingdom, and US. The first patient was enrolled on 25 June 2024.

The input of the SAG-N experts did not favour extrapolation from stage 1 or 2 to stage 3 PN patients, due to the lack of sufficient evidence (please see below).

Hence, the wording of the indication was further discussed at CHMP and an Oral Explanation took place. The outcome was the restriction of the indication to patients with stage 1 or stage 2 polyneuropathy. The following phrase was agreed to be included in section 4.2 Posology: "*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*".

Secondary and exploratory endpoints

The results from the secondary and additional and exploratory endpoints are all supportive of the primary analysis.

Neuropathy Symptoms and Change Score (NSC) at both Week 66 and Week 35, showed that there was very little change in NSC score from baseline in the eplontersen group compared with an increase in NSC score in the placebo group. At Week 66, the LSM change from baseline was -0.03 in the eplontersen group and 8.2 in the external placebo group, with a difference (eplontersen – external placebo) of -8.2 ($p < 0.001$). At Week 35, the LSM change from baseline was 0.8 in the eplontersen group and 4.7 in the external placebo group, with an LSM difference (eplontersen – external placebo) of -3.9 ($p = 0.0005$). The mean change from baseline in NSC score remained stable through Week 85 in the eplontersen group.

Eplontersen showed superiority to external placebo for the change from baseline in SF-36 PCS score at Week 65. At Week 65, only a slight increase in SF-36 PCS score in the eplontersen group compared to a decrease in the external placebo group. At Week 65, the LSM change from baseline was 0.851 in the eplontersen group and -4.455 in the external placebo group, with a difference (eplontersen – external placebo) of 5.305 ($p < 0.001$).

Eplontersen showed superiority to external placebo for the change from baseline in Polyneuropathy Disability Score (PND) at Week 65. At Week 65, the LSM change from baseline was 0.1 in the eplontersen group and 0.3 in the external placebo group, with a difference (eplontersen – external placebo) of -0.2 ($p = 0.024$).

Superiority of eplontersen to external placebo was shown for the change from baseline in mBMI at Week 65. At Week 65, the LSM change from baseline was -8.0655 in the eplontersen group and -90.7645 in the external placebo group, with a difference (eplontersen – external placebo) of 82.6991 ($p < 0.001$).

A number of sensitivity analyses were also supportive of the favourable results of the primary analyses.

Estimand and primary and sensitivity analyses

While no estimand was specified in the protocol or SAP, the applicant confirmed that the primary estimand targets the effect of eplontersen treatment compared to placebo had no treatment discontinuations occurred regardless of changes in vitamin A intake or other changes in hATTR treatment. While the primary MMRM analysis adjusted by propensity score weights, based on the missing at random assumption and including only on-treatment data is aligned to the primary estimand, in line with CHMP advice this estimand based on a hypothetical strategy for treatment

discontinuations is considered less relevant from a regulatory perspective. Instead an estimand based on the treatment policy strategy targeting the effect of eplontersen treatment compared to placebo regardless of any changes in treatment such as discontinuations, changes in vitamin A intake or initiation of other hATTR treatment is considered of highest relevance.

While, overall, the conducted sensitivity analyses cover relevant aspects (alternative missing data handling, additional covariates, etc.), some of the sensitivity analyses are better aligned to the more relevant estimand; in particular sensitivity analyses 3 (CR) and 4 (J2R) applying placebo based multiple imputation. In this regard inclusion of data collected after last intake of treatment (i.e. analysis based on on-study data) is also of particular importance. In their responses, the applicant clarified that for mNIS+7 and Norfolk sensitivity analyses 3 and 4 for week 66 were based on on-treatment data only and consequently provided results of these analyses based on on-study data. No major differences were observed, providing reassurance for the outcome of the study.

Overall few discontinuations occurred and the primary as well as the sensitivity analyses yield similar results. Initially sensitivity analysis 4 (J2R) was considered the most conservative and most appropriate analysis, whose findings should be reported in the SmPC. However, the applicant provided argumentation against reporting results of the J2R analysis (sensitivity analysis 4), which can be followed. According to the applicant, J2R is not an appropriate assumption for missing data when patients continue treatment. Furthermore, the assumptions of J2R are not biologically plausible even for patients discontinuing treatment considering the mechanism of action and the long-lasting effects of eplontersen, which support a monthly dosing schedule. The applicant proposes to report results of a modified CIR based multiple imputation analysis applied to only those missing data following treatment discontinuation for mNIS+7 and Norfolk in the SmPC. This analysis is also aligned to the treatment policy estimand considered to be the estimand of highest relevance.

Based on the available results of the primary analyses and different placebo-based imputation approaches (see Table 16 above), it is apparent that differences in results are only minor and do not impact clinical interpretation. This is supported by the fact that only few patients (n=8) discontinued eplontersen treatment prior to week 66 and had missing week 66 data. Reporting of CIR analysis is consequently supported although there are also some issues with biological plausibility. CIR assumes the effect achieved until treatment discontinuation to be maintained. To avoid any potential confusions for the prescriber by referring to different approaches for the analyses of the primary endpoints TTR, mNIS+7 and Norfolk QoL-DN, the results of only the CIR approach are included in the SmPC. Due to the complexity of the issues with the biological plausibility, it is mentioned in the SmPC that only a reference-based multiple imputation approach (reference=placebo) for the missing data was used. This is considered sufficient as all reference-based multiple imputation approaches yield very similar results and differences between results are minor to have any meaningful clinical impact.

Comparison of eplontersen and concurrent inotersen in CS3 study

Although the main comparison in study CS3 was between eplontersen and external placebo, data from this study (CS3) suggest, according to the applicant, that eplontersen offers several clinically relevant efficacy advantages over inotersen.

As anticipated, the inclusion of patients receiving inotersen in CS3 study (concurrent inotersen) provided reassurance of the eplontersen effect but due to the small size of inotersen group any differences should be interpreted with caution.

Despite that the baseline disease characteristics of concurrent inotersen in study CS3 showed that these patients were in a clearly better condition compared to the eplontersen group, concurrent inotersen and eplontersen achieved similar large reductions in TTR. The mean TTR reduction from

baseline at Week 35 for eplontersen was 82.13% (SD: 11.66), which was numerically greater than the mean reduction seen with concurrent inotersen i.e, 74.26% (SD: 23.28).

Formal comparisons between eplontersen and concurrent inotersen have not been performed, but differences in the neurological index and quality of life have been observed between these molecules indicating potential better target engagement and greater benefit from eplontersen treatment over inotersen. The change from baseline at Week 35 for mNIS+7 achieved by concurrent inotersen was +4.06 (SD: 13.39) (consistent with further deterioration) and for Norfolk QoL-DN was -2.97 (SD: 12.09), whilst in the case of eplontersen these values were -0.04 (SD: 16.22) and -4.79 (SD: 16.51), respectively. Comparisons beyond week 35 are not available since patients receiving concurrent inotersen were switched to eplontersen.

A Table providing an overview of the results from various active substances approved for the treatment of ATTRv-PN and eplontersen was constructed using the EPARs for these substances and the CSR from the inotersen CS2 (NEUTO-TTR) study. Comparison of these results suggest that the effect of eplontersen is larger than that of inotersen (with 75% less administrations) and comparable to the effects of vutrisiran. Vutrisiran is the latest active substance approved for patients with stage 1 or stage 2 ATTRv-PN. This comparison provides further reassurance regarding the robustness of the observed effect of eplontersen.

The small concurrent inotersen treatment arm was included in study CS3 to assess whether response to treatment is similar to that observed in study CS2 supporting the use of CS2's placebo arm as an external control. Concurrent and historical inotersen presented similar efficacy in the change from baseline at week 35 for important neuropathy measurements (PD: reduction of serum TTR, functional: mNIS+7 composite score and QoL: Norfolk QoL-DN score). A difference between historical and concurrent inotersen observed in the reduction of serum TTR should be interpreted with caution due to the small sample size of concurrent inotersen within CS3 (N=21). Any minor differences observed between the two inotersen groups cannot be expected to have any influence on the interpretation of the results and the outcome of CS3 study. Hence, for the comparisons: inotersen and placebo within CS2 and eplontersen from CS3 and external placebo from CS2, the same placebo group from CS2 can be used. The results of the CS3 study can be considered reliable.

Supportive study CS13

The supportive study ION-682884-CS13 is a Phase 3, long-term extension, open-label extension (OLE) study of ION-682884-CS3 and ISIS 420925-CS101 and does not comprise any control group. The study consists of a $\leq$ 8-week Screening and Baseline Assessment Period, a 3-year Treatment Period during which all patients receive eplontersen 45 mg once every 4 weeks (Q4W), and a 24-week Post-treatment Evaluation Period.

No unexpected findings have been recorded up to now with the study CS13 and the results are consistent with the pivotal trial CS3.

Additional expert consultation

The SAG-Neurology, enriched with amyloidosis experts, has been convened:

FINAL SAG NEUROLOGY ANSWERS FOR WAINZUA

1. **Do the experts consider extrapolation of efficacy from patients with stage 1 or 2 PN to patients with stage 3 PN possible (based on the arguments provided by the applicant)?**

The SAG experts agree that the mechanism of action would be the same for stage 3 hATTR related PN and hence, the reduction of serum TTR concentration is expected also to occur in stage 3 hATTR related PN. However, the SAG-N experts considered that the issue at discussion is whether this serum TTR concentration reduction could be translated into clinical benefit(s) considering the substantial neuronal damage already present in stage 3 hATTR related PN.

The SAG-N members agreed that without any data available on stage 3 hATTR related PN it is not possible to know the efficacy of Eplotersen in these patients.

According to majority of the SAG-N experts, data on patients in stage 3 hATTR related PN – even if only exploratory and/or observational in nature- would have been needed to support the use in stage 3 hATTR related PN. Specifically with regard to autonomic dysfunction, data are limited. It was also pointed out by a SAG-N expert that it might have been difficult to observe clinical effects in stage 3 hATTR related PN with the efficacy scales included as co-primary endpoints in the pivotal trial. Ceiling effects may affect assessment using these instruments. In connection with this argument, it was also pointed out by the SAG-N experts that what constitutes a clinical benefit in early stages may not be the same in late stages making the exercise of extrapolation even more difficult in this scenario. Those patients who are wheelchair-bound or bedridden may value other outcomes than which were measured in the study. Moreover, 80% of patients in the study were stage 1 hATTR related PN, making it even more difficult to extrapolate the results to stage 3 hATTR related PN.

The patient's representative noted that there is a huge unmet medical need for stage 3 hATTR related PN. Accordingly, any medicinal product capable to prevent progression in stage 3 hATTR related PN would be welcome. Specifically, the patient's representative noted that patients in stage 3 hATTR related PN continue to progress from aspects other than walking as for example autonomic dysfunction (e.g. diarrhea) that could be very invalidating from a quality-of-life perspective.

2. **What are the expected benefits of reducing TTR levels in patients with stage 3 PN?**

The SAG-N agreed that the medicinal product is expected to reduce serum TTR concentration also in stage 3 hATTR related PN. However, SAG-N experts considered that the expected benefits of reducing TTR levels in patients with stage 3 hATTR related PN are unknown considering that there are no clinical data in stage 3 hATTR related PN. Indeed, the SAG-N experts highlighted that no participants with stage 3 hATTR related PN were included in the pivotal clinical trial. In connection with the answer to the first question, the SAG-N experts questioned whether there is any rescuable neuronal function, related to large sensory and motor fibers, in stage 3 hATTR related PN.

From a purely theoretical point of view, potential benefits from a medicinal product efficacious on stage 3 hATTR related PN could be a prolongation in the time from wheelchair-bound status to bedridden status, maintenance of upper limb function and/or an effect on autonomic dysfunction. There is no currently available data supporting benefit(s) in these aspects, except for COMPASS 31 stabilization as an exploratory endpoint.

The patient's representative acknowledged the above statements but also highlighted that the staging definition is debatable and there may be some misclassification across stages. It was, however, considered that misclassification at stage 3 hATTR related PN can be considered minimal.

3. **Do the experts consider extrapolation of the safety profile observed in patients with stage 1 or 2 PN possible to patients with stage 3 PN? Are there areas of concern or major uncertainties that need to be further investigated?**

The SAG-N experts are also concerned on the extrapolability of safety data from stages 1 and 2 hATTR related PN to stage 3 hATTR related PN because of two main scientific arguments.

First, patients in stage 3 hATTR related PN are a more vulnerable population because the hATTR – that is a multi-systemic disease- is more advanced and more patients may have other organ involvement. Patients in stage 3 hATTR PN are older and may have more comorbidities (i.e. other conditions) and subsequent polytherapy that may affect the condition and the inherited risk of the medicinal product. Also, the consequences of the severe PN itself, including bedsores and an increased risk of DVT may impact how adverse events affect patients.

Second, the uncertainty about the long-term use is higher in stage 3 hATTR related PN because these patients would be treated for a longer time period.

These two sources of uncertainty are interconnected. To illustrate this, the SAG-N experts noted the proteinuria as adverse event of Wainzua. As a multisystemic disease, hATTR may affect kidney preferably in later stages. Further, renal function is decreasing with age (regardless of any disease), a function that could be further deteriorated by other conditions or other medicinal products. The current data do not support that renal deterioration progress over the time but there is no long-term safety data. Another example would be effects of Eplontersen on the eye. Despite oral supplementation, one of the most frequent adverse events is Vitamin A deficiency, which is related to the mechanism of action itself. This condition, together with the high specificity of Eplotersen for the liver target and with the disease progression, could lead to ocular impairment in the late stage. In fact, the ocular synthesis of TTR could not be addressed by Eplotersen and ocular impairment is a typical time-dependant involvement of hereditary ATTR.The patient's representative claimed that Eplotersen seems to have a reasonably good safety profile but ultimately agreed on the above statements and the overall conclusion that extrapolation of safety data to stage 3 hATTR PN is not possible.

Assessment of paediatric data on clinical efficacy

Not Applicable

Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances

Not Applicable

2.6.7. Conclusions on the clinical efficacy

The mechanism of action and the target engagement of eplontersen, a ligand-conjugated ASO administered by subcutaneous injection every 4 weeks, has led to a large and robust pharmacodynamic effect corresponding to reductions of TTR. Large effects in appropriate clinical endpoints have been observed for eplontersen with clear differences compared to external placebo. The initially proposed broad wording of the indication does not reflect the population studied, which comprised patients suffering from ATTRv with stage 1 or stage 2 polyneuropathy. An updated wording was currently proposed, which is acceptable:

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

2.6.8. Clinical safety

The body of the integrated eplontersen safety database in patients with ATTRv amyloidosis with polyneuropathy is based on the ongoing open-label pivotal Phase 3 ION-682884-CS3 study, and its ongoing long-term open-label extension ION-682884-CS13 up to the data cut-off (DCO) 07 April 2023.

Safety data for eplontersen are presented as per the following data sets: comparison of eplontersen versus external placebo/ historical inotersen group with up to Week 66 data (based on ION-682884-CS3 and ISIS 420915-CS2), Week 85 + safety data (additional safety data from patients with completion of the 84-week treatment period in ION-682884-CS3), and data from the pooled analysis using the eplontersen Treated Set (pooled eplontersen data from study CS3 and CS13 [N=167 in total], including the eplontersen 45 mg q4w group [N=144], inotersen 300 mg q1w/eplontersen 45 mg q4w group [N=20], and the IST eplontersen 45 mg q4w group originating from study CS101 [N=3]). The up to Week 66 data from study CS3 form the primary set of the safety comparison to external placebo [N=60] (and historical inotersen [112 patients were dosed]).

The small short-term concurrent inotersen group (N=20) in study CS3 with treatment from Week 1 to Week 34 was primarily intended to provide a descriptive comparison with the historical inotersen group from ISIS 420915-CS2 aiming that no meaningful differences occur between the populations or treatment response between the studies. Thus, concurrent inotersen safety data were only presented for AESI in the Summary of Clinical Safety (SCS). Patients treated with concurrent inotersen had the first eplontersen injection at Week 37 and continued up to the end of the treatment period.

Long-term safety derives from the Eplontersen Treated Set, which includes patients treated continuously with eplontersen from study CS3 to CS13. Supportive data are provided from three completed Phase 1 studies of eplontersen in healthy volunteers (ION-682884-CS1, ION-682884-CS20, and ION-682884-CS21) for a total of 114 patients (14 patients received placebo), which have been summarised individually given the lower number of doses and shorter duration of exposure.

2.6.8.1. Patient exposure

Up to Week 66 (Eplontersen Versus External/Historical Control Groups)

A total of 144 patients had received at least one dose of eplontersen with the mean duration of exposure to eplontersen up to Week 66 (Day 456) being 443.5 days. Mean duration of exposure for eplontersen compared to 418.5 days in the external placebo group and 384.8 days in the historical inotersen group. 137 of 144 patients (95.1%) received eplontersen for ≥ 12 to < 24 months. 24.3% of patients in the eplontersen group had at least one dose pause or missed dose compared to 38.3% and 52.7% of patients in the external placebo and historical inotersen group. Of note, 79.2% of patients in the concurrent inotersen group had dose interruption(s) up to the switch to eplontersen at Week 37.

Discontinuation of study treatment prior to study Day 456 occurred in 5.6% of patients on eplontersen, 16.7% of patients in the concurrent inotersen group, and in 13.3% and 23.0% of patients from the historical placebo and inotersen groups, respectively. The main reason for discontinuation from treatment was AE/ SAE in either of the treatment groups, except for placebo.

Eplontersen 45 mg q4w group of ION-682884-CS3 (Week 85+)

A total of 144 patients had received at least one dose of eplontersen with the mean duration of exposure to eplontersen at Week 85+ being 540.8 days; 137 of 144 patients (95.1%) received eplontersen for ≥ 12 to < 24 months.

Eplontersen Treated Set

A total of 167 patients received at least one dose of eplontersen. Mean exposure to eplontersen was 627.7 days. 102 patients (61.1%) had received eplontersen for ≥ 12 to < 24 months, 47 (28.1%) patients for ≥ 24 to < 36 months, and 2 patients had a duration of exposure of ≥ 36 to < 48 months. The highest recorded duration of exposure to eplontersen was 1134 days (~3.4 years). 26.9% of patients had at least one dose pause or missed dose.

104 of 108 patients treated with eplontersen in study ION-682884-CS13 were continuing eplontersen treatment in the study at the time of the DCO, while 4 patients discontinued (three of them due to SAEs/ stopping criteria met).

2.6.8.2. Adverse events

An overview of adverse events up to the data cut-off 07 April 2023 reported during study CS3 for eplontersen (up to Week 66 and during the 84-week treatment period) as well as combined for studies CS3 and CS13 (Eplontersen Treated Set) compared to external placebo and historical inotersen groups in ISIS 420915-CS2 is presented in Table 20.

Table 20: Overview of adverse events (safety set)

	Up to Week 66 [a]			On Study [b]	
	ISIS 420915-CS2		ION-682884-CS3	ION-682884-CS3	Eplontersen Treated Set (N =167 [d])
Adverse Events Categories, n (%)	**Placebo (N=60)**	**Inotersen 300 mg q1w (N=112)**	**Eplontersen 45 mg q4w [c] (N=144)**	**Eplontersen 45 mg q4w (Week 85 +) [c] (N=144)**	
Any TEAE [e]	**60 (100)**	**111 (99.1)**	**140 (97.2)**	**141 (97.9)**	**163 (97.6)**
TEAEs related to study drug [f]	23 (38.3)	88 (78.6)	53 (36.8)	55 (38.2)	61 (36.5)
TEAEs leading to discontinuation of study drug including death	2 (3.3)	16 (14.3)	6 (4.2)	8 (5.6)	11 (6.6)
TEAEs leading to withdrawal from study	1 (1.7)	7 (6.3)	4 (2.8)	7 (4.9)	8 (4.8)
TEAEs leading to dose reduction	0	3 (2.7)	0	0	0
TEAEs leading to dose interruption (stop/delay)	3 (5.0)	27 (24.1)	12 (8.3)	15 (10.4)	18 (10.8)
TEAEs of special interest [g]	12 (20.0)	45 (40.2)	41 (28.5)	43 (29.9)	50 (29.9)
Leading to discontinuation of study drug including death	0	4 (3.6)	0	0	1 (0.6)
Leading to withdrawal from study	0	1 (0.9)	0	0	0
Other TEAEs of interest [h]	47 (78.3)	102 (91.1)	87 (60.4)	93 (64.6)	111 (66.5)
Leading to discontinuation of study drug including death	1 (1.7)	9 (8.0)	5 (3.5)	6 (4.2)	8 (4.8)
Leading to withdrawal from study	1 (1.7)	3 (2.7)	3 (2.1)	5 (3.5)	6 (3.6)
TEAEs by maximum severity [i]					
Mild	7 (11.7)	20 (17.9)	74 (51.4)	64 (44.4)	72 (43.1)
Moderate	40 (66.7)	61 (54.5)	53 (36.8)	57 (39.6)	65 (38.9)
Severe	13 (21.7)	30 (26.8)	13 (9.0)	20 (13.9)	26 (15.6)
Any serious AE	12 (20.0)	36 (32.1)	22 (15.3)	28 (19.4)	37 (22.2)
Serious TEAEs	12 (20.0)	36 (32.1)	21 (14.6)	27 (18.8)	34 (20.4)
Related to study drug	1 (1.7)	8 (7.1)	0	0	0
Leading to discontinuation of study drug including death	0	11 (9.8)	4 (2.8)	5 (3.5)	8 (4.8)
Leading to withdrawal from study	0	7 (6.3)	4 (2.8)	6 (4.2)	7 (4.2)
Fatal AEs	0	4 (3.6)	2 (1.4)	3 (2.1)	6 (3.6)
Fatal TEAEs	0	4 (3.6)	2 (1.4)	3 (2.1)	6 (3.6)
Fatal TEAEs related to study drug	0	1 (0.9)	0	0	0

a-d: see previous table.
e: TEAE is defined as an AE that first occurred or worsened after the first dose of study drug.
f: Related includes "related," "possible," and missing relationship.
g: TEAEs of special interest include ocular AEs potentially related to vitamin A deficiency, thrombocytopenia, and glomerulonephritis.
h: Other TEAEs of interest include coagulation abnormalities, renal impairment, abnormal liver function, adverse events at the injection site, flu-like symptoms, CNS disorders, haemorrhages, cardiac disorders, and reduced thyroxine.
i: Patients reporting more than one TEAE are counted only once using the worst severity reported.

Common adverse events

Up to Week 66, SOCs with an incidence of TEAEs > 5% 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. The incidence of TEAEs under these SOCs was lower in the eplontersen group as compared to historical inotersen.

The most frequently reported TEAEs in the eplontersen group (>5%, in study CS3; see also Table 21) were *COVID-19, urinary tract infection (UTI), diarrhoea, Vitamin A deficiency, nausea, vomiting, immunisation reaction, oedema peripheral, proteinuria, dizziness, pain in extremity, headache, arthralgia, vision blurred, nasopharyngitis, fall, and upper respiratory tract infection*. The only TEAEs in the eplontersen group that occurred with an incidence of ≥5% of patients and at least ≥2% higher compared to the external placebo group were *COVID-19, vitamin A deficiency, vomiting, immunisation reaction, proteinuria, and vision blurred* (included in Table 21 and shaded in grey).

There was no increased incidence in TEAEs during longer treatment duration with eplontersen as indicated in the eplontersen Treated Set, except for COVID-19.

Adverse events by severity

TEAEs were mainly mild or moderate in the eplontersen group up to Week 66 (Table 20), and more frequently moderate or severe in the external placebo and historical inotersen group. Severe TEAEs were less frequent with eplontersen compared to external placebo (9.0% vs. 21.7%). The only severe TEAE reported in >1 patient on eplontersen was vomiting (2 patients). Renal impairment was severe in a single patient on eplontersen. The SOC with the highest incidence of severe TEAEs in the Eplontersen Treated Set was cardiac disorders (6%). Severe TEAEs reported in > 1 patient in the Eplontersen Treated Set were vomiting (3 patients) and UTI (2 patients). Thrombocytopenia was rated as severe in a single patient on eplontersen. None of the severe events was rated as related to eplontersen.

Adverse Events by Time since First Administration of Study Drug

The highest rate of TEAEs was reported during the first 6 months of treatment with eplontersen (and also for external placebo and historical inotersen) and was lower thereafter. Thrombocytopenia was reported in the first 6 months of treatment in a single patient only. Proteinuria was reported more frequently between 12 and 24 months of treatment.

Study drug related adverse events

The incidence of TEAEs assessed as related to study drug was similar for eplontersen and external placebo (36.8% vs. 38.3%) up to Week 66, and lower as compared to historical inotersen (78.6%). The only study drug related TEAE reported in ≥ 10% of patients in the eplontersen group was vitamin A deficiency (11.8%). Other study drug related TEAEs in the eplontersen group were (in descending order): injection site pain (3.5%), injection site erythema, injection site pruritus, nausea, and headache (each in 2.1% of patients), and fatigue, chills, and thrombocytopenia (each in a single patient). None of the study drug related TEAEs were reported as SAEs in the eplontersen group. No increased incidences in study drug related TEAEs were noted in the Eplontersen Treated Set.

Table 21: TEAEs by PTs reported in ≥ 10% of patients in any treatment group (safety set) and TEAEs with a ≥5% incidence in the eplontersen group (up to week 66) and ≥2% higher incidence in the eplontersen group (up to week 66) than in the external placebo group (up to week 66) by PTs (safety set) (shaded in grey)

	Up to Week 66 [a]						On Study [b]			
	ISIS 420915-CS2				ION-682884-CS3		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)		Eplontersen 45 mg q4w (Week 85 +) [c] (N=144)			
Preferred Term	Patients n (%)	Events N (Rate [e])	Patients n (%)	Events N (Rate [e])	Patients n (%)	Events N (Rate [e])	Patients n (%)	Events N (Rate [e])	Patients n (%)	Events N (Rate [e])
COVID-19 [f]	0	0	0	0	35 (24.3)	36 (20.21)	48 (33.3)	50 (20.72)	60 (35.9)	62 (20.2)
Urinary tract infection	10 (16.7)	12 (16.69)	20 (17.9)	41 (32.25)	24 (16.7)	41 (23.02)	28 (19.4)	52 (21.55)	36 (21.6)	74 (24.1)
Diarrhoea	11 (18.3)	14 (19.47)	26 (23.2)	28 (22.02)	24 (16.7)	28 (15.72)	28 (19.4)	33 (13.67)	33 (19.8)	39 (12.7)
Vitamin A deficiency [g]	0	0	0	0	17 (11.8)	17 (9.55)	17 (11.8)	17 (7.04)	18 (10.8)	19 (6.2)
Nausea	7 (11.7)	9 (12.52)	35 (31.3)	42 (33.03)	16 (11.1)	21 (11.79)	16 (11.1)	21 (8.70)	17 (10.2)	22 (7.2)
Vomiting	3 (5.0)	3 (4.17)	17 (15.2)	21 (16.52)	12 (8.3)	23 (12.91)	13 (9.0)	28 (11.60)	16 (9.6)	31 (10.1)
Oedema peripheral	5 (8.3)	5 (6.95)	21 (18.8)	22 (17.30)	12 (8.3)	14 (7.86)	13 (9.0)	15 (6.22)	15 (9.0)	17 (5.5)
Dizziness	6 (10.0)	6 (8.35)	13 (11.6)	14 (11.01)	10 (6.9)	11 (6.18)	11 (7.6)	12 (4.97)	12 (7.2)	13 (4.2)
Pain in extremity	8 (13.3)	12 (16.69)	9 (8.0)	11 (8.65)	9 (6.3)	11 (6.18)	9 (6.3)	11 (4.56)	11 (6.6)	13 (4.2)
Headache	7 (11.7)	10 (13.91)	25 (22.3)	33 (25.95)	9 (6.3)	10 (5.61)	9 (6.3)	10 (4.14)	13 (7.8)	14 (4.6)
Arthralgia	5 (8.3)	7 (9.74)	15 (13.4)	22 (17.30)	9 (6.3)	9 (5.05)	10 (6.9)	12 (4.97)	14 (8.4)	21 (6.9)
Nasopharyngitis	6 (10.0)	7 (9.74)	9 (8.0)	9 (7.08)	8 (5.6)	11 (6.18)	10 (6.9)	13 (5.39)	10 (6.0)	13 (4.2)
Fall	13 (21.7)	16 (22.26)	19 (17.0)	26 (20.45)	8 (5.6)	9 (5.05)	10 (6.9)	13 (5.39)	12 (7.2)	17 (5.5)
Fatigue	12 (20.0)	14 (19.47)	28 (25.0)	41 (32.25)	7 (4.9)	8 (4.49)	8 (5.6)	9 (3.73)	11 (6.6)	15 (4.9)
Cough	8 (13.3)	8 (11.13)	10 (8.9)	11 (8.65)	7 (4.9)	7 (3.93)	8 (5.6)	8 (3.32)	11 (6.6)	11 (3.6)
Syncope	2 (3.3)	2 (2.78)	12 (10.7)	25 (19.66)	7 (4.9)	7 (3.93)	7 (4.9)	8 (3.32)	7 (4.2)	9 (2.9)
Thermal burn	6 (10.0)	6 (8.35)	6 (5.4)	6 (4.72)	6 (4.2)	8 (4.49)	6 (4.2)	8 (3.32)	8 (4.8)	10 (3.3)
Anaemia	1 (1.7)	1 (1.39)	15 (13.4)	16 (12.58)	6 (4.2)	6 (3.37)	7 (4.9)	8 (3.32)	8 (4.8)	10 (3.3)
Injection site pain	5 (8.3)	8 (11.13)	24 (21.4)	49 (38.54)	5 (3.5)	8 (4.49)	5 (3.5)	8 (3.32)	5 (3.0)	8 (2.6)
Injection site erythema	0	0	35 (31.3)	117 (92.02)	5 (3.5)	7 (3.93)	5 (3.5)	7 (2.90)	5 (3.0)	7 (2.3)
Neuralgia	9 (15.0)	9 (12.52)	4 (3.6)	4 (3.15)	4 (2.8)	6 (3.37)	5 (3.5)	7 (2.90)	6 (3.6)	8 (2.6)
Constipation	6 (10.0)	6 (8.35)	15 (13.4)	17 (13.37)	4 (2.8)	4 (2.25)	4 (2.8)	4 (1.66)	6 (3.6)	6 (2.0)
Injection site pruritus	0	0	15 (13.4)	18 (14.16)	3 (2.1)	5 (2.81)	3 (2.1)	5 (2.07)	3 (1.8)	5 (1.6)
Asthenia	8 (13.3)	11 (15.30)	14 (12.5)	17 (13.37)	3 (2.1)	3 (1.68)	4 (2.8)	5 (2.07)	4 (2.4)	5 (1.6)
Hypoesthesia	6 (10.0)	7 (9.74)	10 (8.9)	11 (8.65)	2 (1.4)	2 (1.12)	2 (1.4)	2 (0.83)	3 (1.8)	3 (1.0)
Platelet count decreased	0	0	12 (10.7)	14 (11.01)	2 (1.4)	2 (1.12)	2 (1.4)	2 (0.83)	2 (1.2)	2 (0.7)
Pyrexia	5 (8.3)	6 (8.35)	22 (19.6)	32 (25.17)	2 (1.4)	2 (1.12)	4 (2.8)	5 (2.07)	5 (3.0)	8 (2.6)
Thrombocytopenia	1 (1.7)	2 (2.78)	15 (13.4)	20 (15.73)	1 (0.7)	2 (1.12)	1 (0.7)	2 (0.83)	2 (1.2)	3 (1.0)
Chills	2 (3.3)	3 (4.17)	19 (17.0)	36 (28.31)	1 (0.7)	1 (0.56)	1 (0.7)	1 (0.41)	2 (1.2)	2 (0.7)
Muscular weakness	6 (10.0)	7 (9.74)	11 (9.8)	11 (8.65)	1 (0.7)	1 (0.56)	1 (0.7)	1 (0.41)	1 (0.6)	1 (0.3)

Pain	8 (13.3)	10 (13.91)	12 (10.7)	19 (14.94)	1 (0.7)	1 (0.56)	1 (0.7)	1 (0.41)	1 (0.6)	1 (0.3)
Immunisation reaction	0	0	0	0	12 (8.3)	18 (10.11)	13 (9.0)	19 (7.87)	13 (7.87)	19 (6.2)
Proteinuria	2 (3.3)	2 (2.78)	7 (6.3)	8 (6.29)	12 (8.3)	13 (7.30)	12 (8.3)	14 (5.80)	16 (9.6)	18 (5.9)
Vision blurred	1 (1.7)	1 (1.39)	2 (1.8)	2 (1.57)	8 (5.6)	11 (6.18)	8 (5.6)	11 (4.56)	8 (4.8)	11 (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 data cut-off or up to last contact, whichever comes first.
c: Includes patients from ION-682884-CS3 study 'Eplontersen 45 mg q4w' arm only and excludes patients from inotersen/eplontersen arm. Week 85 + includes data up to the DCO 07 April 2023.
d: Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.
e: Rate in unit 'per 100 PY'.
f: The COVID-19 pandemic did not exist during the ISIS 420915-CS2 study.
g: Vitamin A laboratory related TEAEs were not reported in the ISIS 420915-CS2 study due to blinding of results to the Investigator and Sponsor.

Note: For each treatment group, a patient is counted only once within each PT; Adverse events are coded using MedDRA version 25.0.
COVID-19, coronavirus disease 2019; CSR, clinical study report; ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with event; N, number of patients in group; PT, Preferred Term; PY, patient-year; q1w, every week; q4w, every 4 weeks.

Identification of ADRs to be included in the product information was justified by the applicant to rely on ongoing signal evaluation based on emerging safety data from all data sources (non-clinical findings, clinical data from ongoing clinical trial programme as well as comparative analyses of randomised comparator/ placebo-controlled pivotal trials in the target populations).

The following ADRs were decided based on the mechanism of action of eplontersen and other drugs in the same class, analysis of frequencies of TEAEs reported compared to the external placebo, and medical, and scientific judgment of all available information (with the data source being the Eplontersen 45 mg q4w (Week 85+) set): *vitamin A decreased (frequency "very common"), vomiting, injection site erythema, injection site pain, and injection site pruritus (each with frequency "common").*

Adverse events of special interest (AESI)

AESI have been identified either as identified risks during the phase 3 studies with inotersen (*thrombocytopenia and glomerulonephritis*) or as potential risk (*ocular AEs potentially related to vitamin A deficiency*) based on the PD effect of inotersen and eplontersen.

28.5%, 20%, and 40.2% of patients reported AESI in the eplontersen, external placebo, and historical inotersen group, respectively (Table 20). No AESI in the eplontersen and placebo group led to discontinuation up to Week 66.

Thrombocytopenia (*any AE with the PTs of thrombocytopenia or platelet count decreased*)

Decreases in platelet counts were observed more frequently in patients with eplontersen treatment compared to external placebo, basically those to Grade 1a: $\geq 100 \times 10^9$/L to $< 140 \times 10^9$/L). Decreases to higher grades were rare and similar in both groups. Decreases in platelet counts were mostly transient, resolved spontaneously with ongoing eplontersen, did not increase with prolonged treatment duration, and did not have a clinical impact, like concomitant haemorrhages.

The incidence of thrombocytopenia AESI was similar in the eplontersen and external placebo group (2.1% vs. 1.7%) up to Week 66, and higher in the historical and concurrent inotersen groups (24.1% and 25%). This is also supported by the respective event rates (per 100 PY). Four (4) TEAEs of thrombocytopenia AESI were reported in 3 patients on eplontersen: 2 events with PT of thrombocytopenia in one patient and 2 events with PT of platelet count decreased in 2 patients. Nadir platelet counts in these patients ranged between 102×10^9/L and 136×10^9/L. No bleeding events were reported for these patients. Thrombocytopenia AESI with eplontersen were mild in severity, non-

serious, and none led to discontinuation or interruption of treatment. Three (3) of 4 TEAEs were assessed as not related, and one TEAE with PT of thrombocytopenia was assessed as possibly related. The events recovered/ resolved with continuous treatment without corrective measures.

Mean platelet counts at baseline were similar in the eplontersen, external placebo and historical inotersen group, i.e. 222.9 x 10^9/L, 212.2 x 10^9/L, and 223.4 x 10^9/L, and remained generally stable over time in the eplontersen group similar to the external placebo group. The mean %-change (decrease) from baseline was less than 5% at any time point during the study, while it was around 25% for historical inotersen at Month 6.

Post-baseline mean nadir platelet counts were similar in the eplontersen and the external placebo group (170.0 x 10^9/L vs. 177.6 x 10^9/L), and lower in the historical inotersen group (131.5 x 10^9/L). The mean change from baseline (SD) in nadir platelet count (10^9/L) was - 52.9 (34.0) with eplontersen, - 34.6 (26.66) for external placebo, and - 91.8 (46.93) for historical inotersen, and larger for patients with a higher baseline platelet count compared to those with a lower baseline platelet count in all treatment groups. Of note, more patients with higher baseline platelet counts were included in the eplontersen group.

Shifts in nadir platelet count in the eplontersen group were basically those from ≥140 x 10^9/L (normal) at baseline to ≥ 100 × 10^9/L to < 140 × 10^9/L post-baseline (27.8% of patients). Shifts to lower platelet counts (higher toxicity grades) occurred (≥ *75 × 10^9/L to < 100 × 10^9/L*: 2 patients; ≥ *50 × 10^9/L to < 75 × 10^9/L*: 1 patient; ≥ *25 × 10^9/L to < 50 × 10^9/L*: 1 patient, rated as laboratory sample issue) at single occasions only, and recovered to normal/ within reference range with continuous eplontersen treatment. No shifts to < *25 × 10^9/L* (Grade 4 thrombocytopenia) were noted.

Abnormal platelet counts < 140 × 10^9/L at any time post-baseline occurred in 31.9% of patients on eplontersen compared to 18.3% of patients on external placebo, and 55.4% and 54.2% of patients in the historical and concurrent inotersen group, respectively. Only 2.8% of patients experienced platelet counts < 100 × 10^9/L in the eplontersen group similar to the external placebo group (3.3%). The median duration of platelet counts < 140 × 10^9/L (< 100 × 10^9/L) in the eplontersen and external placebo group was 3.7 weeks and 6.0 weeks (1.43 weeks and 6.0 weeks), respectively.

A similar median time to first occurrence of platelet counts < 140 × 10^9/L was noted in the eplontersen and external placebo group (23.36 and 24.14 weeks).

The proportion of patients with at least one observed ≥ 30% or ≥ 50% decrease from baseline in platelet counts was higher in the eplontersen group (27.1% and 4.9%) as compared to external placebo (6.7% and 1.7%). In more than half of patients with ≥ 30% decrease from baseline, platelets were at the same time <LLN, while in most of them at single time points only. In patients with more than 1 low platelet count, increases to within the normal range or to Grade 1a occurred during continuous treatment. Likewise, platelet counts with ≥ 50% decrease from baseline and <LLN recovered with continuous treatment.

Based on the results of paired time points from both studies CS3 and CS2 up to Week 66, platelet count decreases were generally transient, while these tended to be persistent in the historical inotersen group.

Thrombocytopenia AESI in the Eplontersen Treated Set were similar to the up to Week 66 data regarding incidence (2.4% vs. 2.1%) and severity of events. SAEs were not reported except for a single patient, who had a severe SAE of thrombocytopenia (platelet counts 129 × 10^9/L on Day 633, reported as SAE) that led to discontinuation of eplontersen, and rated as unlikely related. Nadir platelet counts were 16 × 10^9/L on Days 654 and 656, after being off treatment with eplontersen. The patient was reported with multiple confounders, including anticoagulant treatment, systemic cellulitis, COVID-19 infection, medical history of blood dyscrasias/ thrombocytopenia, and CMML. The patient suffered

from various bleeding events during studies CS3 and CS13, one of which led to a fatal outcome (*GI haemorrhage*); however, none occurred during times of very low platelet counts.

Laboratory assessments of platelet counts in the Eplontersen Treated Set were similar to the up to Week 66 data with no evidence of an increased risk for low platelet counts.

Glomerulonephritis

No TEAEs of glomerulonephritis were reported in patients treated with eplontersen during the clinical studies. According to the SCS, two patients each in the external placebo and historical inotersen groups had TEAEs of glomerulonephritis AESI, while the numbers are discrepant with regard to the evaluation in EMEA/H/C/004782: here, serious glomerulonephritis was reported in 3 subjects (2.7%) in the inotersen study CS2 (and in an additional patient in its LTE), all of which were rated possibly related to inotersen and in one subject on placebo (1.7%).

Ocular adverse events potentially related to Vitamin A deficiency

The incidence of ocular AEs potentially related to vitamin A deficiency AESI was higher in the eplontersen group (27.1%) as compared to external placebo, historical inotersen, and concurrent inotersen (15%, 18.8%, and 16.7%, respectively) up to Week 66. The imbalance between eplontersen and external placebo was mainly driven by TEAEs of vitamin A deficiency and vitamin A decreased in the eplontersen group, which have not been reported as TEAEs in study ISIS 420915-CS2 due to blinding of laboratory values. The incidence of ocular AEs potentially related to vitamin A deficiency AESI was similar between eplontersen and external placebo after exclusion of vitamin A decreased/ deficiency (16.7% and 15%). Overall, TEAEs were non-serious, and mild to moderate in severity. None led to study drug discontinuation. TEAEs of vitamin A deficiency and vitamin A decreased were non-serious and mainly mild or moderate in severity; related or possibly related as per the Investigator; did not lead to dose interruption or discontinuation of the study drug; and most of the TEAEs were ongoing at the time of DCO. More patients on eplontersen as compared to external placebo and historical inotersen reported *Vision blurred* (5.6%, 1.7%, and 1.8%). The patients with vision blurred were stated to have had risk factors and alternative aetiologies (including medical history of cataract/ cataract surgery, astigmatism, myopia, and vitreous floaters, and concomitant treatments). Three (3) of 8 patients with vision blurred on eplontersen had vitamin A values <LLN prior to event onset.

Mean vitamin A values gradually decreased in the eplontersen group and remained lower compared to external placebo. The mean percent change (decrease) from baseline at Week 65 was 72.6%, 1.27%, and 62.6% for eplontersen, external placebo, and historical inotersen. Most of the patients in the eplontersen and historical inotersen group (95.1% and 90.1%) had post-baseline vitamin A value < LLN, compared with 3.3% of patients in the external placebo group. *Vitamin A decreased* is an ADR for eplontersen in section 4.8 of the SmPC. There were no TEAEs of night blindness in any of the treatment groups. Mean retinyl palmitate values remained close to baseline values through Week 66.

Available ophthalmology examination results did not reveal findings consistent with vitamin A deficiency after baseline.

Ocular AEs potentially related to vitamin A deficiency AESI in the Eplontersen Treated Set were roughly consistent with up to Week 66 data in study CS3, and generally mild to moderate (except one severe TEAE of *ulcerative keratitis*; medical history of dry eye; corrective treatment needed; unlikely related to eplontersen, ongoing at the time of the DCO), and non-serious (except one SAE of *blindness transient* with moderate severity; alternative aetiology in place; corrective treatment needed). One patient with a medical history of dry eyes and significant eye issues at screening, was reported with a TEAE of *xerophthalmia* (mild, non-serious) on Day 518, required corrective treatment, and was rated as not related. The event resolved ~3 weeks later with continuous eplontersen treatment.

Recommendation of vitamin A supplementation as well as a warning regarding ocular signs of vitamin A deficiency is included in product information.

Other adverse events of interest (OAEI)

No TEAEs related to ***coagulation abnormalities*** OAEI were reported up to Week 66 in study CS3 and during longer treatment duration in the Eplontersen Treated Set. Moreover, coagulation parameters (aPTT, prothrombin time, and INR) were not found clinically significantly different between eplontersen and external placebo/ inotersen when evaluated for mean changes from baseline, and did not change with longer eplontersen treatment.

Despite the lack of glomerulonephritis with eplontersen, ***renal impairment*** OAEI have been evaluated throughout the clinical studies: 15.3% of subjects treated with eplontersen in study CS3 and 10% and 20.5% of patients treated with external placebo and historical inotersen in study CS2 reported TEAEs of renal impairment OAEI, while TEAEs in the Renal and Urinary Disorders SOC were similar in eplontersen- and external placebo-treated subjects (23.6% vs. 26.7%). The numerical imbalance between eplontersen and external placebo was mainly due to renal function laboratory abnormalities, i.e. TEAEs of *proteinuria* (8.3% vs. 3.3%), and *renal impairment* (5 patients [3.5%] vs. 0%). TEAEs of renal impairment OAEI with eplontersen were generally mild or moderate in severity and non-serious; except for one PT of *renal impairment* in one patient with abnormal baseline eGFR (SAE of severe intensity [eGFR 30 mL/min/1.73 m^2] leading to discontinuation of eplontersen; not rated related to study drug but to renal amyloidosis ,and not resolved at follow-up). A majority of renal impairment TEAEs resolved during treatment without interruption or discontinuation of eplontersen. The Investigator assessed the majority of the TEAEs as not related to eplontersen. The 5 patients with renal impairment TEAEs had risk factors and alternative aetiologies. Likewise, TEAEs of proteinuria were mild to moderate and none was serious. The events were rarely rated as related, resolved during ongoing treatment with eplontersen, and a majority of patients had abnormal renal laboratory results at baseline. Of the 12 patients with proteinuria, one had study drug withdrawal due to proteinuria of moderate intensity (rated as related to eplontersen) and one had a dose interruption.

Renal function was assessed by serum and urine parameters while assessments were conducted more frequently in study CS3 as compared to study CS2. Mean eGFR remained >90 mL/min/1.73 m^2 over time in the eplontersen group, with no clinically meaningful changes compared to external placebo. At Week 65, the mean %-change from baseline in eGFR was - 1.81% and 2.92% for eplontersen and external placebo, respectively (- 7.22% and – 7.19% for historical and concurrent inotersen). Although, the incidence of shifts from baseline eGFR to nadir post-baseline was higher in the eplontersen group as compared to external placebo (40.28% and 28.33% of patients), these were mainly shifts from ≥ 90 mL/min/1.73 m^2 to ≥ 60-< 90 mL/min/1.73 m^2 (31.5%). Shifts from ≥ 90 mL/min/1.73 m^2 to ≥ 30-< 60 mL/min/1.73 m^2 were less frequently observed with eplontersen compared to external placebo (8.4% vs. 16.6%). One patient (see SAE *renal impairment* above) in the eplontersen group had a shift in nadir eGFR from ≥ 30-< 60 mL/min/1.73 m^2 at baseline to ≥ 15-< 30 mL/min/1.73 m^2 post-baseline. More patients on eplontersen than on external placebo had a decrease in eGFR ≥ 25% from baseline (18.8% and 10.0%, respectively), mainly pertaining to single occurrences, returning to normal/ baseline levels thereafter, with a peak eGFR increase any time after the eGFR ≥ 25% decrease to >LLN. The incidence of patients with ≥ 50% eGFR decrease from baseline was low and similar for eplontersen and external placebo (1.4% vs. 0). Decreases in eGFR were mostly transient, and – according to the applicant - due to natural variation in eGFR and confounding factors, i.e. (cardiac-related) comorbidities and concomitant medications. *Mean serum creatinine* was not found markedly different over time between eplontersen and external placebo, while remaining similar to baseline values and within the normal range (0.5 – 1.4 mg/dL). There were no differences between the eplontersen and external placebo group regarding proportion of patients with *serum creatinine > ULN* at any time post-baseline (≤10%), as well as serum creatinine increases >

0.5 mg/dL (44.2 µmol/L) from baseline (2.1% and 1.7%). No meaningful difference in serum creatinine shifts was noted between eplontersen and external placebo.

Laboratory assessments related to proteinuria did not show any clinically meaningful differences in urine protein, urine albumin, UPCR, and UACR between the eplontersen group and the external placebo group. The majority of the patients reported with TEAEs of proteinuria had abnormal renal laboratory results (ie, proteinuria, microalbuminuria, and increased UPCR) at baseline.

The proportion and presentation of renal impairment OAEI in the Eplontersen Treated Set was similar to the up to Week 66 data (18.6%). Two additional noteworthy AEs were recorded during study CS13, both of which were not rated related to eplontersen: a SAE of *glomerular filtration rate decreased* in a subject with a medical history of urinary retention, UTI, and nephrolithiasis on Day 493 (40 mL/min/1.73 m^2), for which study drug was interrupted; the subject also had two AEs of proteinuria. Severe *proteinuria* was also reported in study CS13 in a patient with *pneumonia and cardiac failure acute.* Moreover, there was no clinically meaningful difference in renal function assessments (eGFR and other renal function laboratory parameters) between the Eplontersen Treated Set and the data collected up to Week 66 in the eplontersen group.

The incidence of ***abnormal liver function*** OAEI was similar for eplontersen and external placebo (6.3% and 6.7%), and lower than for historical inotersen (12.5%) when compared up to Week 66 in studies CS3 and CS2. TEAEs of liver function OAEI were mild or moderate in severity, non-serious, and most of them were not related to eplontersen and resolved during treatment without corrective measures. One TEAE (PT *transaminases abnormal*) led to discontinuation of eplontersen. TEAEs were basically those of liver enzyme increases. *Hepatic function laboratory parameters* were measured throughout the studies. Mean ALT, AST, total bilirubin, direct bilirubin, and GGT values in the eplontersen group remained within the normal range up to Week 66 and any changes were similar to the external placebo group, while slight mean increases in GGT have been noted starting at Week 37. Of note, GGT was not measured in the ISIS 420915-CS2 study. The proportion of patients with hepatic parameters (ALT, AST, ALP, total bilirubin, and direct bilirubin) > ULN any time post-baseline was lower for eplontersen compared to external placebo. The incidence of post-baseline hepatobiliary laboratory abnormalities was 10.4% in the eplontersen group compared to 15% with external placebo and 17% with historical inotersen. The proportion of patients with liver abnormalities ALT ≥ 3 × ULN, AST ≥ 3 × ULN, and total bilirubin >2 × ULN was similar in the eplontersen and the external placebo group. No case of Hy's law was reported for eplontersen and external placebo.

One patient on eplontersen met the criteria of AST or ALT ≥ 3 × ULN any time post-baseline without simultaneous increase in total bilirubin (two occurrences), which led to withdrawal of eplontersen (mild event of *transaminases abnormal*). The Investigator assessed the events as possibly related, while rated unlikely related by the Sponsor (GGT was already elevated at screening and baseline; ALT and AST elevation on Day 351 was at a single time point; and onset of second event of ALT and AST increases began after a 120-day dose pause).

The incidence of abnormal liver function OAEI did not increase in the Eplontersen Treated Set over up to Week 66 data (8.4% and 6.3%), with the event rate being lower. Most of the events were assessed as not related, and mainly resolved with ongoing treatment without corrective measures. The following additional events were noted: a severe TEAE of *GGT increased*; two SAEs of *ascites* (moderate severity) in a single patient, assessed as not related to eplontersen, and resolved without dose interruption. *Hepatic function laboratory parameters,* including any abnormalities did not increase beyond those obtained through Week 66 in study CS3. One additional patient presented with ALT or AST ≥ 3 × ULN any time post baseline with no simultaneous increase in total bilirubin > 2 × ULN (mild, non-serious TEAEs of *ALT increased*, *hypertransaminasaemia, and AST increased*), which was not rated related to eplontersen and resolved during continuous treatment.

Adverse events at the injection site OAEI concerned any AE with HLT "Injection site reaction" and "administration site reactions NEC". Of note, the frequency of administrations of study drug was different in study CS3 (q4w for eplontersen) and historical groups (q1w for external placebo and inotersen). The incidence of TEAEs was similar for eplontersen and external placebo (9% and 11.7%), and lower than in the historical and concurrent inotersen groups (52.7% and 50%). The most frequently mentioned PTs in the eplontersen group were *injection site pain* (5 patients; 3.5%), *injection site erythema* (5 patients; 3.5%), and *injection site pruritus* (3 patients; 2.1%). *IS bruising*, *discoloration*, *haemorrhage*, and *vessel puncture site haemorrhage* occurred in a single patient each. Most of the events were mild (not severe or serious), mostly transient, and mainly resolved within 1 day without treatment interruption. None led to discontinuation of eplontersen.

To further characterise TEAEs at the injection site, analyses were performed of injection-site reactions and local cutaneous reactions at the injection site (LCRIS). Injection-site (IS) reactions were defined as TEAEs with MedDRA PTs containing the text "injection site". These broadly complied with the incidence and presentation of adverse events at the injection site OAEI. The analysis of LCR+IS focused on events known to be associated with SC ASO injections (*IS erythema, IS swelling, IS pruritus, IS pain, and IS tenderness*) and aimed to eliminate transient (< 2 days) events. LCRIS was reported in two patients (1.4%) in the eplontersen group, none in the external placebo group, and 33.9% in the historical inotersen group, similar to concurrent inotersen (29.2%). The two TEAEs related to LCRIS in the eplontersen group were non-serious IS erythema of mild severity, and treatment was continued without interruption. Adverse events at the injection site OAEI in the Eplontersen Treated Set were consistent with up to Week 66 data.

Flu-like symptoms (defined as *influenza-like illness or pyrexia PLUS any other constitutional symptom* starting at the day or the day after injection*)* were not reported in the eplontersen group. The incidence of TEAEs related to flu-like symptoms OAEI was 3.3%, 14.3%, and 16.7% in the external placebo, historical inotersen, and concurrent inotersen group. In the up to Week 85+ data of CS3, a single patient in the eplontersen group was reported with pyrexia (4 TEAEs of pyrexia and 1 TEAE of feeling hot) related to flu-like symptoms OAEI. TEAEs were mild in severity and non-serious and resolved with continuous eplontersen without interruption or discontinuation. All events were reported as related to eplontersen.

CNS disorders OAEI were reported with a lower incidence in the eplontersen group compared to external placebo and inotersen (29.9% vs. 53.3% and 59.8%). The most frequently reported PTs for eplontersen in more than 3 subjects were: dizziness (6.9%), headache (6.3%), syncope (4.9%), neuralgia (2.8%), and paraesthesia (2.1%). Events were mainly mild to moderate, consistent with manifestations of the underlying disease, and a majority resolved/ recovered without corrective treatment. A total of 4 SAEs of CNS disorder OAEI were reported in 3 patients treated with eplontersen: two TEAEs with PT *syncope* in two patients (both moderate in severity); one TEAE with PT *cerebral haemorrhage* (severe and fatal); and one TEAE with PT *metabolic encephalopathy* (moderate in severity) in one patient (the same patient, who was reported with syncope). No other severe events were reported. None of the SAEs led to study drug discontinuation (except the fatal SAE of cerebral haemorrhage) or was rated related to eplontersen. The incidence of CNS disorder OAEI did not increase in the Eplontersen Treated Set (32.3%). Additional SAEs not reported up to Week 66 in study CS3 were: 2 SAEs of *syncope* (one of which was severe), and one SAE of *cerebral infarction* (moderate in severity). None of the SAEs were considered as related to eplontersen.

Haemorrhage OAEI were reported less frequently with eplontersen as compared to external placebo/ historical inotersen/ concurrent inotersen (13.2% vs. 33.3%, 36.6%, and 29.2%). None of the haemorrhage OAEI occurred at a notably higher incidence in the eplontersen group compared to the external placebo and historical inotersen groups. The most frequently reported PTs with eplontersen occurred in ≤3 patients and included *haematuria, conjunctival haemorrhage, rectal haemorrhage,*

haematoma and haemoglobin increased, and most of them were mild to moderate in severity. Three SAEs were reported in 3 patients and were rated as not related: *haematuria* (severe; resolved during treatment), *cerebral haemorrhage* (severe, fatal), and *gastric haemorrhage* (moderate; ongoing at the time of DCO). Platelet counts around onset of these SAEs were normal (> 140 × 10^9/L). There was no increase in incidence of haemorrhage OAEI in the Eplontersen Treated Set (13.8%). Most of the TEAEs were mild to moderate in severity, non-serious, and resolved during treatment. In addition to the data up to Week 66, one further SAE of *gastrointestinal haemorrhage* (severe, fatal event; see death section; not rated as related to eplontersen).

Cardiac disorder OAEI occurred less frequently with eplontersen as compared to external placebo and historical inotersen (13.9% vs. 21.7% and 22.3%). Notably, no TEAE was reported in the concurrent inotersen group up to Week 37. Most frequently reported PTs in the eplontersen group (in > 1 patient) were *atrioventricular (AV) block first degree* (3 patients), *arrhythmia, AV block, AV block second degree, bundle branch block left, and left ventricular hypertrophy* in 2 patients each. TEAEs were mostly mild to moderate in severity, and the patients continued treatment without interruption or discontinuation. 4 SAEs of cardiac disorder OAEI were reported in 4 patients on eplontersen: *angina unstable (severe), arrhythmia (fatal; severe)*, *AV block second degree (life-threatening; moderate)*, and *AV block (severe, life-threatening)*. No other severe events were reported. In the external placebo group, two SAEs have been noted, left ventricular failure and cardiac failure in one patient each. None of the TEAEs, SAEs or severe TEAEs was assessed as related to eplontersen.

The incidence of TEAEs related to cardiac disorder OAEI with eplontersen slightly increased with longer treatment duration beyond Week 66 data (Week 85+: 17.4%; Eplontersen Treated Set: 20.4%). TEAEs were mild to moderate in the majority of patients. In the Eplontersen Treated Set, 12 patients (7.2%) were reported with 17 SAEs, with 13 of them reported as severe. The additional SAEs not captured in the up to Week 66 data include *AV block complete* (2 patients), *cardiac failure congestive* (1 patient with 2 events), *acute myocardial infarction*, *atrial flutter, cardiac arrest, cardiac failure, cardiac failure acute, cardio-respiratory arrest, cardiogenic shock, pericardial effusion, and supraventricular tachycardia*. In 4 of the 12 patients with SAEs, the outcome was fatal (see section on deaths), while these patients had a diagnosis of ATTRv-CM and substantial cardiac history at baseline. None of the severe, serious or fatal TEAEs was rated related to eplontersen.

15% of thyroxine is transported via TTR protein, while 65% of thyroxine is transported by thyroxine blinding globulin and 20% by albumin and retinol. ***Hypothyroid states*** might therefore theoretically occur with eplontersen treatment. Reduced thyroxine OAEIs were reported in 2.1% of patients on eplontersen and 5% of patients on external placebo (and 5.4% of patients in the historical inotersen group). The PTs reported for eplontersen were *blood thyroid stimulating hormone increased* (1.4%) and *hypothyroidism* (0.7%). None of the reduced thyroxine OAEI was severe or serious, and no patient discontinued due to TEAEs. Mean post-baseline thyrotropin in the eplontersen group remained similar to baseline levels. Increases in thyrotropin to > ULN at any time post-baseline occurred in 16.7% of patients on eplontersen compared to 23.7% of patients on external placebo. There was no increased reporting of TEAEs with longer treatment in the Eplontersen Treated Set.

Other adverse events not rated OAEI

- No increased incidence of TEAEs of ***hypersensitivity*** was noted for eplontersen as compared to external placebo (18.8% vs. 26.7%; 31.3% for historical inotersen). Reported events were mild to moderate, not severe or serious, a majority was not rated related to eplontersen, and none led to discontinuation. No TEAEs of anaphylaxis were noted. Two SAEs in one patient were reported in the Eplontersen Treated Set (*respiratory failure and shock*, both severe), which were not rated as related to eplontersen and resolved with corrective treatment.

- No increased incidence of TEAEs of ***immune-mediated effects*** was noted for eplontersen as compared to external placebo (6.9% and 10%). The majority of events was from the nervous system disorders SOC in line with the underlying ATTRv-PN. One TEAE of *ulcerative keratitis* was rated as severe in the Eplontersen Treated Set and did not recover at the time of the DCO (see AESI section). TEAEs were assessed as not related to eplontersen and none led to discontinuation.
- No increased incidence of TEAEs of ***accidents and injuries*** was noted for eplontersen as compared to external placebo (19.4% vs. 45%), while these events increased in the Eplontersen Treated Set (29.3%), mainly related to *fall, thermal burn, limb injury, and foot fracture*.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

A total of 6 death cases were reported in the Eplontersen Treated Set up to the DCO, including 3 fatal events (two deaths up to Week 66 and one death occurring after Week 66 and prior to Week 85 assessment) in study CS3 and 3 fatal events in study CS13. None of the deaths was assessed as related to eplontersen. An additional patient died after the Week 85 analysis was completed in Study CS3; however, death (due to pneumonia sepsis) was not recorded in the presented data sets given that it was reported during survival follow-up and 64 weeks after discontinuation of eplontersen.

The three fatal events in study CS3 concerned:

- a fatal SAE of Arrhythmia, in a patient with baseline cardiac conditions accompanied with abnormal levels of NT-proBNP and hs-troponin T, as well as diagnosis of ATTRv-CM. The patient was reported with a severe SAE of arrhythmia at Day 100.
- a fatal SAE of Cerebral haemorrhage, secondary to a head trauma after a fall; the patient had no history of bleeding and platelet counts >LLN throughout the study.
- a fatal SAE of acute myocardial infarction, in a subject with diagnosis of ATTRv-CM at baseline. No other cardiac medical history was reported despite "arterial hypertension" being a component of the subjects ATTRv. Sudden death occurred on Day 513. Concomitant medications ongoing at the time of death were oral clonazepam, fludrocortisone acetate, and domperidone as needed.

The three fatal events in study CS13 concerned:

- a fatal SAE of cardiac arrest, in a patient with ATTRv-CM and several baseline ECG abnormalities. The patient presented with various SAEs during the studies. Cardiac arrest followed a syncope on Day 885; the cause of death was ascribed to cardiac amyloidosis.
- a fatal SAE of Gastrointestinal haemorrhage, see AESI thrombocytopenia. Death occurred around normal platelet counts and after 110 days off treatment. Various confounding factors have been identified, including concomitant anticoagulant treatment and medical history.
- a fatal SAE of cardiogenic shock, in a patient with diagnosis of ATTRv-CM at baseline. Multiple baseline cardiac and non-cardiac conditions were noted. Other life-threatening SAEs preceded the fatal cardiogenic shock and included respiratory failure and shock.

Serious adverse events (SAEs), including deaths

The incidence of SAEs was 14.6% for eplontersen and 20% for external placebo (32.1% for historical inotersen), while the EAER was higher in the eplontersen group (29.76 per 100 PY vs. 19.47 per 100 PY for external placebo). SAEs reported in more than one patient in the eplontersen group were *vomiting* (3.5%), and *nausea*, *UTI, COVID-19 pneumonia, and syncope* (in 1.4% of patients each).

SAEs reported up to Week 66 in single patients on eplontersen were: *angina unstable, arrhythmia, atrioventricular block, atrioventricular block second degree, vertigo, impaired gastric emptying, gastric haemorrhage, gastritis, COVID-19, cellulitis, gastroenteritis, nasopharyngitis, pneumonia, pyelonephritis, soft tissue infection, streptococcal sepsis, urosepsis, burns third degree, foot fracture, clostridium test positive, dehydration, hypokalaemia, hyponatraemia, cerebral haemorrhage, metabolic encephalopathy, haematuria, renal impairment, and urinary retention*.

Apart from COVID-19, the pattern of SAEs observed in the eplontersen group was generally consistent with those reported in the patient population. None of the SAEs was rated as related to eplontersen. Two of the SAEs resulted in a fatal outcome (*arrhythmia* and *cerebral haemorrhage*; see above).

Additional SAEs reported between Week 66 and 85 for eplontersen were *acute myocardial infarction (fatal), AV block complete, cardiac failure, cardio-respiratory arrest, supraventricular tachycardia, ileus, asthenia, skin infection, femoral neck fracture, GFR decreased, and syncope*.

The incidence of SAEs in the Eplontersen Treated Set was slightly higher compared to Week 66 (20.4% vs. 14.6%), mainly due to an increase of cardiac disorders SAEs (7.2%; 2.8% up to Week 66). None of these SAEs were rated as related to eplontersen. Six SAEs were reported as fatal and are discussed above. Most of the SAEs were considered known complications of the underlying disease (e.g. infections, cardiac disorders, GI disorders, nervous system disorders, metabolism and nutrition disorders). SAEs reported in more than one patient 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). Additional SAEs (in one patient each) in study CS13 were: *iron deficiency anaemia, thrombocytopenia, cardiac failure congestive, cardiac arrest, cardiac failure acute, cardiogenic shock, pericardial effusion, blindness transient, ascites, diarrhoea, GI haemorrhage, sepsis, pneumonia, arthritis bacterial, cellulitis, UTI, dehydration, hypovolaemia, cerebral infarction, syncope, pleural effusion, respiratory failure, hypotension, and shoc*k. Except for a single SAE of thrombocytopenia in the Eplontersen Treated Set, none of the reported SAEs was found to be in accordance with pre-defined AESI.

2.6.8.4. Laboratory findings

Haematology evaluations

Notably, collection of haematology parameters per patient was conducted ~40% more frequently for eplontersen as compared to external placebo.

Eplontersen treatment was not found to be associated with any clinically meaningful changes in mean haematology parameters over time, including red blood cell parameters (haemoglobin and haematocrit) and white blood cell parameters (leukocytes, lymphocytes, and neutrophils). For platelet counts, reference is made to the AESI section.

The incidence of abnormalities of haemoglobin and haematocrit <LLN was similar in the eplontersen group and for external placebo, while shifts in haemoglobin nadir (to lower grades) from baseline were mainly those from Grade 0 to Grade 1. The proportions of patients with TEAEs related to haemoglobin or haematocrit (anaemia macrocytic, iron deficiency anaemia, haemoglobin decreased, and haematocrit decreased) in the eplontersen group was similar to external placebo.

The incidence of WBC counts < LLN was higher for eplontersen compared to external placebo: leucocytes (34.0% vs. 8.3%), lymphocytes (54.9% vs. 26.7%), and neutrophils (11.1% vs. 6.7%), and likewise more shifts were reported from normal at baseline to lower counts post-baseline. Most of the shifts in leukocytes decreased, lymphocytes decreased and neutrophils decreased were those to Grade 1 or Grade 2, while shifts to Grade 3 in lymphocytes counts (< 0.5 to 0.2 × 10^9/L) were solely

reported in the eplontersen group (7.6% of patients). 9% of patients had a shift to Grade 3 in neutrophil counts and in 2 patients to Grade 4. Most of the shifts from baseline to worst post-baseline grades were transient and returned to normal levels in subsequent visits in both groups.

According to the applicant, reductions in lymphocyte counts might be a consequence of COVID-19 infection and SARS-CoV-2 mRNA vaccination, not relevant during the CS2 study, but could also be related to more frequent assessment of haematology parameters with eplontersen compared to the external placebo group. TEAEs reported as being related to decreases in WBC counts occurred with eplontersen but not with external placebo: leukopenia (2.1%), white blood count decreased (0.7%); lymphopenia (2.8%); and neutropenia (0.7%). TEAEs were mild to moderate in severity and non-serious. Most of them were reported as not related, transient and resolved with ongoing eplontersen treatment. There were no differences in the incidence of TEAEs within infections and infestations SOC for eplontersen and external placebo (59.0% and 63.3%). No worsening of haematology results and related TEAEs was noted in the Eplontersen Treated Set despite a single patient with shift from normal at baseline to abnormal Grade 4 post-baseline decrease in lymphocytes. Overall, based on the provided narratives, patients with Grade 3 or Grade 4 decreases in WBC counts had no interruption of eplontersen, no need for corrective treatment, and values returned to normal within the next visit.

Clinical chemistry evaluations

Eplontersen treatment was not found to be associated with any clinically meaningful changes in mean chemistry parameters over time, including albumin, calcium, magnesium, potassium, and immunoglobulins (IgG and IgM). Grade 1 and 2 abnormalities in low calcium, magnesium, and potassium in eplontersen-treated subjects concerned few subjects only. One SAE of hypokalaemia was not related to eplontersen but to persistent vomiting. All other abnormalities were evenly distributed across treatment groups. Some immunological alterations have been noted by findings of post-baseline abnormalities (>ULN) in IgG and IgM with a higher incidence for eplontersen as compared to external placebo; only few TEAEs in line with these abnormalities have been reported that were, however, not rated as related to eplontersen. C-reactive protein (measured as hsCRP) is known to increase during treatment with antisense oligonucleotides. However, no relevant alterations in hs-CRP derived from treatment with eplontersen as compared to external placebo.

Vital signs, physical findings, and other observations related to safety

The incidence of mean changes, potentially clinically significant abnormalities, or shifts from baseline to the highest or lowest post-baseline category in vital sign assessments (i.e. SBP, DBP, HR, respiratory rate, body temperature, and body weight) up to Week 66 in the eplontersen group compared to the external placebo group did not show any consistent pattern which would raise new safety concerns for eplontersen. No patient had post-baseline abnormalities of SBP > 160 mmHg and DBP > 100 mmHg in the eplontersen and the external placebo group. *Orthostatic hypotension* (mild to moderate, non-serious, not leading to interruption or discontinuation of eplontersen and not related to the study drug) was reported for 3.5% of patients on eplontersen compared to none on external placebo. These patients had a cardiac-related medical history including orthostatic hypotension, hypertension, or AV block. Mean values over time in vital signs in the Eplontersen Treated Set remained consistent with up to Week 66 data, while the proportion of patients with SBP > 160 mmHg and DBP > 100 mmHg was 12% and 9%, respectively. The incidence of *orthostatic hypotension* was similar to Week 66, and all patients had cardiac-related past medical history, including orthostatic hypotension, hypertension, or AV block. None of the patients became hypotensive (< 90/60 mmHg).

Electrocardiograms (ECGs):

ECGs were conducted at screening, Day 85, Week 35, Week 65, and EOT or early termination visit. Changes in mean ECG parameters over time were not markedly different between eplontersen and

external placebo. The proportion of patients with abnormal but not clinically significant baseline ECG findings was lower for eplontersen than for external placebo (50.7% vs. 71.7%), while there were more patients with clinically significant abnormal baseline ECG findings in the eplontersen group compared to external placebo (15.2% vs. 6.7%). At Week 35 and Week 65, no changes were noted for eplontersen compared to baseline, with a similar trend in both, the CM and non-CM subgroups. Abnormalities in QTcF interval of > 450, > 480, or > 500 msec at any visit post-baseline were similar between eplontersen and external placebo. However, more patients in the eplontersen than in the external placebo group had a > 30 msec and > 60 msec increase from baseline (11.8% vs. 6.7%, and 4.9% vs. 0%). In the eplontersen group, the majority of the patients with an increase in QTcF > 60 msec from baseline had pre-existing cardiac-related conditions and abnormal ECG findings at baseline.

Relevant shifts in QTcF were overall low and similar between eplontersen and external placebo, and mainly concerned those from ≤450 msec at baseline to post-baseline categories > 450 to ≤ 480 msec or > 480 to ≤ 500 msec. Post-baseline QTcF shifts to > 500 msec occurred in 5 patients (3.5%) in the eplontersen group and 2 patients (3.3%) in the external placebo group. Shifts to higher post-baseline QTcF categories were more frequently reported in patients belonging to the CM subgroup as compared to the non-CM subgroup. In the Eplontersen Treated Set, 5% of patients had a shift in QTcF to >500 msec.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Table 22: AEs by age range – up to week 65 (safety analysis set)

	Eplontersen					Placebo				
MedDRA Terms	Age <65 (N=100) n (%)	Age 65-74 (N=36) n (%)	Age 75-84 (N=8) n (%)	Age 85+ (N=0) n (%)	Total (N=144)	Age <65 (N=34) n (%)	Age 65-74 (N=17) n (%)	Age 75-84 (N=9) n (%)	Age 85+ (N=0) n (%)	Total (N=60)
Total AEs	98 (98%)	34 (94.4%)	8 (100%)	0	140 (97.2%)	34 (100%)	17 (100%)	9 (100%)	0	60 (100%)
Serious AEs – Total	12 (12%)	6 (16.7%)	3 (37.5%)	0	21 (14.6%)	3 (8.8%)	7 (41.2%)	2 (22.2%)	0	12 (20%)
- Fatal	1 (1%)	1 (2.8%)	0	0	2 (1.4%)	0	0	0	0	0
- Hospitalization/prolong existing hospitalization	11 (11%)	6 (16.7%)	2 (25%)	0	19 (13.2%)	3 (8.8%)	6 (35.3%)	2 (22.2%)	0	11 (18.3%)
- Life-threatening	3 (3%)	0	0	0	3 (2.1%)	0	0	0	0	0
- Disability/incapacity	2 (2%)	1 (2.8%)	1 (12.5%)	0	4 (2.8%)	0	0	0	0	0
- Other (medically significant)	3 (3%)	1 (2.8%)	2 (25%)	0	6 (4.2%)	2 (5.9%)	2 (11.8%)	1 (11.1%)	0	5 (8.3%)
AE leading to drop-out	4 (4%)	1 (2.8%)	1 (12.5%)	0	6 (4.2%)	2 (5.9%)	0	0	0	2 (3.3%)
Psychiatric disorders [a]	9 (9%)	4 (11.1%)	0	0	13 (9%)	8 (23.5%)	4 (23.5%)	0	0	12 (20%)
Nervous system disorders [a]	25 (25%)	16 (44.4%)	2 (25%)	0	43 (29.9%)	18 (52.9%)	10 (58.8%)	4 (44.4%)	0	32 (53.3%)
Accidents and injuries [b]	21 (21%)	4 (11.1%)	5 (62.5%)	0	30 (20.8%)	17 (50%)	9 (52.9%)	6 (66.7%)	0	32 (53.3%)
Cardiac disorders [a]	12 (12%)	5 (13.9%)	3 (37.5%)	0	20 (13.9%)	7 (20.6%)	5 (29.4%)	1 (11.1%)	0	13 (21.7%)
Vascular disorders [a]	9 (9%)	5 (13.9%)	4 (50%)	0	18 (12.5%)	4 (11.8%)	4 (23.5%)	1 (11.1%)	0	9 (15%)
Cerebrovascular disorders [c]	0	1 (2.8%)	0	0	1 (0.7%)	0	0	0	0	0
Infections and infestations [a]	58 (58%)	22 (61.1%)	5 (62.5%)	0	85 (59%)	20 (58.8%)	13 (76.5%)	5 (55.6%)	0	38 (63.3%)
Anticholinergic syndrome [d]	0	0	0	0	0	0	0	0	0	0
Quality of life decreased [e]	0	0	0	0	0	0	0	0	0	0

	Eplontersen					Placebo				
MedDRA Terms	Age <65 (N=100) n (%)	Age 65-74 (N=36) n (%)	Age 75-84 (N=8) n (%)	Age 85+ (N=0) n (%)	Total (N=144)	Age <65 (N=34) n (%)	Age 65-74 (N=17) n (%)	Age 75-84 (N=9) n (%)	Age 85+ (N=0) n (%)	Total (N=60)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [f]	16 (16%)	8 (22.2%)	3 (37.5%)	0	27 (18.8%)	7 (20.6%)	7 (41.2%)	4 (44.4%)	0	18 (30%)
other AE appearing more frequently in older patients	26 (26%)	12 (33.3%)	5 (62.5%)	0	43 (29.9%)	13 (38.2%)	15 (88.2%)	6 (66.7%)	0	34 (56.7%)
Dysphagia	1 (1%)	0	0	0	1 (0.7%)	0	3 (17.6%)	0	0	3 (5%)
Fall	3 (3%)	2 (5.6%)	3 (37.5%	0	8 (5.6%)	3 (8.8%)	7 (41.2%)	3 (33.3%)	0	13 (21.7%)
Fatigue	4 (4%)	3 (8.3%)	0	0	7 (4.9%)	4 (11.8%)	6 (35.3%)	2 (22.2%)	0	12 (20%)
Oedema	0	0	0	0	0	0	2 (11.8%)	1 (11.1%)	0	3 (5%)
Oedema peripheral	4 (4%)	5 (13.9%)	3 (37.5%)	0	12 (8.3%)	2 (5.9%)	2 (11.8%)	1 (11.1%)	0	5 (8.3%)
Urinary tract infection	15 (15%)	6 (16.7%)	3 (37.5%)	0	24 (16.7%)	4 (11.8%)	5 (29.4%)	1 (11.1%)	0	10 (16.7%)

a Includes the corresponding SOC.
b Included SOC Injury, poisoning and procedural complications.
c Includes HLTs Central nervous system haemorrhage and cerebrovascular accidents, Cerebrovascular and spinal necrosis and vascular insufficiency, Cerebrovascular and spinal vascular disorders NEC, Cerebrovascular aneurysms and dissections, Cerebrovascular embolism and thrombosis, Cerebrovascular venous and sinus thrombosis, and Transient cerebrovascular events.
d Includes the corresponding PT.
e Includes PTs Quality of life decreased and Impaired quality of life.
f Includes PTs Orthostatic hypotension, Fall. Loss of consciousness, Syncope, Dizziness, Ataxia, and Fracture.
TEAE is defined as adverse events that first occurred or worsened after the first dose of study drug. Patients with multiple occurrences are counted once per preferred term regardless of the number of occurrences. Adverse events were coded using MedDRA version 25.0. HLT = high level term; MedDRA = Medical Dictionary of Regulatory Activities; N = number of patients per treatment group; NEC = not elsewhere clarified; SOC = system organ class; TEAE = treatment-emergent adverse event.

Table 23: AE by special population – up to week 65 (safety analysis set)

	Eplontersen				Placebo			
MedDRA Terms	Hepatically impaired* (N=0) n (%)	Renally impaired** (N=0) n (%)	Pregnant (N=0) n (%)	Other (N=0) n (%)	Hepatically impaired* (N=0) n (%)	Renally impaired** (N=1) n (%)	Pregnant (N=0) n (%)	Other (N=0) n (%)
Total AEs	0	0	0	NA	0	1 (100%)	0	NA
Serious AEs – Total	0	0	0	NA	0	0	0	NA
- Fatal	0	0	0	NA	0	0	0	NA
- Hospitalization/prolong existing hospitalization	0	0	0	NA	0	0	0	NA
- Life-threatening	0	0	0	NA	0	0	0	NA
- Disability/incapacity	0	0	0	NA	0	0	0	NA
- Other (medically significant)	0	0	0	NA	0	0	0	NA
AE leading to drop-out	0	0	0	NA	0	0	0	NA

* Hepatic impairment is defined as having Child-Pugh score B or C
** Renal impairment is defined as having CKD Stage 3b, 4 or 5 (eGFR < 45 mL/min/1.73 m^2)
"Other" is presented as NA as there is no other specific population.
TEAE is defined as adverse events that first occurred or worsened after the first dose of study drug.
Patients with multiple occurrences are counted once per preferred term regardless of the number of occurrences.
Adverse events were coded using MedDRA version 25.0.
CKD = chronic kidney disease; MedDRA = Medical Dictionary of Regulatory Activities; N = number of patients per treatment group; TEAE = treatment-emergent adverse event; NA = not applicable

Safety in special populations has been analysed by subgroup analysis of patients with continuous eplontersen treatment in the Eplontersen Treated Set (n=144) up to the DCO, and based on study entry/ screening/ baseline status. Patients from the concurrent inotersen group and from the IST study were not included. TEAEs by subgroups have been analysed focussing on SOCs and PTs with absolute differences of > 10% frequency across subgroups. Evaluation for external placebo, concurrent inotersen, and by SAEs was not provided.

As of the DCO (7 April 2023), according to the applicant, the TEAE profile in eplontersen-treated patients was generally consistent across predefined subgroups based on demographic and baseline disease characteristics, i.e. the **intrinsic factors** age (<65 years, 65 to 74 years, and ≥75 years), sex (male, female), race (White, non-White), disease stage (Stage 1, Stage 2), PND score (I/II, IIIa/IIIb), Val30Met TTR genotype (yes, no), FAC clinical diagnosis (yes, no), CM subgroup (yes, no), and eGFR (<60, ≥ 60 mL/min/1.73m^2). Notable observations regarding intrinsic factors are as follows:

Age: Only 8 patients were ≥ 75 years-old hampering meaningful conclusions for this subgroup. There was a higher incidence of TEAEs in the SOCs of infections and infestations (83.3% vs. 67%), renal and urinary disorders (36.1% vs. 23%), nervous system disorders, eye disorders, investigations, and neoplasms benign, malignant and unspecified (including cysts and polyps) in patients 65 to 74 years compared to patients < 65 years. The only notable differences between subgroups on the PT level was lymphopenia (11.1% vs. 1% in patients 65 to 74 years and < 65 years, respectively).

Sex: Female compared to male patients had a > 10% higher incidence of TEAEs in the SOCs blood and lymphatic system disorders, GI disorders; general disorders and administration site conditions; infections and infestations; musculoskeletal and connective tissue disorders; nervous systems disorders; renal and urinary disorders; skin and subcutaneous tissue disorders; and vascular disorders;

and for the PTs UTI (40.9% vs. 13%), nausea, vomiting, renal impairment (11.4% vs. 0%), vitamin A decreased, cataract, vitamin A deficiency, injection site erythema, and hypotension.

Race: Most of the subjects were White (78.3%), 15.4% were Asian, and < 5% of patients were either Black or Other. Thus, the relevance of a > 10% higher incidence in non-Whites compared to Whites with regard to Vitamin A deficiency (20% vs. 8.8%) and vision blurred (20% vs. 1.8%) is unclear.

Disease stage and PND score: In general, it appears that higher disease stage and higher PND score is associated with higher incidences in TEAEs by SOCs or PTs in line with the underlying amyloidosis, e.g. infections and infestations (driven by PT *UTI*); injury, poisoning and procedural complications (driven by PT *fall*); nervous system disorders; metabolism and nutrition disorders; cardiac disorders; and PT of peripheral oedema.

FAC clinical diagnosis and CM subgroup: approx. 1/3 of patients had a FAC clinical diagnosis at baseline or were included in the CM subgroup. In general, it appears that these patients had a higher incidence of cardiac disorders TEAEs but also for eye disorders (driven by cataract), nervous system disorders; metabolism and nutrition disorders; respiratory, thoracic and mediastinal disorders; psychiatric disorders, consistent with the organ manifestation of amyloidosis.

eGFR: Only 6 patients had an eGFR of < 60 mL/min/1.73m^2 at baseline hampering meaningful conclusions.

According to the applicant, the TEAE profile in eplontersen-treated patients was generally consistent across predefined subgroups based on **extrinsic factors** region (North America, Europe and South America /Australia/Asia), and previous treatment with Vyndaqel or diflunisal (yes, no).

Regarding *region*, 14.6%, 37.5%, and 47.9% of patients were from North America, Europe, and South America/ Australia/ Asia, respectively. Notably, the latter had a higher incidence of vitamin A deficiency as compared to European patients (23.2% vs. 0%; i.e., TEAEs of Vitamin A deficiency were exclusively reported from South America/ Australia/ Asia).

As of the DCO, no **pregnancies** have been reported in the eplontersen clinical development programme. As of the DCO, two patients had accidental eplontersen **overdoses.** Both received a 120 mg dose at Week 17 instead of 45 mg in the CS3 study. Two weeks after the overdose (Day 126), one patient had hepatic enzyme increased (ALT 68 U/L, NR: 0- 50 U/L) of mild severity, which returned to normal one day later without corrective treatment, and rated related to eplontersen. The other patient had no TEAEs within 30 days of overdose.

Supportive safety results deriving from **Phase 1 HV studies** applying either single or multiple doses of 45 mg, 60 mg, or 90 mg eplontersen or single doses of 120 mg (or placebo) have been provided. Noteworthy findings that are not labelled include *ALT increased* in the high dose groups (90 mg, multiple dose cohort in CS1), but also at the recommended 45 mg dose in CS21 (3 subjects, 2 of whom discontinued the study, all rated as related to eplontersen). Moreover, *GFR decreased* was reported at the recommended dose, which led to discontinuation from study in a single subject, who had no medical history/ medication that would have contributed to the event; however, given that mean eGFR values post-dosing were unremarkable in study CS21, a causal relation cannot be confirmed. Moreover, a single subject was reported with *deep vein thrombosis*, which remained unresolved by the end of the study and was rated as possibly related to eplontersen.

No dedicated studies have been conducted in **patients with renal or hepatic impairment** and the applicant did not address this issue in the SCS. Available information derives from E-R analysis together with popPKPD analysis. Based on the results, no dose adjustment is required in patients with

- mild to moderate renal impairment (eGFR ≥ 45 to < 90 mL/min). Eplontersen has not been studied in patients with eGFR <45 mL/min/1.73 m2 or end-stage renal disease;

- 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.

No information has been provided regarding **patients with liver transplant**. Prior liver transplant or anticipated liver transplant within one year of screening was an exclusion criterion in clinical studies with eplontersen; cases of liver transplant rejection have been reported in patients treated with inotersen, too.

2.6.8.7. Immunological events

Anti-drug antibody testing in study CS3 was performed on study Day 1, Day 29, Day 85, Day 225, Day 337, Day 449 (Week 65), and at Week 85 (EOT). In the 20-week Post Treatment Evaluation Period (for patients who did not enter the open-label extension study CS13), immunogenicity assessments were performed at Day 729 (Week 105), and upon Early Termination.

The impact of immunogenicity on PK revealed higher plasma eplontersen C_{trough} levels in both healthy volunteers and patients with ATTRv-PN, who had treatment-emergent ADA compared with subjects with treatment-unaffected ADA or ADA-negative subjects. At the same time, peak (C_{max}) and total (AUC) plasma PK exposure metrics were unaltered.

The impact of the immunogenicity status on clinical safety has been examined based on patients who received eplontersen treatment in study CS3 up to the DCO (Week 85+), excluding patients from the concurrent inotersen group.

Anti-drug antibodies were detected in 45.8% of eplontersen-treated patients in study CS3 up to the DCO, covering a mean treatment duration with eplontersen of 540.8 days. 40.3% of patients had treatment-emergent ADA. Titers were persistent in most of the subjects tested positive for ADA. In 2 patients, ADAs were treatment-boosted. The median onset of ADA was not before 223 days (range 24 to 603), and median time to reach peak titer was after 446 days. The median (range) duration time was 393 (1 to 701) days. Median peak antibody titers were rather low (200) but there were single patients with high ADA titers up to 25600.

Demographic and baseline characteristics in the eplontersen group were broadly comparable between ADA-positive and ADA-negative patients.

Immunogenicity status had no clinically meaningful impact on TEAEs, AESI, OAEI, or laboratory test results reported following eplontersen treatment.

The incidence of TEAEs for eplontersen was similar between ADA-positive and ADA-negative patients (98.5% and 97.4%). The SOCs with ≥ 10% higher incidence of TEAEs in ADA-positive patients vs. ADA-negative patients were GI disorders (60.6% vs. 37.2%; mainly due to an increase in diarrhoea, vomiting and nausea), and metabolism and nutrition disorders (31.8% vs. 19.2%; mainly due to Vitamin A deficiency). All PTs had a difference between ADA-positive and ADA-negative patients of < 10%. There was no clinically meaningful difference in the incidence of TEAEs by titer quartiles.

Incidences of TEAEs by *severity* were generally similar between ADA-positive and ADA-negative patients. The incidence of *TEAEs assessed as related to the study drug* was higher in ADA-positive than in ADA-negative patients (42.4% vs. 34.6%), driven by more TEAEs in the SOC of general disorders and administration site conditions among ADA-positive patients (16.7% vs. 5.1%). There was no clear association between peak ADA titers and incidence of study drug related TEAEs.

No significant difference in the incidence of SAEs and LCRIS was noted with regard to immunogenicity status. The incidence of TEAEs of *AESIs* (with the exception of PT *Vitamin A deficiency* that was more

frequently reported in ADA positive patients) as well as *OAEIs* was generally similar between ADA-positive and ADA-negative patients (33.3% vs. 26.9% and 63.6% vs. 65.4%). Injection site reactions occurred in an overall similar incidence in ADA positive and ADA negative patients while more patients reported IS erythema while being ADA positive (6.1% vs. 1.3%).

In general, the incidence of TEAEs was similar between *treatment-emergent ADA-positive patients* and *ADA-negative patients*, as were the incidences of all TEAEs, TEAEs by severity, serious TEAEs, and study drug related TEAEs.

ADA assessment of patients with continuous eplontersen treatment during studies CS3 and CS13 (in n=144 patients) revealed only one additional patient becoming ADA-positive compared to the CS3 study, based on a mean treatment duration of 661.6 days. The eplontersen safety profile by immunogenicity status (ADA-positive or treatment emergent ADA-positive and ADA-negative patients) in the ISS analysis was consistent with results from study CS3. Any potential longer-term safety consequences remain unknown.

2.6.8.8. Safety related to drug-drug interactions and other interactions

In vitro drug-drug interaction studies were conducted to evaluate the potential for eplontersen to

- interact with warfarin and ibuprofen with regard to plasma protein-binding displacement,
- inhibit and induce major CYP isoenzymes, and
- act as inhibitor and substrate for major drug transporters.

These studies indicated a lack of interaction potential, and therefore clinical drug-drug interaction studies were not conducted. Eplontersen has a very low potential to have drug-drug interactions with other drugs via CYPs, transporters, or protein binding.

2.6.8.9. Discontinuation due to adverse events

Discontinuations from study drug due to TEAEs were similarly reported for eplontersen and external placebo (4.2% and 3.3%) and more frequently for the historical and concurrent inotersen groups (>10%) up to Week 66 in study CS3. There was no accumulation of a specific TEAE in either group. TEAEs leading to discontinuation occurred in one subject each and were not in line with defined AESI. The six TEAEs that led to discontinuation of eplontersen were *arrhythmia* (fatal), *cerebral haemorrhage (fatal), urosepsis, proteinuria, renal impairment, and abnormal transaminases* (each in one patient). All events were serious, except for proteinuria and abnormal transaminases. The latter were the only two events assessed as related to eplontersen by the Investigator. *Pain, weight increased, arthralgia, and proteinuria* led to discontinuation from external placebo. Two additional TEAEs leading to discontinuation occurred between Week 66 and Week 85, i.e. *acute myocardial infarction* (fatal) and *lung neoplasm malignant*. Overall, 11 TEAEs (6.6%) led to discontinuation of eplontersen in the Eplontersen Treated Set with 3 additional (fatal) TEAEs in study CS13, i.e. *cardiac arrest, GI haemorrhage*, and *cardiogenic shock*.

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

Safety database and exposure:

The main body of evidence for clinical safety of eplontersen in the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv) includes patients aged 24 to 82 years at study entry, who were dosed every 4 weeks in two clinical studies, i.e. in the ongoing pivotal Phase 3 ION-682884-**CS3** study and its open-label extension ION-682884-**CS13**. The data cut-off for safety data is 07 April 2023. Presentation of safety is mainly based on the analysis up to Week 66, which compares to the duration of treatment with placebo and inotersen in the ISIS 420915-CS2 study used for indirect comparison. Additional safety data is provided up to Week 85+ (incl. data from post-treatment evaluation period), while the "Eplontersen Treated Set" combines data from studies CS3 and CS13 for long-term safety analysis. Study CS13 is also ongoing and aims to add an additional 3-years data upon conclusion, while additional long-term data will not be provided within this procedure. Despite generation of a new interim database lock for study CS13 in Q1 2025 – no interim CSR is planned to be submitted. Any emerging safety issues will be handled in a Periodic benefit-risk evaluation report. A final CSR for study CS13 will be submitted upon end of the study. Overall, 167 ATTRv–PN patients were exposed to eplontersen in the clinical programme: 144 patients received at least one dose of eplontersen in study CS3, while 20 patients in the concurrent inotersen group were switched to eplontersen at Week 37 and received eplontersen thereafter. Up to Week 66, 8 patients (5.6%) discontinued eplontersen, mainly due to adverse effects, which was lower compared to the other treatment groups, ranging from 13.3% in the external placebo group to 23% in the historical inotersen group. More patients had discontinuations and dose pauses in the external placebo and inotersen group as compared to eplontersen (38.3% and 52.7%, vs. 24.3%), which did not increase with longer treatment (26.9% in the Eplontersen Treated Set). The reasons for dose interruptions in the eplontersen group were mainly due to procedural issues and less often due to adverse events. 137 of 144 patients were exposed to eplontersen for ≥ 12 months (versus 52 of 60 subjects in the external placebo group). Additional treatment exposure derives from the Eplontersen Treated Set (overall mean 627.7 days), and 41 of 167 patients (28.1%), received treatment with eplontersen between 24 and 36 months. Taking into consideration that ATTRv amyloidosis is an orphan disease, the size of the safety database is considered adequate.

The main safety comparison for eplontersen in study CS3 was made to the external placebo group. The latter is considered informative in order to distinguish effects deriving from the underlying disease from drug-related adverse effects. Although, studies CS3 and CS2 were both sponsored by Ionis, and CS3 was designed to be highly similar to CS2, some baseline differences were noted in the external placebo group compared to the eplontersen population that need to be considered when interpreting the safety results. These differences mainly relate to the fact that the external placebo population was older, with higher frequency of Stage 2 disease, and performed worse on the Norfolk QoL-DN than the eplontersen population. Thus, it appears that external placebo patients were more affected by their amyloidosis, also including a higher percentage of cardiac involvement (based on ATTRv-CM diagnosis and mean NT-proBNP levels) contrasting the primary neurological indices, which indicate external placebo patients to be in a better condition. Moreover, treatment was blinded in the CS2 study whereas it was open-label in the CS3 study. These limitations render the within-study comparison of eplontersen and concurrent inotersen (N=42 patients) also relevant. Overall, **demographics** and **baseline disease characteristics** of eplontersen-treated subjects in study CS3 were found in accordance with the underlying disease.

Adverse events

Up to Week 66, incidences of TEAEs (incl. AESI, OAEI, severe TEAEs, SAEs, AEs relating to treatment discontinuation, and to withdrawal from study, as well as TEAEs leading to interruptions of dosing) in

the eplontersen group compared similarly to external placebo and favourably to historical and concurrent inotersen groups. Overall, TEAEs did not increase over time in the Eplontersen Treated Set except for slight increases in severe TEAEs, SAEs, and fatal TEAEs, all of which indicating worsening of the underlying disease.

Common adverse events

The most frequently reported TEAEs (≥ 10%) up to Week 66 in the eplontersen group in study CS3 were urinary tract infection (UTI), COVID-19, diarrhoea, nausea, and Vitamin A deficiency.

In the external placebo group, the most frequently reported TEAEs (≥ 10%) were UTI, diarrhoea, nausea, dizziness, pain in extremity, headache, nasopharyngitis, fall, fatigue, thermal burn, cough, neuralgia, constipation, asthenia, pain, hypoaesthesia, and muscular weakness.

In the historical inotersen group the most frequently reported TEAEs (≥ 10%) were UTI, diarrhoea, vomiting, nausea, oedema peripheral, dizziness, headache, arthralgia, fall, fatigue, IS erythema, syncope, anaemia, IS pain, IS pruritus, constipation, asthenia, platelet count decreased, pyrexia, thrombocytopenia, chills, and pain.

The most frequently reported TEAEs in > 5% of patients on eplontersen up to Week 66 (with those occurring with a difference of >2% to placebo in parentheses) were *COVID-19 (24.3% vs. 0%)*, urinary tract infection (UTI), diarrhoea, *Vitamin A deficiency (11.8% vs. 0%)*, nausea, *vomiting (8.3% vs. 5%)*, *immunisation reaction (8.3% vs. 0%),* oedema peripheral, *proteinuria (8.3% vs. 3.3%),* dizziness, pain in extremity, headache, arthralgia, *vision blurred (5.6% vs. 1.7%)*, nasopharyngitis, fall, and upper respiratory tract infection. Most TEAEs of vomiting in the eplontersen group were mild to moderate in severity, but 2 subjects had severe vomiting and 5 reported SAEs. Since the applicant identified some risk factors (vomiting prior to the first dose of eplontersen; concurrent TEAEs of oesophagitis, gastritis, hiatus hernia, oesophageal motility disorder, impaired gastric emptying, acute kidney injury, and urinary tract infection, as well as concomitant medication (carbamazepine), a discussion has been requested whether prophylactic treatment is needed before administration of eplontersen in patients at risk of vomiting. The applicant clarified that routine vomiting prophylaxis is not required because most of vomiting AEs reported were of mild severity. Moreover, since eplontersen does not cross the BBB, CNS-mediated vomiting is not expected.

The majority of TEAEs did not increase with longer treatment duration in the Eplontersen Treated Set, is consistent with the underlying (and progressing) ATTRv and increased autonomic neuropathy (e.g. oedema peripheral, renal presentations, ocular events, GI symptoms; Conceição et al., 2016; Gondim et al., 2022), while COVID-19 (and in this context, immunisations reactions) was not relevant at the time of study CS2. Contrasting the experience with inotersen in study CS2, ASO – specific safety issues like injection site reactions, constitutional symptoms, and thrombocytopenia are not among the common adverse events with eplontersen. Most TEAEs were mild to moderate in severity, and most of the events had their peak incidence within the first 6 months of treatment and decreased thereafter.

Study drug related adverse events/ adverse drug reactions (ADRs) proposed in the SmPC

Study drug related events occurred in a similar percentage of patients on eplontersen and external placebo (36.8% and 38.3%), and twice as high in the historical and concurrent inotersen group. The most common study drug related TEAEs (≥ 3% of patients) in the eplontersen group were Vitamin A deficiency (11.8%), proteinuria (4.2%), and IS pain (3.5%). ADRs were either a consequence of the mechanism of action (vitamin A deficiency) or general tolerability issues, e.g. injection site reactions. Except for thrombocytopenia and Vitamin A deficiency, drug-related TEAEs were not AESI.

The following ADRs have been proposed for eplontersen: *vitamin A decreased* (< LLN based on laboratory assessments), *vomiting, injection site erythema, injection site pain, and injection site*

pruritus. The methodology used to define the ADRs proposed to be included in section 4.8 of the SmPC has been described upon request: 29 TEAEs were identified in the search of studies CS3 and CS2 based on the Week 66 (Day 456) data that fulfil the requirement of occurring with an incidence of > 2% in any of the treatment groups and that occurred at least twice as frequently in the eplontersen compared with the external placebo group in studies CS3 and CS2. These were then reviewed for biological plausibility and temporal relationship. Moreover, the applicant presented justification for ADRs included in the Tegsedi PI but not proposed for the eplontersen PI. As a result, no additional ADRs have been proposed based on the indirect analysis of TEAEs in studies CS3 and CS2 despite the higher incidence in the eplontersen group as compared to external placebo given that (1) a number of these TEAEs are either known complications/ manifestations/ disease progression of ATTR or (2) were not persisting (WBC count decreases) or (3) could have been detected for more frequently for eplontersen due to a more frequent monitoring (renal TEAEs) or (4) did not reveal a mechanistic rational or (5) were specific to the COVID-19 pandemic not relevant at the time of study CS2.

AEs of special interest, serious adverse events and deaths, other significant events

Thrombocytopenia has been reported following AON treatment in preclinical species but appears to be compound-specific rather than a common class effect (Frazier et al., 2015). Other sources attributed thrombocytopenia to the class of AONs caused by the AON backbone and not by a specific nucleotide sequence. Less marked platelet reductions have so far been described for GalNAc-conjugated ASOs in monkeys (Zanardi et al., 2021). Nevertheless, eplontersen severely decreased platelet counts in one monkey in one of the chronic toxicity studies, accompanied by spontaneous haemorrhage, haematoma and petechiae. For inotersen, two different mechanisms were discussed in platelet count decreases. One is considered to be immune–mediated leading to a sudden and severe decline in platelets, which has not been reported with eplontersen in the Phase 1 CS1 study with multiple (different) dosing or in the Phase 3 studies in patients. The percentage of patients with thrombocytopenia AESI was similar for eplontersen and external placebo up to Week 66 (< 5% in both groups). 4 TEAEs were reported with eplontersen, all of them mild in severity, not serious, with platelet nadir remaining >100 x 10^9/L; TEAEs did not lead to dose interruption or discontinuation, did not require treatment, resolved with continuous eplontersen, and were not rated as causally related. No concomitant bleeding events were reported. Mean platelet count decrease from baseline with eplontersen was < 5% at any time point contrasting the experience with inotersen (25%) and remained stable with longer treatment. Patients with higher baseline platelet counts were found to have larger decreases post-baseline, and more patients in the eplontersen group compared to external placebo had baseline platelet counts of ≥ 200 × 10^9/L; thus, the mean change from baseline in nadir platelet counts was more pronounced for eplontersen compared to external placebo. Platelet abnormalities, i.e. < 140 × 10^9/L, were reported in 31.9% of patients in the eplontersen group, and based on the results from shift analyses, these were mainly those to Grade 1a (≥ 100 × 10^9/L to < 140 × 10^9/L; 27.8% of patients). Shifts to more severe grades occurred in single patients only and resolved with continuous treatment. Up to Week 66, there were no post-baseline shifts in platelet counts in 69.5% of patients in the eplontersen group, 83.4% of patients on external placebo, 44.1% of patients on historical inotersen, 45.8% of patients in the concurrent inotersen group, and in 75.0% of patients in the inotersen-eplontersen post-switch group. No patient had Grade 4 platelet count decrease up to Week 66. Less patients on eplontersen as compared to historical inotersen had ⩾ 30% or 50% decreases in platelet counts from baseline, platelet counts <LLN were rather transient than persisting, and the median duration of low platelet counts was shorter. Continuous treatment with eplontersen did not increase the risk for thrombocytopenia AESI in the Eplontersen Treated Set. However, there was a single patient, who had to discontinue eplontersen due to a severe SAE of thrombocytopenia Grade 4 (< 25 × 10^9/L) on study Day 611. The event was rated as not related to eplontersen despite various bleeding events with one of them leading to death (GI haemorrhage); however, none of them was timely related to platelet count decreases of Grade 2 or higher. Instead, there were various confounders involved, while a

contribution of eplontersen in this multifactorial cause cannot firmly be excluded. Based on the comprehensive evaluation of the risk for thrombocytopenia with eplontersen, routine monitoring of platelet counts is not foreseen by the applicant in the absence of a clear clinical risk, and thrombocytopenia is not included in the RMP. It is agreed with the applicant that a general warning is not needed based on the following facts:

- The overall monthly dose of eplontersen is 25% of the inotersen dose based on the GalNAc moiety enabling selective liver targeting; moreover, the proinflammatory potential of eplontersen is reduced due to mixture of phosphorothioate and phosphodiester linkages.

- The decrease in platelet counts between ≥100 to <140 × 10^9/L (29.2% for eplontersen and 15% for external placebo) had no clinical impact and resolved with ongoing eplontersen treatment, while the incidence of clinically meaningful platelet count declines (≥ Grade 1b; i.e. ≥75 to <100) was low and similar for eplontersen and external placebo.

- Bleeding events (actual bleeds at or not at the injection site) were overall less frequently reported with eplontersen as compared to external placebo or historical inotersen.

- A similar number of patients from the eplontersen and the external placebo group had ≥ Grade 1b thrombocytopenia while being on anti-platelet or anticoagulant agents or none, while the number of patients from the historical and concurrent inotersen groups with ≥ Grade 1b thrombocytopenia and concomitant use of these medications was (much) higher.

- The bleeding risk for eplontersen is not increased with concomitant antiplatelet agents, and it is similar for all treatment groups in the presence of anticoagulant agents.

- A baseline platelet value seems dispensable since there appears to be no risk for thrombocytopenia in patients treated with eplontersen contrasting the experience with inotersen.

Glomerulonephritis, an important identified risk for inotersen, has not been reported with eplontersen.

Ocular adverse events potentially related to vitamin A deficiency can be expected based on eplontersen's secondary pharmacodynamic effect to reduce serum TTR, which occurred in both CS3 treatment groups and likewise in the historical inotersen group in study CS2.

Ocular involvement of ATTRv-PN is frequent and its prevalence seems to increase with disease duration, including dry eye syndrome (~70%), amyloid deposition on the iris (38%) or on the anterior capsule of the lens (33%), pupillary disorders (as scalloped iris in ~28%), glaucoma (20%), vitreous opacity (17%), abnormal conjunctiva vessels (14%), and amyloidotic retinal angiopathy (4%) (Luigetti et al., 2020). On the other hand, Vitamin A deficiency is potentially related to ocular symptoms such as reduced night vision/ night blindness, persistent dry eyes, eye inflammation, and corneal inflammation/ ulceration/ thickening/ perforation. In nonclinical studies, no toxicological findings related to vitamin A deficiency by eplontersen have been identified, including ophthalmological and histological examinations of the eyes. No negative findings of ocular toxicity related to reduced serum vitamin A levels have been identified in the inotersen, patisiran, and vutrisiran clinical studies. Laboratory values for vitamin A but not for retinyl palmitate (the principal storage form of retinol/ vitamin A) were found reduced in almost every subject treated with eplontersen. Since the reduction of TTR levels and, subsequently, vitamin A levels (despite vitamin A supplementation) were more pronounced with eplontersen compared to inotersen (~73% vs. ~63% mean decrease from baseline), ocular toxicity might be different. Upon request, the applicant clarified that the small difference in mean %-change from baseline in serum TTR between eplontersen and historical inotersen (-82.96% and -76.41%; i.e. a difference of ~6%) is unlikely to cause a clinically significant difference between eplontersen and inotersen in serum vitamin A levels given that the ratio of TTR binding to RBP4 is 3.3:1. Reporting of *vitamin A deficiency* and *vitamin A decreased* as TEAEs (all drug-related) drove the

higher incidence of ocular AEs potentially related to vitamin A deficiency AESI for eplontersen as compared to external placebo/ historical inotersen (27.1% vs. 15% and 18.8%). *Vision blurred* was more frequently reported with eplontersen compared to external placebo and inotersen (5.6% vs. 1.7% and 1.8%), but the events were confounded by concomitant eye conditions or other medications. Moreover, the higher reporting of TEAEs of *vision blurred* at the expense of eplontersen mainly derived from study sites in study CS3, which were not previously involved in study CS2, and therefore not familiar with the MoA and not blinded to report vitamin A levels in CS3. In addition, the applicant confirmed that the reporting of *vision blurred* was highest at study sites from Taiwan in CS3 with all three patients having the A97S TTR genotype, which is associated with ocular manifestation of ATTRv. For vision blurred, no clear correlation to any TTR %-change from baseline categories could be confirmed for eplontersen. Overall, AESI were non-serious, mild to moderate in severity, did not lead to discontinuation, and the incidence did not increase with longer treatment duration. One SAE of *blindness transient* (resolved), one severe TEAE of *ulcerative keratitis* (not resolved), and a mild event of *xerophthalmia*, required corrective treatment despite continuation with eplontersen and were rated as not related to eplontersen but to ongoing or medical history of eye disorders. Based on the totality of data, no clear safety signal with regard to ocular toxicity due to vitamin A deficiency could be identified. The warning regarding reduced vitamin A levels in section 4.4 of the SmPC, including recommendation of vitamin A supplementation, has basically been brought in line with inotersen and vutrisiran. Vitamin A decreased is also included as ADR in section 4.8 with frequency "very common", which is based on laboratory Vitamin A values <LLN (in 96.5% of patients) that have been reported as TEAEs in study CS3 but not in the inotersen study CS2 (due to blinding of laboratory results in study CS2). Moreover, ocular AEs due to Vitamin A deficiency is rated a potential risk for eplontersen in the RMP.

Coagulation abnormalities have not been reported with eplontersen and laboratory data (aPTT, INR, PT) do not indicate prolongation of coagulation.

Renal impairment can be triggered by antisense oligonucleotides due to accumulation in the proximal tubules of the kidneys (Henry et al., 2007). Glomerular filtration with endocytotic re-absorption into the lysosomes of brush border epithelial cells of the proximal kidney tubules have been previously described for other phosphorothioate oligonucleotides including those with 2'-MOE modifications (Butler et al., 1997; Engelhardt et al., 2016). Moreover, renal impairment, in particular presenting with abnormal urinary protein excretion, is a common feature of the underlying ATTRv regardless of the genetic variant and affects approx. one-third of patients (Ferraro et al., 2021).

The incidence of renal impairment OAEI was higher for eplontersen compared to external placebo (15.3% vs. 10%) as was the event rate, but lower than for historical and concurrent inotersen (20.5% and 20.8%); all except one event were mild or moderate in severity, non-serious, did not lead to dose interruption, and almost half were rated as possibly related to eplontersen. eGFR and urinalysis were conducted more frequently in the eplontersen study CS3 as compared to external placebo, which might have contributed to the increased number of findings, especially TEAEs of *proteinuria* (8.3% vs. 3.3%, and *renal impairment* (3.5% vs. 0%). A single patient with low eGRF (53 mL/min/1.73 m^2) at screening had a SAE of *renal impairment* that was severe and presented with progressive decrease in eGFR with a nadir of 27 mL/min/1.73 m^2, which led to permanent discontinuation of eplontersen and improved thereafter without full recovery during follow-up; while the underlying ATTRv is assumed to be causative, eplontersen could have had at least a contributing role. A further TEAE of *proteinuria* (moderate) in a patient with high baseline UPCR and urine protein led to discontinuation, and was rated as related despite fluctuations during treatment. eGFR was always in the normal range. A contribution of eplontersen cannot be excluded given the lack of a relevant medical history or any concomitant medication known to worsen renal function. Renal impairment OAEI were not found to increase with longer treatment in the Eplontersen Treated Set. One additional SAE (*GFR decreased*)

and one severe AE of *proteinuria* were reported, both rated as not related to eplontersen, but to other risk factors and medical conditions.

Renal function assessed by serum and urine parameters was not impacted to a clinically significantly extent in subjects treated with eplontersen, and was similar to external placebo. Mean eGFR with eplontersen was always > 90 mL/min/1.73 m^2, contrasting the slight mean decrease in eGFR with historical inotersen that has likewise been observed in the concurrent inotersen group. Shifts from ≥90 mL/min/1.73 m^2 to ≥60 to <90 mL/min/1.73 m^2 were more frequently reported for eplontersen and also for concurrent inotersen as compared to external placebo and historical inotersen; again being a likely consequence of more frequent assessments in study CS3. Overall, less patients treated with eplontersen as compared to external placebo/ historical inotersen were reported with moderate or severe renal function declines. No remarkable differences were noted for serum creatinine and urinalysis results between eplontersen and external placebo. Available data do not suggest worsening of renal function over time. Based on these data, the applicant does not consider routine renal monitoring to be warranted. Upon request, a summary of six patients treated with eplontersen despite a decreased renal function at screening/baseline (eGFR of > 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2) has been provided. In 4 of 6 patients, the eGFR fluctuated considerably during continuous treatment with eplontersen but basically around baseline levels up to Day 456. In 2 of 6 patients, renal function worsened during treatment with eplontersen, while alternative explanations for the decrease in eGFR have been provided (including significant baseline renal dysfunction, medical conditions, and concomitant medications). However, a contributing role of eplontersen in deterioration of an impaired renal function in these two patients cannot be fully excluded. Overall, there is no clear contribution of eplontersen in the decline in renal function in patients with a baseline eGFR of < 60 mL/min/1.73 m^2 to > 45 mL/min/1.73 m^2 that would warrant baseline/ routine renal monitoring or a contraindication. A review of patients with concomitant nephrotoxic medication during treatment with eplontersen revealed 3 patients with concomitant gentamicin and tobramycin. There was no substantial renal function decline ascribed to eplontersen treatment. Moreover, eplontersen is not considered to cause protein binding displacement of nephrotoxic medication, which would increase the risk for nephrotoxicity. Thus, based on these data, a dedicated statement on the use of concomitant nephrotoxic medications in Section 4.5 of the SmPC for eplontersen is not clinically warranted.

Extensive distribution of inotersen to the liver could be demonstrated in mice and monkeys and also for eplontersen with the primary microscopic finding being basophilic granules (minimal to moderate in severity) in hepatocytes (the predominant location for eplontersen) and in Kupffer cells (predominant location for inotersen), lacking accompanying increases in serum ALT or abnormal hepatic morphology at exposure levels > 100-fold the proposed clinical doses. This finding is basically in line with the known uptake and accumulation of ASO in tissues (Henry et al., 2007). There were some reports of ALT increases in the high-dose group (90 mg) in the Phase 1 study CS1, and three subjects with ALT increased in study CS21 (administration of 45 mg, the dose recommended in the product information), which were rated related to eplontersen. One case of accidental eplontersen overdose in study CS3 leading to a 2.5-times increased exposure was reported with a mild TEAE of hepatic enzyme increased (related to eplontersen).

Abnormal liver function OAEI were found in a similar magnitude for eplontersen and external placebo (6.3% and 6.7%), and lower as compared to historical and concurrent inotersen (12.5% and 16.7%). The higher event rate reported for eplontersen as compared to external placebo for abnormal liver function OAEI (15.72 vs. 9.74 per 100 PY) derives from slightly more events of ALT and GGT increased, while GGT increased was not included in the liver panel in the CS2 study. Most frequently reported PTs for eplontersen were *ALT increased, GGT increased*, and *transaminases increased* (3.5%, 2.8%, and 1.4%, respectively). No SAEs or cases of Hy's law were reported, and no increased risk with longer treatment duration could be identified. *Transaminases abnormal* (ALT and AST ≥ 3 × ULN) led

to treatment interruption and discontinuation of eplontersen after reoccurrence at a later time point in a single patient for which a contribution of eplontersen cannot be ruled out despite increased GGT at baseline and absence of a timely relation between dosing and the event. One subject in study CS13 had ALT or AST ≥ 3 × ULN any time post baseline (at various time points) with no simultaneous increase in total bilirubin > 2 × ULN, which was not rated related and resolved with continuous eplontersen treatment. Mean changes in most liver chemistry parameters were similar for eplontersen and external placebo and lower as for historical and concurrent inotersen. Within-study comparisons for GGT indicate lower values for eplontersen as compared to concurrent inotersen. The majority of abnormal liver test results for eplontersen post-baseline were ≤3 x ULN regarding ALT or AST, and ≤ 2 x ULN regarding total bilirubin. Frequency of any higher values was low and similar to external placebo. The totality of liver function parameters did not raise serious concerns on liver toxicity with eplontersen, while effects are dose-related and cannot be ruled out in patients with hepatic impairment. At present, routine liver monitoring is not considered warranted.

ASO administered SC can induce injection site reactions (ISR), appearing as symmetrical erythematous skin lesions, often accompanied by discomfort, pain, itch, induration and/or ulceration, variable in size, and with variable resolution times between compounds and individuals. This local immune response is in line with the pro-inflammatory potential of ASO in humans (van Meer et al, 2016). In this context, the 4-times lower dosing frequency and especially the lower dose applied with eplontersen as compared to inotersen appears to mitigate pro-inflammatory effects. There is no evidence for major tolerability or safety issues deriving from ISR related TEAEs/ OAEIs with eplontersen, which were mainly mild in severity, and neither severe nor serious, with similar incidence in patients on eplontersen and external placebo (9% and 12%). The most frequent presentations were *injection site pain*, *injection site erythema*, and *injection site pruritus*, each in < 5% of patients, and included as ADRs in section 4.8 of the SmPC with the frequency "common" given that these were rated drug-related. Two patients were reported with Local Cutaneous Reactions at the Injection Site (LCRIS) with mild *IS erythema*. No worsening with longer treatment duration was noted.

The incidence of CNS disorders OAEI (mainly *dizziness, headache, syncope, neuralgia, and paraesthesia*) was lower in patients treated with eplontersen as compared to external placebo and historical inotersen. Overall, 7 SAEs were reported in 5 patients in the Eplontersen Treated Set, none of which was rated related to eplontersen, but compatible with the underlying disease-related effects in the CNS and medical history of these patients.

Bleeding events are common in amyloidosis, most frequently ecchymosis and purpura; gastrointestinal and renal tract haemorrhages are also common and a consequence of amyloid deposits (Nicol et al., 2022; Napolitano et al., 2023), but can also occur as a consequence of ASO-induced platelet count reductions. Based on the provided data, no specific bleeding pattern was noted and an increased risk by eplontersen seems to be absent. The incidence of haemorrhage OAEI with eplontersen was below that for external (and concurrent) treatment groups, and did not increase over time. The 4 SAEs in the Eplontersen Treated Set, i.e. *haematuria, gastric haemorrhage*, *cerebral haemorrhage (fatal) and GI haemorrhage (fatal)*, were not rated related to eplontersen and did not present with simultaneous platelet count decreases < 75 × 10^9/L (Grade 2 or worse).

The mechanism of action, available pre-clinical data, ECG data from the Phase 1 study CS1 performed in healthy volunteers, and the experience meanwhile gained with other 2'-MOE phosphorothioate ASO or GalNAc-conjugated siRNAs in animals or healthy volunteers including inotersen and vutrisiran (Kim et al., 2014; Yu et al., 2017; EPARs of "Tegsedi" and "Amvuttra"), respectively, do not point towards a clear cardiac risk for eplontersen. The type of cardiac TEAEs was generally consistent for the eplontersen and the external placebo group (mainly conduction abnormalities, which is a common manifestation of ATTRv), and incidences and event rates were found consistently lower in the eplontersen group compared to external placebo, thus, suggesting that a causal association with

eplontersen is unlikely. None of the cardiac OAEI including SAEs was rated related to eplontersen and the incidence was similar to external placebo (2.8% and 3.3%) and compatible with a medical cardiac history or ATTRv-CM, except for one patient with *AV block second degree*, without alternative explanation and a time to onset within the first month of initiation of eplontersen. Based on the Eplontersen Treated Set, there were 2 patients with AV block complete (and none on placebo and inotersen). The FDA label includes the following ADR information "*Three serious adverse reactions of atrioventricular (AV) heart block (2%) occurred in WAINUA-treated patients, including 1 case of complete AV block*". This information has been based on the cardiac effects of patisiran (TTR-lowering agent) known to provoke intraventricular septum thinning, which in turn can lead to conduction abnormalities (Solomon et al., 2019). Upon request, the applicant did not consider the inclusion of the SAEs of AV block in section 4.8 of the SmPC to be warranted given the similar incidence of AV block TEAEs up to Week 66 for eplontersen and external placebo in the CS3 and CS2 study, respectively. Moreover, the investigator did not find a causal relation of these TEAEs to eplontersen. Based on the provided literature it can be agreed that the most frequently reported conduction abnormality seen in ATTRv-CM patients is AV block first degree. The pattern of AV block TEAEs in studies CS3 and CS2 is rather in line with the underlying ATTRv as being a drug effect. It is also agreed that the 4 patients with SAEs in the eplontersen and in the inotersen/ eplontersen switching group in study CS3 had pre-existing cardiac conduction abnormalities or cardiac disease as a risk factor. 3 of 4 patients were also reported with ATTRv-CM at baseline. Based on these data, it is agreed to omit information on (serious) ADRs of AV block with eplontersen in section 4.8 of the SmPC.

The only event leading to study drug withdrawal with eplontersen was a fatal SAE of arrhythmia. The within-study CS3 comparison revealed a striking imbalance in the incidence of cardiac disorders OAEI for eplontersen and concurrent inotersen (13.9% vs. 0%).

According to the applicant, various baseline imbalances between the eplontersen and concurrent inotersen group in study CS3 could have been explanatory for the observed difference in the incidence of cardiac disorders OEAIs (13.9% vs. 0%). These include - for the eplontersen group - a slightly higher mean age, a slightly higher mean NT-proBNP value, more patients with non-Val30Met TTR mutation, and more patients with cardiac medical history. There were 21 patients (14.6%) in the eplontersen group with the A97S genotype (associated with progressive cardiomyopathy) as compared to 2 patients (8.3%) in the concurrent inotersen group. In addition, in the eplontersen group (but not the concurrent inotersen group) amyloid cardiomyopathy was prevalent for 10% of patients as well as clinically significant baseline ECG abnormalities (15%). The same picture is observed for baseline conduction abnormalities. It is therefore generally concurred with the applicant that patients in the eplontersen group could have been predestined for cardiac disorders OAEIs.

The incidence of cardiac disorders OAEI AEs and SAEs slightly increased during long-term treatment in the Eplontersen Treated Set as compared to the eplontersen group up to Week 66. In 4 of 12 subjects with cardiac disorders SAEs, the event was fatal but not causally related. SAEs all occurred in subjects with a diagnosis of ATTRv-CM and often with substantial cardiac history at baseline indicating worsening of the underlying disease. A majority of patients in the eplontersen and external placebo group had abnormal baseline ECGs; however, in more patients from the eplontersen group compared to the external placebo group these were abnormal and clinically significant (15.2% vs. 6.7%), which could have contributed to a higher incidence in patients with a > 30 msec and > 60 msec QTcF increase from baseline (11.8% vs. 6.7%, and 4.9% vs. 0%). Moreover, patients with increases in QTcF > 60 msec were stated to have had pre-existing cardiac-related conditions. A similar percentage of patients in both groups presented with a post-baseline QTcF interval of >500 msec while a majority of them already had elevated QTcF interval at baseline. Eight (8) patients in total had shifts to >500 msec in QTcF, amongst them, 5 patients with CM, one with a pacemaker, and one with subclinical CM. Moreover, in 3 of 8 patients, QT prolonging medication was reported. Upon request, the

applicant provided clarification that the lower incidence of ATTRv-CM and higher incidence of abnormal ECGs findings in the eplontersen group are not mutually exclusive given that amyloid fibrils can affect different structures and function in the heart. QTcF prolongation is described as a likely consequence of intraventricular delay in more than half of the patients with ATTRv (Cappelli et al 2020), and also due to amyloid fibril infiltration in the conduction system (Rapezzi C, et.al. 2009).

The applicant considers eplontersen less immunogenic than inotersen due to replacement of PS linkages with POs known to reduce immunogenic properties (Pollak et al., 2022). Overall, eplontersen reveals broad similarities with inotersen regarding ADA development (see EMEA/H/C/004782/0000), while an increased risk for hypersensitivity reactions as compared to external placebo could not be confirmed. Neutralising ADA testing was not performed neither with inotersen nor for eplontersen given that the drugs work at the intracellular level, which is inaccessible to antibodies that could neutralise the binding of eplontersen to its target. No clear impact on safety regarding formation and persistence of anti-drug antibodies in 45.8% of patients treated with eplontersen could be identified within a mean duration of 540 days in study CS3 (including TEAEs, SAEs, their severity and relatedness, AESI and OAEI, as well as laboratory results), while some quantitative differences were found, i.e. a ≥ 10% higher incidence of TEAEs in ADA positive vs. ADA negative patients was noted for GI disorders and Vitamin A deficiency. In the historical inotersen group, 30% of patients were ADA positive, which might indicate a higher immunogenicity potential of eplontersen. A majority of ADAs with eplontersen emerged at later time points (median onset 223 days), were persistent, and titers were rather low (median: 200). Single patients presented with high titers from Week 33. Upon request, the applicant presented a summary of safety results in ADA positive patients by titre quartiles for the eplontersen group. It appears that the safety of eplontersen in patients with the highest titre quartile (i.e. Q4 (800; 25600) is not different as compared to those having lower titres. No specific safety issues have been recorded for these patients. . The incidence of ADA positivity remained stable with 46.5% of patients during a mean treatment duration of 661.6 days in the Eplontersen Treated Set. However, any potential longer-term effects of immunogenicity on the safety profile remains undetermined and will be followed-up post-marketing based on study CS13 data. Switching from inotersen to eplontersen treatment after Week 37 was found to result in an increased incidence of treatment-emergent ADAs (at the Week 85+ analysis, 70.8% of patients had anti-Inotersen or anti-Eplontersen antibodies) with median ADA titers (anti-eplontersen) being substantially increased as compared to the eplontersen-only group (more than 10-fold) raising the question of whether patients can be safely switched from inotersen to eplontersen. The applicant clarified that the bioanalytical assays are not capable to differentiate between anti-eplontersen and anti-inotersen antibodies given their binding to the negatively charged backbone. Moreover, after switching from inotersen to eplontersen, there was no noteworthy increase in ADA – inotersen titers plateauing at Week 32. Three patients were reported with high anti-eplontersen ADA titers (defined as a titer > 12800 as upper quartile of peak titer distribution), while their $C_{through}$ concentrations were similar as compared to the patients with anti-eplontersen ADA titers < 12800 indicating that pharmacokinetics of eplontersen are similar irrespective of the ADA titers. A summary of safety results for anti-eplontersen ADAs by titre quartiles for the inotersen/eplontersen switching group (Q1 [50,200], Q2 [200,3200], Q3 [3200,12800], and Q4 [12800, 25600]) and ADA negative patients revealed that the safety of eplontersen in patients with the highest titre quartile (i.e. Q4 (12800; 25600) is not different as compared to those having lower titres. Two of the three patients had SAEs that were not rated as related to eplontersen but to the underlying disease (patient 2468-1080 with a SAE of Adverse Drug Reaction, patient 2469-1441 with SAE of AV block complete/ atrial fibrillation).

Up to the Week 66 analysis, 2 subjects died in the eplontersen group and 4 in the historical inotersen group. A total of 6 deaths were reported up to the DCO in the eplontersen group, none of which was considered related. 4 of the 6 deaths were cardiac related (arrhythmia, acute myocardial infarction, cardiac arrest, cardiogenic shock) and all of them occurred in patients diagnosed with ATTRv-CM, and

various baseline cardiac conditions. Upon request, the applicant provided further information for the fatal event of *acute myocardial infarction*, which - despite not being a typical presentation in ATTRv-CM – can occur as a result of disease progression. It is agreed that no firm conclusion can be raised given that an autopsy has not been performed. The fatal event of *cerebral haemorrhage* was not associated with low platelet counts but occurred as a consequence of a head trauma after a fall. *Gastrointestinal haemorrhage* occurred in a patient with multiple confounding factors (see "thrombocytopenia AESI"). At the time around death, platelet counts were in the normal range with the last eplontersen dose administered 110 days prior to the event. *Pneumonia sepsis* occurred as a 7th fatal event during a survival follow-up and the last dose was administered 20 months ago, which rules out a relation to eplontersen.

The incidence of *SAEs* was lower for eplontersen as compared to the external comparator groups (14.6% vs. 20% and 32.1%) up to Week 66, and similar to the concurrent inotersen group with shorter exposure (12.5%), and no SAE was considered related to eplontersen but 7.1% of SAEs in the historical inotersen group. The most common SAE in the eplontersen group was vomiting (in 3.5% of patients). SAEs mainly derived from the cardiac disorders, GI disorders, and infection and infestations SOCs, which is in line with general findings/ complications for ATTRv. In general, longer exposure to eplontersen does not seem to increase the incidence of SAEs in general.

According to the applicant, the safety profile of eplontersen was consistent across the predefined subgroups by age, sex, race, disease stage, PND score, genotype (V30M or non-V30M mutation), FAC clinical diagnosis, CM subgroup, eGFR, geographic region, and previous treatment with Vyndaqel or diflunisal, respectively. Upon request, the applicant presented comparative TEAE and SAE data from the external placebo group and – despite the limited number of subjects – the concurrent inotersen group up to Day 239. Notable results were an increased incidence of Cardiac disorders and renal and urinary disorders TEAEs with eplontersen by age. Nevertheless, the overall limited number of patients in the oldest subgroup >=75 years needs to be interpreted with caution. Eye disorders had a higher incidence in non-White as compared to White, especially for cataract (13.3% vs. 0%) and vision blurred (13.3% vs. 1.8%) in the eplontersen group. TESAEs did not reveal an increased risk with eplontersen by the aforementioned subgroups analyses. Notably, all of the TEAEs related to Vitamin A deficiency (16 patients; 11.1%) were reported in the South America/ Australia/ Asia subgroup. The applicant provided supplementary data indicating that patients in Europe had higher baseline Vitamin A values as compared to the North America and South America/ Australasia/ Asia region. Moreover, it is acknowledged that all patients reported with TEAEs related to Vitamin A deficiency exclusively derived from new study sites not previously involved in the inotersen CS2 study. Therefore, the imbalance in reporting Vitamin A deficiency as TEAE in the South America/ Australia/ Asia region is reasonable. Moreover, no dedicated studies were conducted in patients with renal or hepatic impairment, while the only available information derives from E-R analysis together with popPKPD analysis. Based on the results, no dose adjustment is required in patients with mild to moderate renal impairment and mild hepatic impairment, as reflected in section 4.2 of the SmPC. Eplontersen has not been studied in patients with severe/ end stage renal disease and patients with moderate or severe hepatic impairment, and also not in patients with prior liver transplant, all of which are included in the RMP for inotersen (either as missing information or potential risk), but not reflected in the RMP for eplontersen. Moreover, two tables on age distribution for TEAEs and special population have been asked for. In the age groups <65 years and 65 – 74 years, safety in the eplontersen group seems to be not worse than placebo. In the age group 75 – 84 years with few patients included, there seem to be more AEs related to cardiac and vascular disorders; however, interpretation is clearly hampered by the small numbers of patients in each treatment arm. The table on special populations, i.e. patients with hepatic impairment (Child Pugh score B or C) and with renal impairment (CKD Stage 3b, 4 or 5 (KDIGO definition), corresponding to an eGFR < 45 mL/min/1.73 m^2) indicates a single patient on placebo fulfilling the

requirement of renal impairment. Therefore, no further safety information derives from special populations.

No clear safety signal derived from the provided haematology and chemistry evaluations. Mean WBC counts were found similar for eplontersen and external placebo, while there were clearly more incidences of leukocytes, lymphocytes, and neutrophils <LLN for eplontersen as compared to external placebo, and likewise more shifts from normal at baseline to abnormal Grade 1 and Grade 2 post-baseline, and for lymphocytes and neutrophils, also to Grade 3 and even Grade 4 (2 patients with Grade 4 neutropenia). Supplementary information by the applicant indicates that for 14 out of 63 patients (22%) with Grade 2 or 3 lymphocyte nadir counts, the lymphocyte count was rated as timely related to a COVID-19 infection or vaccination. Therefore, the vast majority of low lymphocyte counts could not have been attributed to COVID-19 as has been hypothesised earlier by the applicant. However, the findings on reduced WBC counts were rather transient, and few patients had corresponding TEAEs that were not rated as related to eplontersen and resolved with continuous treatment. There was no sign of an increased risk in infections in these patients.

Any shifts in blood chemistry parameters were similar for eplontersen and external placebo, while a single SAE of hypokalaemia was reported, which was related to persistent vomiting.

No safety concerns relating to vital signs (SBP, DBP, HR, weight, and respiratory rate) derive from data up to Week 66 and during longer treatment duration. *Orthostatic hypotension* (mild and non-serious; not related) occurred in 3.5% of patients with cardiac-related medical history (including orthostatic hypotension, hypertension, or AV block) in the eplontersen group vs. none on placebo, and the incidence did not change with longer treatment duration.

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

N/A

Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances

N/A

2.6.10. Conclusions on the clinical safety

Overall, 167 patients with ATTRv amyloidosis with polyneuropathy were exposed to eplontersen in the clinical programme. The clinical safety evaluation, which informs the product information is based on the Week 85+ data cut-off in the pivotal ongoing study CS3 and includes 144 patients with at least one dose of eplontersen at the recommended dose of 45 mg with a mean exposure of 540.8 days. Of these, 137 patients (95.1%) received eplontersen for ≥ 12 months as of the latest safety DCO (07 April 2023). Long-term safety from study CS13 is expected to add an additional 3 years of data upon completion.

Taking into consideration that ATTRv amyloidosis is an orphan disease, the size of the safety database is considered adequate at the time of potential marketing authorisation.

A limitation of the clinical programme is the open-label design of study CS3 with external placebo and historical inotersen from the CS2 study used for indirect comparison for which some baseline differences in demographics and disease characteristics have been noted, while a small concurrent inotersen group in study CS3 provides descriptive data up to Week 37.

However, eplontersen is a GalNAc-conjugated 2'-MOE- gapmer ASO with a structure that has been reported to maintain the desired target mRNA affinity, while increasing metabolic stability and reducing the pro-inflammatory side effects observed with inotersen. Therefore, the long-term experience with inotersen and the external comparison to this precursor product is supportive for the database.

At present the only ADRs identified by the applicant are *vitamin A decreased* (< LLN based on laboratory assessments), *vomiting, injection site erythema, injection site pain, and injection site pruritus,* each with common frequency except for Vitamin A decreased, which occurred in almost all patients in line with the proposed MoA. Serum vitamin A reduction with eplontersen appears to be slightly higher as compared to inotersen (median reduction - 74% vs. - 68%) and also as compared to other TTR-lowering agents like vutrisiran and patisiran (median reduction - 66.5% and - 68.3% at Month 9), which, however, does not appear to entail a higher risk for ocular toxicity. The higher reporting of vision blurred in the eplontersen group cannot be clearly attributed to eplontersen but might also be a consequence from (1) an increased reporting from study sites not previously involved in the CS2 study with inotersen, (2) the fact that investigators were not blinded to report vitamin A levels in the CS3 study, and (3) an increased reporting of vision blurred in subjects with the A97S TTR genotype, which is known to be associated with ocular manifestation of ATTRv. While a clear ocular toxicity due to vitamin A deficiency could not be identified in neither of the clinical programmes, an increased risk with longer treatment cannot be ruled out and will be further addressed post-marketing. ISRs were reported with a similar frequency as for external placebo, were mainly mild, not serious or severe and did not lead to discontinuation. No major objection is raised on clinical safety.

In summary, the safety issues identified for eplontersen are thought to be manageable with the proposed risk minimisation measures in the product label and in the RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP (version 1.3):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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

2.7.1.1. Discussion on safety specification

The applicant intends to include 'Ocular adverse events due to vitamin A deficiency' as an important potential risk in the list of safety concerns. Through the mechanism of action of eplontersen i.e. inhibition of TTR translation, a decrease in the plasma concentration of vitamin A is expected. This has

also been consistently observed in the clinical development program of eplontersen. A mean decrease in vitamin A levels at week 65 in study CS3 was ~73% from baseline for eplontersen, which is higher than the decrease of ~63% noticed in the historical inotersen group. PTs more frequently reported with eplontersen than with external placebo were vision blurred, cataract, dry eye, and visual impairment. Additionally, a higher incidence of ocular AEs potentially related to vitamin A deficiency was noticed for eplontersen compared to external placebo/historical inotersen groups (27.1% vs. 15% and 18.8%).

The applicant provided a comparison of TEAEs with PT vision blurred by level of TTR reduction, which showed that no clear correlation to the TTR %-change from baseline categories could be confirmed for eplontersen. The applicant further argued that a higher reporting of TEAEs of vision blurred might have derived from study sites in study CS3, which were not previously involved in study CS2, and were therefore not familiar with the MoA and not blinded to report vitamin A levels in study CS3. In addition, the applicant confirmed that the reporting of vision blurred was highest at study sites from Taiwan in CS3 with all three patients having the A97S TTR genotype, which is associated with ocular manifestation of ATTRv. As described in the clinical safety section above, in summary, the applicant presented adequate justification for not adding vision blurred as an ADR in the SmPC for eplontersen. However, with regard to the unknown long-term effect of vitamin A deficiency caused by eplontersen on the development of ocular adverse events (not just including blurred vision but also other potentially severe events as described throughout the previous Clinical assessment reports and in the Overview), 'Ocular adverse events due to vitamin A deficiency' should still remain as important potential risk in the RMP. While it is agreed with previous MS comments that only routine RMM will be established to minimise this potential risk, it is noted that the SmPC advises on important specific clinical actions to be taken regarding the risk of vitamin A deficiency (and associated ocular events), which warrants inclusion of this potential risk in the summary of safety concerns in the RMP. The applicant will further implement a specific adverse reaction follow-up questionnaire (as included in Annex 4 of the RMP) to gain further detailed information about ocular adverse events due to vitamin A deficiency in the post-marketing setting and further data might also derive from the extension of study ION-682884-CS13 to further characterise (or maybe refute) this potential risk in the future. Taking the above into account, the ongoing clinical study ION-682884-CS13 was included as a category 3 PASS in the PhV plan of the RMP, as requested. However, in Table V-2 the study was erroneously added to the Missing Information '*Use in pregnant women.*' instead to the Important Potential Risk '*Ocular events due to vitamin A deficiency*'. The RMP (1.4) has been updated accordingly.

It is noted that consequences of vitamin A deficiency are also included in RMPs of further TTR-lowering therapies, including inotersen, an ASO with similar sequence. It is also noted that beside the ocular symptoms, vitamin A deficiency may also result in accumulation of immunological and dermatological symptoms. However, there were no substantial differences in the frequency of dermatological and immunological events related to vitamin A deficiency between the eplontersen group and the external placebo group. The frequencies of the events were slightly higher in the placebo group i.e. 59.0% versus 63.3% for infections and infestations TEAEs and 21.5% versus 25.0% for dermatological TEAEs, respectively. Infections and infestations events in the eplontersen group were mainly mild or moderate in severity. No serious dermatological events were reported and the majority were mild in severity. Whereas non-ocular events are theoretically possible consequences of vitamin A deficiency, they would be expected upon long-term vitamin A deficiency, which would be detected through the earlier occurrence of ocular manifestations. No non-ocular events consequent to vitamin A deficiency are currently considered eligible for inclusion as a safety concern in the RMP.

The applicant could not specify any anticipation for a different safety profile upon eplontersen long-term use. Hence, long-term safety is not eligible for inclusion as missing information in the RMP according to GVP module V. The applicant removed long-term safety as an area of missing information from the summary of safety concerns in the RMP and aligned other relevant parts. Nevertheless the

applicant intends to monitor long-term safety >36 months in the context of study ION-682884-CS13. The applicant confirmed to report on any emerging long-term safety issues observed within study CS13 in the PSURs.

Patients with renal insufficiency defined by eGFR < 45 mL/min/1.73 m^2 were excluded from the pivotal clinical study CS3. The safety assessment spotted proteinuria and renal impairment as the two most frequently reported PTs in the eplontersen group. Both PTs were more frequently reported than in the external placebo group, 8.3% vs. 3.3% and 3.5% vs 0%, respectively. The higher incidence of PTs proteinuria and renal impairment might be attributed to the open-label nature of CS3 study. Consequently, urine protein laboratory assessments were performed more frequently for patients in the eplontersen group compared with the external placebo group, increasing the chance to detect abnormalities. It is agreed that for proteinuria, all relevant laboratory measurements were not increased for eplontersen. For renal impairment it can be argued that eGFR did not demonstrate an increased risk with eplontersen over external placebo. Higher proportion of patients presented with >25% eGFR decrease by CKD-EPI from Baseline in the eplontersen group compared to the external placebo group. It is noted that most of the patients (23/27) had single occurrences while on eplontersen. Of these, 21/23 patients returned to normal or baseline levels following the eGFR ≥ 25% decrease; and their peak eGFR increase any time after the eGFR ≥ 25% decrease ranged from 81 to 118 mL/min/1.73 m^2. One returned to baseline level, while one with several confounding factors did not. The remaining 4/27 patients had eGFR decline ≥ 25% at 2 to 4-time points and returned to Baseline levels while continued on eplontersen treatment. Based on the currently available PK and safety data, the safety profile of eplontersen is not expected to be different in patients with eGFR < 45 mL/min/1.73 m^2, and an inclusion as missing information is currently not warranted.

In the healthy volunteer study CS21, ALT increased was reported in three individuals, of whom two discontinued the study. The pivotal study did not show imbalances between eplontersen and the external placebo group. From the clinical development program, no strong anticipation on liver injury can be currently derived. However, hepatotoxicity is an identified risk for inotersen and use in patients with hepatic impairment is missing information in the RMP. The applicant will closely monitor hepatotoxicity cases and report on use in patients with hepatic impairment in the PSURs.

No data were generated on patients with prior or anticipated liver transplant as this was an exclusion criteria in the clinical development program for eplontersen. Orthotopic liver transplant remains a treatment option in ATTRv (previously known as hATTR) patients and this patient population is not excluded from (future) treatment with eplontersen as per the current SmPC. Liver transplant rejection is inflammatory in nature. Pre-clinical data suggested a lower inflammatory profile of eplontersen in comparison to inotersen. This might be attributed to the phosphodiester modifications at the backbone of eplontersen contrasting the sole presence of phosphorothioate linkages with inotersen. Additionally, eplontersen is delivered at a monthly dose 25-fold lower than that of inotersen due to the liver-targeting through the GalNAc moiety. However, and due to sequence relatedness to inotersen, cases of liver transplant rejection should be closely monitored and presented in details in the PSURs.

Decreases in platelets count observed with eplontersen were generally mild and transient, with a mean duration of 4 weeks, substantially shorter than 26 weeks observed with inotersen. Routine monitoring of platelets is currently not warranted in the SmPC. Nevertheless, in the eplontersen group, a larger proportion of patients was found to have ≥30% and ≥50% decreases in the platelet count as compared to external placebo (27.1% vs 6.7% and 4.9% vs 1.7%, respectively). The applicant agreed to closely monitor thrombocytopenia cases in the PSURs.

Pregnancy and lactation were exclusion criteria in the clinical development program. A direct mechanistic effect of eplontersen is not expected. However, there are potential concerns regarding foetal damage due to vitamin A deficiency. It is noted that onset of familial ATTR might be as early as

30 years old. Thus, treatment of pregnant women with eplontersen cannot be excluded, even with a wording in section 4.6 of the SmPC. The applicant has accepted to include 'Use in pregnant women and effects on pregnancy outcomes' as missing information. Part VI.2.2 of the RMP has been revised, as requested, to rename the missing information 'Use in pregnancy' into 'Use in pregnant women and effects on pregnancy outcomes'.

With regard to lactation, no clinical or pre-clinical data on eplontersen secretion in breast milk were generated. The applicant referred to a pre- and postnatal development (PPND) study for inotersen held in mice (Study No. 420915-AS14). Findings from the study showed a liver/breast milk concentration ratio of >600 fold (liver tissue in g, milk in ml), indicating a low transfer into milk. The macromolecular size and hydrophilicity of ASOs likely interfere with their passage into milk. The GalNAc moiety in the structure of eplontersen is expected to increase the specificity toward the maternal liver and reduce off-target distribution, including distribution into breast milk. It is noted that that ASGR1 receptors, the targets of GalNAc moieties, are apparently absent at the mammary glands. The applicant also highlighted the 25-fold lower dose of eplontersen in comparison to inotersen, which should further reduce the amount that might be transferred into breast-fed infants. This is agreed. The low oral permeability of ASOs is also acknowledged. Taken together, inclusion of 'use during lactation' as an area of missing information is currently not warranted.

2.7.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, the Rapporteur agrees that the safety concerns listed by the applicant are appropriate.

Additionally, the following issues will be closely monitored in the PSURs:

- Hepatotoxicity
- Safety in patients with hepatic impairment
- Thrombocytopenia
- Liver transplant rejection cases

2.7.1.3. Protected Personal Data (PPD) and Commercially Confidential Information (CCI) considerations for the RMP Safety Specification

The Safety Specification of the RMP does not contain PPD/CCI.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in the updated RMP submitted with the responses.

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaires for ocular adverse events due to vitamin A deficiency:

A structured targeted questionnaire will be used to obtain further information regarding reported suspected adverse reactions of ocular adverse events due to vitamin A deficiency.

The questionnaire has been designed to collect information pertaining to the clinical course of the event, the signs and symptoms observed, eplontersen treatment received, relevant medical history, concomitant medications, risk factors, treatment received for the event, relevant laboratory results and other signs and symptoms of Vitamin A deficiency. The targeted questionnaire is provided in Annex 4 of the RMP.

Summary of planned additional PhV activities from RMP

Not applicable

Overall conclusions on the PhV Plan

The applicant confirmed that pregnancy cases will be appropriately followed-up and summarised and presented in PSURs as requested in the PRAC outcome.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed activities are appropriate.

However, since additional data could also be obtained from the extension study ION-682884-CS13 to further characterize (or possibly refute) the potential risk of *ocular adverse events due to vitamin A deficiency*, this ongoing clinical study ION-682884-CS13 should be included as a Category 3 PASS in the PhV plan.

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Ocular adverse events due to vitamin A deficiency	Routine risk communication: SmPC Section 4.4 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance on the investigation of signs and symptoms of vitamin A deficiency and the need for evaluation of ocular signs or symptoms of vitamin A deficiency prior to initiation of eplontersen treatment in SmPC Section 4.4 and PIL Section 2 Recommendation for oral supplementation of vitamin A in SmPC Section 4.4 and PIL Section 2 Guidance on the ocular symptoms that should trigger an ophthalmology referral in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status (prescription only medication)

Safety concern	Routine risk minimisation activities
Use in pregnant women and effects on pregnancy outcomes	Routine risk communication: SmPC Sections 4.4 and 4.6 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation that pregnancy should be excluded prior to initiation of treatment, that women of childbearing potential should practice effective contraception during treatment, and details of actions that should be taken should a woman intend to become pregnant or should an unplanned pregnancy occur during eplontersen treatment in SmPC Section 4.6 and PIL Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status (prescription only medication)

The applicant did not propose additional risk minimisation measures for the important potential risk of *Ocular adverse events due to vitamin A deficiency.*

A decrease in serum concentration of vitamin A is an expected consequence of the mechanism of action of eplontersen with ocular AEs including reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening or corneal perforation.

A warning in the SmPC includes a recommendation for oral supplementation to reduce the risks due to vitamin A deficiency and referral for ophthalmological assessment if patients develop corresponding ocular symptoms. The SmPC also contains a warning about an increased risk of foetal malformations if vitamin A levels are too high or too low in the first 60 days of pregnancy.

Clinical consequences of vitamin A deficiency, including ocular AEs, are included in the list of safety concerns for the TTR silencers inotersen, patisiran, and vutrisiran.

There is a patient alert card for Inotersen which, among other safety concerns, refers to the risk of adverse ocular effects due to vitamin A deficiency. The patient alert card includes the recommendation to refer patients for ophthalmological assessment if they develop ocular symptoms consistent with vitamin A deficiency.

However, routine risk minimisation appears to be sufficient for eplontersen at this stage. According to the CHMP Rapporteur's assessment, ocular AESIs reported in study CS3 were non-serious, and mild to moderate in severity. None led to study drug discontinuation and the incidence did not increase with longer treatment duration. As requested by the CHMP Rapporteur, the product information should be updated and the relevant safety information must also be included in the RMP.

The PRAC Rapporteur having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

PRAC outcome

The PRAC noted the proposal from the applicant for a non-interventional longitudinal pregnancy surveillance program (study D8451R00002), aimed to collect data on pregnancy outcomes and infants'

adverse events through the first year of life leveraging AstraZeneca's global Pharmacovigilance system, as a category 3 additional PhV activity. While structured description of spontaneous reports of pregnancy exposures is of importance, it is expected that these are presented in the PSURs as part of routine pharmacovigilance. It is understood that the proposed study will not use e.g. registry data, but spontaneously reported data. Such data source is not considered sufficiently robust as basis for a category 3 PASS. Given the rarity of the disease itself, and thereby, anticipation of very few cases of exposed pregnancies occurring in the post marketing setting, introduction of a dedicated PASS is not considered meaningful. To conclude, this category 3 PhV activity should be removed from the RMP. In addition, the applicant should confirm that pregnancy cases will be appropriately followed-up and summarised and presented in PSURs. Additionally, the applicant should discuss the feasibility of analyses of pregnancies captured in ATTR disease registries e.g. THAOS registry.

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan updated to version 1.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

2.9. Non-conformity of paediatric studies

N/A

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Wainzua (Eplontersen) is included in the additional monitoring list as it contains a new active substance, which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Hereditary transthyretin-mediated amyloidosis, also known as variant transthyretin-mediated amyloidosis (ATTRv), is a rare, autosomal dominant, rapidly progressive, multi systemic disease caused by variants in the transthyretin (TTR) gene that results in debilitating morbidity and high mortality. Amyloid deposits accumulate in multiple organs, particularly the peripheral nervous system, gastrointestinal tract, kidney, and heart, which manifests in progressive polyneuropathy including sensorimotor neuropathy and autonomic neuropathy. Cardiomyopathy, nephropathy, and gastrointestinal dysfunction frequently develop simultaneously. The phenotypic presentation of the disease is dependent on the pattern of affected organs. The most common manifestations of ATTRv amyloidosis are polyneuropathy and cardiomyopathy.

The worldwide prevalence of ATTRv-PN has been estimated at approximately 10,000 patients. In Europe, the incidence is estimated from 0.003 to 0.10 cases per 10,000 per year, with a preponderance in Portugal, France, Italy, and in the UK. In Europe, the prevalence is highest in northern Portugal and northern Sweden (as high as 50 per 100,000 inhabitants).

There are over 120 reported TTR genetic variants associated with ATTRv amyloidosis with heterogeneity in disease presentation from predominantly neuropathic, predominantly cardiac or mixed phenotypes. V30M is predominantly associated with polyneuropathy and is found primarily in families with heritage from Portugal, Sweden, Japan, and Brazil. V122I is associated with predominantly cardiac manifestations but also can be associated with concurrent polyneuropathy and predominates in the US.

The current application of eplontersen is for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv), and is not restricted with regard to disease stage.

Eplontersen is a 2'-MOE-modified chimeric gapmer antisense oligonucleotide with a mixed backbone of PS and PO internucleotide linkages, conjugated to a triantennary N-acetyl galactosamine (GalNAc) ligand for enhanced uptake by hepatocytes, the principal source of systemically circulating transthyretin protein. Eplontersen shares the same mechanism of action with inotersen.

3.1.2. Available therapies and unmet medical need

Orthotopic liver transplantation was the first disease-modifying therapy used to treat ATTRv polyneuropathy, which was found to be more effective in individuals with the Val30Met variant of TTR who have early-onset ATTRv polyneuropathy than in those who have late onset or other variants.

Before the approval of TTR gene silencers, pharmacotherapeutic strategies to treat ATTRv included tafamidis or off-label use of diflunisal, both of which are TTR stabilisers that work by preventing dissociation of the tetramer into amyloid-forming monomers.

Tafamidis ("Vyndaqel"; EMEA/H/C/2294) was approved across the EU for the treatment of ATTR in adult subjects with Stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment. Tafamidis acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers.

Diflunisal is a non-steroidal anti-inflammatory drug (NSAID) that is presently used off-label in subjects with Stage 1 and Stage 2 disease; however, the cardiovascular and renal side effects associated with the NSAID class limit the use of this drug in older patients with ATTRv-PN or patients with ATTRv-CM.

In addition to the TTR stabiliser Tafamidis, there are currently three TTR gene silencers approved in the European Union for the treatment of ATTRv amyloidosis in adults with polyneuropathy:

ONPATTRO (patisiran), TEGSEDI (inotersen), and AMVUTTRA (vutrisiran). The principle aim of TTR gene silencing is to degrade mRNA of both variant and wild-type TTR alleles in hepatocytes to limit liver TTR synthesis. Patisiran and vutrisiran act through ribonucleic acid interference (RNAi); and inotersen acts through RNAse H-mediated cleavage.

However, despite the fact that a number of treatment options are available for patients with ATTRv amyloidosis with polyneuropathy, there is still unmet need for improved products that address the underlying physiological basis of the disease (not stabilisers), being highly effective in improving neuropathy and delay or stop disease progression, have convenient dosing, minimize the need for health care encounters and have acceptable safety profiles without the need for intensive laboratory or clinical monitoring.

3.1.3. Main clinical studies

ION-682884-CS3 is an ongoing open-label, externally controlled, randomized (6:1 eplontersen and concurrent inotersen) phase 3 study to evaluate the efficacy of SC administered eplontersen 45 mg q4w (hereafter referred to as the eplontersen group) versus the external placebo group from ISIS 420915-CS2 (hereafter referred to as the external placebo group) in slowing disease progression in patients with ATTRv-polyneuropathy (PN) with documented genetic mutation in the TTR gene. The study population included only ATTRv-PN patients with stage 1 (ambulatory without assistance) or stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy or Coutinho Stage.

Patients were randomized 6:1 to eplontersen (eplontersen SC 45 mg q4w) or inotersen-eplontersen (inotersen SC 300 mg q1w until Week 34, then switched to eplontersen SC 45 mg q4w from Week 37). An interim analysis was conducted after all patients in ION-682884-CS3 had the opportunity to complete 35 weeks of treatment. The final placebo-controlled analysis was conducted at Week 66 since there was no external placebo data beyond this timepoint.

The study consisted of a $\leq$ 10-week screening period, an 84-week treatment period (last dose administered at Week 81), and a 20 week post-treatment evaluation period or enrolment into the long-term extension study ION-682884-CS13.

ION-682884-CS3 included 168 randomized patients, all of whom received at least one dose of study drug. Of the 144 patients randomized to eplontersen, 140 (97.2%), 135 (93.8%) and 130 (90.3%) patients completed study treatment through Week 35, Week 66, and Week 85, respectively.

Of the 24 patients randomized to the concurrent inotersen group, 20 (83.3 %) completed the 35 weeks inotersen treatment, all of whom switched to eplontersen treatment from Week 37 and completed treatment through Week 66.

The primary objective was to evaluate the efficacy of eplontersen, compared with external placebo, with regards to serum TTR concentration, mNIS+7 composite score, and Norfolk QoL-DN total score over 65/66 weeks of treatment.

The supportive study ION-682884-CS13 is a Phase 3, long-term extension, open-label extension (OLE) study of ION-682884-CS3 and ISIS 420925-CS101 and therefore does not comprise any control group. The study consists of a ≤ 8-week Screening and Baseline Assessment Period, a 3-year Treatment Period during which all patients receive eplontersen 45 mg once every 4 weeks (Q4W), and a 24-week Post-treatment Evaluation Period.

3.2. Favourable effects

The main comparison in the clinical program was between eplontersen in CS3 study and external placebo group from CS2 study.

In the Week 66 final analysis, the 3 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 65, change in mNIS+7 composite score from baseline to Week 66, and change in Norfolk QoL-DN total score from baseline to Week 66) were analysed.

Substantial reductions in TTR levels were recorded with eplontersen treatment which were sustained at least up to week 85 with mean percent changes from baseline of -82.13, -82.96 and -81.83 at week 35, 65 and 85, respectively. The LSM difference between eplontersen and external placebo of 70.4% (95% CI: 75.2%, -65.7%) at Week 65. It is believed that achieving a significant reduction in TTR protein through a targeted mechanism of action will lead to clinical benefit for patients suffering from ATTRv-PN. As more knowledge about the disease has accumulated in recent years, it could even be argued that the observed large effect on the TTR levels alone may be sufficient to justify the use of eplontersen in these patients. The inclusion of an inotersen arm in the study allowed the results to be contextualised and provided reassurance on the robustness. Similar reductions in serum TTR have been achieved with inotersen (-74.3) and eplontersen (-82.1).

Eplontersen was found superior to external placebo for all primary efficacy endpoints in the Week 35 interim analysis, with sustained effects observed in the Week 66 final analysis:

- Percentage change in serum TTR concentration:
    - At Week 35: -66.64% (95% CI: -71.61, -61.53)
    - At Week 65: -70.14% (95% CI: -75.02, 65.15)
- Change in mNIS+7 composite score:
    - At Week 35: -8.8 (95% CI: -13.21, -4.34)
    - At Week 66: -23.1 (95% CI: -29.26, -17.01)
- Change in Norfolk QoL-DN total score:
    - At Week 35: -11.3 (95% CI; -16.26, -6.30)
    - At Week 66: -19.3 (95% CI; -24.99, -13.53)

The observed large effects together with the mechanism of action, the target engagement and a clear and large pharmacodynamic effect on the TTR levels are quite reassuring for the efficacy of eplontersen in patients with stage 1 or stage 2 ATTRv-PN based on established pharmacodynamics and clinical endpoints.

While overall the conducted sensitivity analyses cover relevant aspects (alternative missing data handling, additional covariates, etc.), some of the sensitivity analyses better aligned to a probably more relevant estimand.

Although the main comparison in study ION-682884-CS3 was between eplontersen and external placebo, data from this study (CS3) suggest, according to the applicant, that eplontersen offers several clinically relevant efficacy advantages over inotersen. Despite that the baseline disease characteristics of concurrent inotersen in study CS3 showed that these patients were in a clearly better condition compared to the eplontersen group, concurrent inotersen and eplontersen achieved similar large reductions in TTR. The mean TTR reduction from baseline at Week 35 for eplontersen was 82.13% (SD: 11.66), which was numerically greater than the mean reduction seen with concurrent inotersen i.e, 74.26% (SD: 23.28). Formal comparisons between eplontersen and concurrent inotersen have not been performed, but differences in the neurological index and quality of life have been observed between these molecules indicating potential greater benefit from eplontersen treatment over inotersen. The change from baseline at Week 35 for mNIS+7 achieved by concurrent inotersen was +4.06 (SD: 13.39) (consistent with further deterioration) and for Norfolk QoL-DN -2.97 (SD: 12.09), whilst in the case of eplontersen these values were -0.04 (SD: 16.22) and -4.79 (SD: 16.51), respectively. Comparisons beyond week 35 are not available since patients receiving concurrent inotersen were switched to eplontersen.

A comparison of treatment effects between the concurrent inotersen group (study ION-682884-CS3) and the historical inotersen group (study ISIS 420915-CS2) has been provided. Concurrent and historical inotersen presented similar effects in the change from baseline at week 35 for important neuropathy measurements (PD: reduction of serum TTR, functional: mNIS+7 composite score and QoL: Norfolk QoL-DN score). The results of the CS3 study with the comparison of eplontersen and the external placebo group from CS2 study can be considered reliable.

In study CS3, predefined subgroup analyses of the primary endpoints (i.e. difference in LSM percent change in serum TTR concentration, LSM change in mNIS+7 composite score, and LSM change in Norfolk QoL-DN total score) across all prespecified 9 different demographic and disease baseline characteristics based on sex, race, age, region, CM subgroup, previous treatment, Val30Met TTR mutation, disease stage, and ATTRv-CM clinical diagnosis showed at week 65 consistent statistically significant effects of eplontersen vs placebo.

Consistent and statistically significant effects across all the subgroups analysed was also shown when additional post-hoc subgroup analyses based on additional disease-related baseline characteristics (mNIS+7 composite score, NIS composite score, Norfolk QoL-DN total score, PND score, NYHA classification, and NT-proBNP concentration) were performed.

The supportive study ION-682884-CS13 is a Phase 3, long-term extension, open-label extension (OLE) study of ION-682884-CS3 and ISIS 420925-CS101 and therefore does not comprise any control group. The study consists of a ≤ 8-week Screening and Baseline Assessment Period, a 3-year Treatment Period during which all patients receive eplontersen 45 mg once every 4 weeks (Q4W), and a 24-week Post-treatment Evaluation Period.

No unexpected findings have been recorded up to now with the study CS13 and the results are consistent with the pivotal trial CS3.

3.3. Uncertainties and limitations about favourable effects

The applicant has argued that while the pivotal study (CS3) only included patients with stage 1 and stage 2, there is no apparent biological rationale for why patients with more severe disease (ie, Stage

3 - bedridden or wheelchair bound) would not benefit from the eplontersen mechanism of action as seen by the consistency of the serum TTR concentration reductions and clinical benefits across various levels of severity. It is agreed that there is biological plausibility that patients with stage 3 could benefit from the reduction of TTR and amyloid deposition. Based on the target engagement and mechanism of action efficacy could be extrapolated to stage 3 patients. The unmet medical need for patients with ATTRv and stage 3 polyneuropathy can definitely be acknowledged. However, there were no FAP stage 3 patients recruited and any potential benefit in these bedridden or wheelchair bound patients has not been evaluated.

The applicant clarified that data from only 3 patients (in the eplontersen arm), who progressed to stage 3 (PND score IV) polyneuropathy during the course of the study ION-682884-CS3 are currently available. Two (2) out of 3 patients who progressed to stage 3 disease, improved again and this is acknowledged. It is welcomed also that the applicant is committed to collect data in stage 1 to 3 polyneuropathy patients through an ongoing registry study (MaesTTRo).

The data from the applicant and relevant publications for stage 3 polyneuropathy patients are very limited and the input of the SAG-N experts did not recommend extrapolation of the results from stage 1 or 2 to stage 3 PN patients (please see final answers from SAG-N).

Consequently, this issue was discussed at CHMP.

After the Oral Explanation, the CHMP considered that extrapolation from stage 1 or 2 patients to stage 3 cannot be justified based only on the mechanism of action and the target engagement of eplontersen. However, patients who progress to stage 3 should be allowed to continue to receive treatment.

On a different topic, since week 66 endpoints are most relevant, change from baseline to week 66 in TTR, mNIS+7 and Norfolk QOL-DN are considered pivotal/primary for the current application and these are reported in the product information.

The SmPC was updated with the results from the copy increments from reference (CIR) based multiple imputation analysis applied to only those missing data following treatment discontinuation for mNIS+7 and Norfolk. To avoid any potential confusions for the prescriber by applying different approaches for the analyses of the primary endpoints TTR, mNIS+7 and Norfolk QoL-DN, the results of only the CIR approach are included in the product information. Due to the complexity of the issues with the biological plausibility, the SmPC currently mentions that only a reference-based multiple imputation approach for the missing data was used. This is considered sufficient as all reference-based multiple imputation approaches yield very similar results and differences between results are minor to have any meaningful clinical impact.

3.4. Unfavourable effects

In accordance with findings described for inotersen and other non-conjugated phosphorothioate 2'-MOE ASOs or later developed GalNAc-conjugated successors (Frazier, 2015; Crooke et al., 2021; Zanardi et al., 2021), the observed pro-inflammatory effects and toxicities of eplontersen in repeat-dose toxicity studies in mice, rats and monkeys represent rather pharmaceutical class effects of oligonucleotides, which are impacted by the frequency of s.c. injections, the respective backbone chemistry and reflect the uptake and extensive tissue distribution and accumulation of oligonucleotides. Eplontersen dose-dependently accumulated as minimal/mild basophilic granules within cytoplasmic vacuoles of macrophages and/or monocytes at injection sites and in lymph nodes, proximal tubular kidney epithelia, hypertrophied hepatocytes and in hepatic Kupffer cells of mice, rats and monkeys.

Overall, the incidences of TEAEs, drug-related TEAEs, TEAEs leading to discontinuation, TEAEs leading to dose reduction or interruption, and SAEs were similar for eplontersen and external placebo and lower as compared to historical inotersen. Most TEAEs were mild to moderate in severity, while severe TEAEs were less frequently reported in subjects on eplontersen as compared to external placebo and inotersen.

Six subjects died while being treated with eplontersen in studies CS3 and CS13. The fatal SAEs in study CS3 were arrhythmia, cerebral haemorrhage, and acute myocardial infarction (after Week 66), and in study CS13 cardiac arrest, gastrointestinal haemorrhage, and cardiogenic shock. None of the deaths was rated as related to eplontersen but all either had a (cardiac) medical history, confounding factors, or alternative reasons that have contributed to the fatal outcomes. A further death (SAE of pneumonia sepsis) was recorded after the Week 85+ analysis in study CS3 in a patient, who was off eplontersen for ~20 months, thus, ruling out any contribution.

Up to Week 66, TEAEs in > 5% of patients in the eplontersen group (with those occurring with a difference of >2% to placebo in parentheses) were *COVID-19 (24.3% vs. 0%)*, urinary tract infection (UTI), diarrhoea, *Vitamin A deficiency (11.8% vs. 0%)*, nausea, *vomiting (8.3% vs. 5%)*, *immunisation reaction (8.3% vs. 0%),* oedema peripheral, *proteinuria (8.3% vs. 3.3%),* dizziness, pain in extremity, headache, arthralgia, *vision blurred (5.6% vs. 1.7%)*, nasopharyngitis, fall, and upper respiratory tract infection. The majority of TEAEs did not increase with longer treatment duration.

Adverse drug reactions (ADRs) with eplontersen were based on the mechanism of action, preclinical findings, class effects of ASO, and scientific plausibility and retrieved from the Week 66 analysis in at least 2% of patients in any treatment group, i.e. *Vitamin A decreased* (< LLN based on laboratory assessments; frequency "very common"), *vomiting, injection site erythema, injection site pain, and injection site pruritus* (each with a frequency "common").

The incidence of **thrombocytopenia AESI** was similar for eplontersen and external placebo (2.1% and 1.7%), and lower as compared to historical and concurrent inotersen (24.1% and 25%). Four thrombocytopenia AESI were reported in 3 patients on eplontersen with nadir platelet counts being Grade 1 (according to CTCAE), and 3 of 4 TEAEs were rated as not related. TEAEs were mild, non-serious, no patient required dose interruption or discontinuation, and all events recovered/ resolved with continuous treatment without corrective measures. No bleeding events were reported. Mean percent reduction in platelet counts from baseline was less than 5% at any time point, and around 25% for historical inotersen at Month 6. The only post-baseline platelet abnormalities reported more frequently with eplontersen as compared to external placebo were those being Grade 1a ($\geq$ 100 to < 140 x 10^9/L; 29.2% vs. 15%). Continuous treatment with eplontersen did not increase the risk over time. A single patient discontinued eplontersen due to a severe SAE of thrombocytopenia Grade 4 (< 25 × 10^9/L) in study CS13, which was confounded by medical history and concomitant medication.

A decrease in serum levels of vitamin A is an expected secondary pharmacodynamic effect of reducing serum TTR with the mean %-decrease from baseline being higher with eplontersen as compared to inotersen (~73% vs. ~63%) despite supplementation with Recommended Daily Allowance (RDA) of 3000 IU of Vitamin A. Most of the patients in the eplontersen and historical inotersen group (95.1% and 90.1%) had post-baseline vitamin A values < LLN; thus, Vitamin A decreased is an ADR for eplontersen in section 4.8 with frequency "very common". No toxicological findings related to TTR inhibition and vitamin A deficiency by eplontersen including ophthalmological and histological examinations of the eyes were noted in repeat-dose studies in animals. **Ocular adverse events potentially related to Vitamin A deficiency** were reported for 27.1% of patients in the eplontersen group and for 15%, 18.8%, and 16.7% of patients on external placebo, historical inotersen, and concurrent inotersen, respectively. The incidence was 16.7% for eplontersen after exclusion of *vitamin A deficiency* and *vitamin A decreased* (Vitamin A laboratory values were not reported as TEAEs in study

CS2 due to blinding of the results). Ocular AEs potentially related to vitamin A deficiency were non-serious, and mild to moderate in severity. None led to study drug discontinuation. TEAEs of vitamin A deficiency and vitamin A decreases were (possibly) related, did not lead to dose interruption, and most were ongoing at the time of the DCO. *Vision blurred* was reported in more patients on eplontersen than on external placebo (5.6% and 1.7%). Ocular adverse events due to vitamin A deficiency is a potential risk for eplontersen in the RMP.

Eplontersen-related effects on the kidneys are expected to occur due to accumulation and renal excretion, therefore being a target organ of toxicity. TEAEs of *glomerulonephritis* were not reported in patients treated with eplontersen. **Renal impairment** OAEI were reported by more patients on eplontersen as compared to external placebo (15.3% vs. 10%) and for 20.5% of patients treated with historical inotersen, with the main presentations being proteinuria (8.3% vs. 3.3% and 6.3%) and renal impairment (3.5% vs. 0% and 3.6%). TEAEs of renal impairment OAEI up to Week 66 with eplontersen were mainly mild or moderate in severity and non-serious, and half of them were related to eplontersen. Based on the Eplontersen Treated Set, 4 of 31 patients with renal impairment OAEI had either serious (*renal impairment* and *GFR decreased*) or severe TEAEs (*renal impairment* and *proteinuria*), or TEAEs leading to withdrawal of the study drug (*proteinuria (2 AEs)* and *renal impairment*), none of which was assessed as related to eplontersen. Any changes in mean eGFR with eplontersen from baseline were similar to external placebo. Shifts from baseline eGFR mainly occurred from ≥ 90 mL/min/1.73 m^2 to ≥ 60-< 90 mL/min/1.73 m^2 and more frequently for eplontersen as compared to external placebo (31.5% vs. 11.7%), in line with a higher reporting of eGFR ≥25% decrease from baseline (18.8% vs. 10%). No remarkable differences were noted for serum creatinine and urinalysis results between eplontersen and external placebo.

The incidence of **abnormal liver function OAEI** was similar for eplontersen and external placebo (6.3% and 6.7%), and lower than for historical inotersen (12.5%). TEAEs were mild or moderate in severity, non-serious, and most were not related to eplontersen and resolved during treatment without corrective measures. *Transaminases abnormal* led to discontinuation of eplontersen in one patient (possibly related to eplontersen). Most frequently reported PTs for eplontersen were *ALT increased, GGT increased*, and *transaminases increased* (3.5%, 2.8%, and 1.4%, respectively). The majority of abnormal liver test results for eplontersen post-baseline were ≤3 x ULN regarding ALT or AST, and ≤ 2 x ULN regarding total bilirubin. No cases of Hy's law were reported, and no increased risk with longer treatment duration could be identified.

The incidence of AEs at the **injection site OAEI** was similar for eplontersen and external placebo (9% and 11.7%), and lower than in the historical inotersen (52.7%). AEs were mainly mild in severity, and neither severe nor serious and did not lead to discontinuation. The most frequent presentations were *IS pain*, *IS erythema*, and *IS pruritus* (each in < 5% of patients), and these are rated ADRs in section 4.8 of the SmPC with the frequency "common". Two patients were reported with Local Cutaneous Reactions at the Injection Site (LCRIS) with the mild *IS erythema*. No worsening with longer treatment duration was noted.

Remaining **other adverse events of interest**, like coagulation abnormalities, flu-like symptoms, CNS disorders, haemorrhages, cardiac disorders, as well as hypersensitivity TEAEs, immune-mediated reactions, and TEAEs related to accidents and injuries were reported at lower or similar incidences for eplontersen and external placebo and less frequently as compared to historical inotersen.

45.8% of eplontersen-treated patients were positive to anti-drug antibodies compared to 30% of patients from historical inotersen. Based on the provided analyses, no clear impact on safety could be identified despite quantitative differences in the occurrence of GI disorders and Vitamin A deficiency (≥ 10% higher incidence of TEAEs in ADA positive vs. ADA negative patients).

3.5. Uncertainties and limitations about unfavourable effects

The long-term safety of eplontersen relies on the evaluation of safety from study CS3 through CS13 up to the DCO 07 April 2023. So far, 41 of 167 patients in the Eplontersen Treated Set (28.1%) have received treatment with eplontersen between 24 and 36 months. Study CS13 is still ongoing and aims to add an additional 3-years data upon conclusion. Additional long-term data will not be provided within this procedure but any emerging safety issues will be reported as part of a periodic benefit-risk evaluation (PBRER) until the final CSR will be available.

General uncertainties on the unfavourable effects of eplontersen result from the safety evidence that is based on data from an uncontrolled clinical study (CS3), which is compared to external placebo/ historical inotersen data from study CS2. The main safety comparison for eplontersen was made to the external placebo group. Although, study CS3 was designed in order to be highly similar to the CS2 study, there are some baseline differences regarding treatment groups, which might impair comparability of results. External placebo patients were older, more often had stage 2 disease, had a worse score in the quality of life measure Norfolk QoL-DN as compared to the eplontersen population. While the differences between groups are somewhat blurred with regard to neurological involvement (see also discussion on clinical efficacy), the cardiac involvement is clearly higher in external placebo patients as compared to the eplontersen group (based on ATTRv-CM diagnosis and mean NT-proBNP levels). Although, no clear *cardiac risk* could be identified for eplontersen, the following findings regarding cardiac safety have been noted and discussed:

- The within-study comparison of eplontersen and concurrent inotersen in study CS3 revealed an imbalance in the incidence of cardiac disorders OAEIs (13.9% vs. 0%). After the switch to eplontersen at Week 37, two patients (10%) were reported with cardiac disorders. Upon review, baseline differences between the eplontersen and concurrent inotersen group at the expense of eplontersen have been identified that reasonably justify a higher incidence in cardiac disorders OAEI.
- The imbalance noted for post-baseline QTcF interval increases of >30 msec and >60 msec with more patients in the eplontersen group compared to external placebo with such abnormalities (>30 msec: 11.8% vs. 6.7%; >60 msec: 4.9% vs. 0%) is likely a consequence of a higher proportion of patients with clinically significantly abnormal baseline ECG findings in the eplontersen group (15.2%) than for external placebo (6.7%). Eight (8) patients (5%) in the Eplontersen Treated Set were found with a QTcF shift to >500 msec, all of whom had either abnormal baseline ECGs, established ATTRv-CM or concomitant QT prolonging medication.
- The sudden cardiac death (*acute myocardial infarction*) in one patient is not a typical presentation in ATTRv-CM and, despite potentially concomitant treatment with domperidone (known to prolong QTc interval), no other cardiac related history could be identified. However, the lack of an autopsy impedes further evaluation.

Dose pauses with eplontersen (~27%) were found less frequent as compared to external placebo and historical inotersen. While the reasons for the latter were platelet count decreases and renal TEAEs, the reasons for dose interruptions with eplontersen were mainly due to procedural issues and less often due to adverse events.

Based on the comprehensive evaluation of the risk for thrombocytopenia with eplontersen, the applicant considered routine monitoring of platelet counts dispensable in the absence of a clear clinical risk contrasting inotersen; moreover, thrombocytopenia is not included in the eplontersen RMP. Further discussion on the need for a general warning including the need for a baseline platelet count, the risk for bleeding events with low platelet counts in patients with concomitant medication (e.g. antithrombotic agents, antiplatelet agents), and special situations were monitoring might be required

has been provided. The applicant could reasonably justify that the incidence of clinically meaningful platelet count decreases (≥ Grade 1b; i.e. ≥75 to <100) was low and similar for eplontersen and external placebo, thus neither warranting a baseline nor routine monitoring based on the lack of an increased risk. Likewise, no evidence for an increased risk of bleeding (actual bleeds at or not at the injection site) could be identified for eplontersen alone or in combination with antiplatelet or anticoagulant agents, so that a dedicated warning in the SmPC is not required.

Reduction of TTR levels and as a consequence, vitamin A levels, with eplontersen seems to be slightly higher compared to historical inotersen, while a clear signal for ocular toxicity cannot be deduced from the respective comparison with the external placebo and inotersen group as well as the detailed analysis of the reported (related) TEAEs in the eplontersen group. The numerical imbalance with regard to TEAEs of *vision blurred* in the eplontersen group compared to the external placebo and historical inotersen groups (5.6% vs. 1.7% and 1.8%) have been explained as a consequence of different study sites involved in studies CS3 and CS2, the lack of blinding to vitamin A levels in CS3, as well as involvement of the A97S TTR genotype in these TEAEs being associated with ocular manifestation of ATTRv.

Available data do not suggest worsening of renal function over time in the Eplontersen Treated Set, with incidences of renal impairment OAEI and any renal function abnormalities being similar to the Week 66 safety data in study CS3. The slightly higher incidence of renal impairment OAEI as compared to external placebo is explained to result from a higher frequency of renal function monitoring and urinalysis in study CS3 compared to study CS2. The applicant does not consider routine renal monitoring to be warranted based on a similar profile for eplontersen and external placebo, and this has been further substantiated by the applicant. No clear risk of renal function decline in n=6 patients with an impaired renal function (eGFR of > 45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) at baseline could be deduced, while a contributing role of eplontersen in deterioration of an already impaired renal function in two of the six patients cannot be fully excluded despite alternative explanations. Based on an evaluation of renal function in three eplontersen-treated patients with probable/ definite nephrotoxic comedication and the lack of protein binding displacement of nephrotoxic medication by eplontersen, a dedicated statement in section 4.5 is not justified. At present, the statement in SmPC section 4.2 seems sufficient ("*Eplontersen has not been studied in patients with eGFR < 45 mL/min/1.73 m^2 or end-stage renal disease (see section 5.2) and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk*").

The emergence of anti-drug antibodies during eplontersen treatment does not raise clear safety concerns and it appears - based on the provided analysis - that the safety is not different in patients with (very) high ADA titers during treatment, even after the switch from inotersen to eplontersen treatment, which could be a relevant scenario in clinical practise. Although, not included in the applicant's immunogenicity assessment in the summary of clinical safety, treatment-emergent ADA in patients from the concurrent inotersen group, who switched to eplontersen at Week 37 revealed 17 of 24 patients (70.8%) at the Week 85 analysis with anti-inotersen or anti-eplontersen antibodies.

The applicant's conclusion that the safety profile of eplontersen is generally consistent across the analysed subgroups (by age, sex, race, disease stage, PND score, genotype (V30M or non-V30M mutation), FAC diagnosis, CM status, region, and previous treatment, respectively) has been substantiated by comprehensible and comparative data up to Day 239.

No dedicated studies have been conducted in *patients with renal or hepatic impairment* while the only available information derives from E-R analysis together with popPKPD analysis. No data is available in patients with moderate or severe hepatic impairment, in patients with severe or end-stage renal impairment, in patients with prior liver transplant or anticipated liver transplant, and in pregnant or lactating women.

3.6. Effects Table

Table 24: Effects table for Wainzua (eplontersen), formerly Eplontersen AstraZeneca AB, in the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv) (data cut-off: 07 April 2023)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
Favourable Effects (Full Analysis Set, FAS)								
Serum TTR percent change from baseline At week 35	Serum TTR (g/L) at Week 66 Final Analysis b Full Analysis Set **At week 35**	%	N = 140 LSM percent change from baseline (SE) = -81.3 (1.8) [-84.83, -77.71] N = 136 # Mean change from baseline (SD) **-81.98** (11.702)	N = 20# Mean change from baseline (SD) **-74.26** (23.281)	N = 59 LSM percent change from baseline (SE) = -14.7 (2.2) [-18.96, -10.44] N = 57* Mean change from baseline (SD) = -9.64 (16.787)	N = 93* Mean change from baseline (SD) = -74.03 (13.045)	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-66.64%** (95% CI: -71.61, -61.53)	(1)
Serum TTR percent change from baseline At week 65	Serum TTR (g/L) at Week 66 Final Analysis b Full Analysis Set **At week 65**	%	N = 141 LSM percent change from baseline (SE) = -80.2 (1.8) [-83.75, -76.72] N = 135 § Mean change from baseline (SD, SEM) **-82.96** (10.374, 0.893)	N = 20 § Mean change from baseline (SD, SEM) **-79.89** (12.007, 2.685)	N = 59 LSM percent change from baseline (SE) = -10.2 (2.2) [-14.43, -5.87] N = 51* Mean change from baseline (SD) = -5.24 (18.204)	N = 84* Mean change from baseline (SD) = -71.09 (15.097)	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-70.14%** (95% CI: -75.02, -65.15)a	(1)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
mNIS+7 Composite Score J2R At week 35	mNIS+7 Composite Score at Week 66 Final Analysis c,d Full Analysis set **At week 35**		N=140 LSM change from baseline (SE) = 1.1 (1.8) [-2.47, 4.77] N = 137# Mean score (SD) **79.35** (42.868)	N = 19# Mean score (SD) **66.27** (37.489)	N=59 LSM change from baseline (SE) = 9.9 (1.9) [6.29, 13.56] N = 55* LSM change from baseline (SE) = 11.20 (1.956)	N = 95* LSM change from baseline (SE) = 2.50 (1.543) Difference in LSM from CS2 placebo -8.69 (95% CI -13.49, -3.90) p-value 0.0005	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-8.8** (95% CI: -13.21, -4.34)**a**	(1)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
mNIS+7 Composite Score J2R At week 66	mNIS+7 Composite Score at Week 66 Final Analysis b Full Analysis set **At week 66**		N=141 LSM change from baseline (SE) = 3.2 (2.5) [-1.75, 8.18] N = 138 § Mean score (SD, SEM) **79.68** (44.919, 3.970)	N = 19 § Mean score (SD, SEM) **67.28** (44.374, 10.180)	N=59 LSM change from baseline (SE) = 26.3 (2.6) [21.32, 31.38] N = 52* LSM change from baseline (SE) = 25.53 (2.690)	N = 85* LSM change from baseline (SE) = 5.80 (2.17) Difference in LSM from CS2 placebo -19.73 (95% CI -26.43, -13.03) p-value 0.00000004	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-23.1** [-29.26; -17.01]**a**	(1)
Norfolk QoL-DN J2R at week 35	Norfolk QOL-DN Total Score at Week 66 Final Analysis b Full Analysis Set **At week 35**		N = 140 LSM change from baseline (SE) = -2.8 (2.1) [-6.87, 1.19] N = 135# Mean (SD) **38.47** (26.814)	N = 20# Mean (SD) **34.30** (21.964)	N = 59 LSM change from baseline (SE) = 8.4 (2.1) [4.30, 12.58] N = 57* LSM change from baseline (SE) = 6.95 (2.288)	N = 94* LSM change from baseline (SE) = 0.81 (1.811) Difference in LSM from CS2 placebo -6.14 (95% CI -11.77, -0.52) p-value 0.032	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-11.3** (95% CI: -16.26, -6.30)**a**	(1)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
Norfolk QoL-DN J2R at week 66	Norfolk QOL-DN Total Score at Week 66 Final Analysis c,d Full Analysis Set **At week 66**		N = 141 LSM change from baseline (SE) = -5.5 (2.4) [-10.19, -0.91] N = 135 § Mean score (SD, SEM) **35.60** (26.305, 2.264)	N = 20 § Mean score (SD, SEM) **34.90** (25.676, 5.741)	N = 59 LSM change from baseline (SE) = 13.7 (2.4) [8.92, 18.50] N = 52* LSM change from baseline (SE) = 12.67 (2.666)	N = 94* LSM change from baseline (SE) = 0.99 (2.117) Difference in LSM from CS2 placebo -11.68 (95% CI -18.29, -5.06) p-value 0.0006	**SoE:** Difference in LSM (CS3 Eplontersen 45mg Q4W - NEURO-TTR Placebo) **-19.3** (95% CI: -24.99, -13.53)**a**	(1)
Unfavourable Effects								
Thrombocytopenia AESI	Incidence of thrombocytopenia (including thrombocytopenia and platelet count decreased)	%	2.1	25	1.7	24.1	Uncertainties regarding the need for a warning in section 4.4, concomitant medication known to reduce platelet counts, and monitoring in patients at risk have been discussed and clarified.	(1)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
Ocular AEs potentially related to vitamin A deficiency	Incidence of Ocular AEs potentially related to vitamin A deficiency	%	27.1	16.7	15	18.8	Mainly related to TEAEs of Vit A deficiency and Vit A decreased (not reported as TEAEs in ISIS 420915-CS2). More pronounced decrease in Vit. A for eplontersen compared to inotersen; imbalance of vision blurred at the expense of eplontersen	(1)
	Vision blurred	%	5.6		1.7	1.8		
Renal impairment OAEI	Incidence of renal impairment OAEI	%	15.3		10	20.5	More frequent monitoring in study CS3 as compared to CS2. Higher incidence mainly due to TEAEs of proteinuria and renal impairment. Uncertainties regarding baseline conditions/ concomitant medication on renal function decline have been discussed and clarified. No data available in patients with severe or end-stage renal impairment.	(1)
	Incidence of glomerulonephritis	%	0	0	1.7	2.7	-	(1)
Abnormal liver function OAEI	Incidence of Abnormal liver function OAEI	%	6.3		6.7	12.5	No data available in patients with moderate or severe hepatic impairment and in patients with liver transplant.	(1)

Effect	Short Description	Unit	ION-682884-CS3 Eplontersen 45 mg q4w	ION-682884-CS3 Concurrent inotersen	ISIS 420915-CS2 External Placebo	ISIS 420915-CS2 Historical inotersen	Uncertainties/ Strength of evidence	References
Injection site OAEI	Incidence of Injection site OAEI	%	9		11.7	52.7	-	(1)
Cardiac disorders	Incidence of cardiac disorders	%	13.9	0	21.7	22.3	Uncertainty regarding imbalance between eplontersen/ concurrent inotersen in study CS3 have been discussed.	(1)
	Incidence of abnormal QTcF at any visit - >30 msec increase from baseline - >60 msec increase from baseline - shift to QTcF >500 msec	%	 11.8 4.9 4.8		 6.7 0	 8.0 2.7	Abnormalities are not in line with baseline disease characteristics indicating less cardiac involvement in the eplontersen group. However, lower incidence of ATTRv-CM and higher incidence of abnormal ECGs findings in the eplontersen group are not mutually exclusive given that amyloid fibrils can affect different structures and function in the heart.	(1) (2)
Immunogenicity	Number (percentage) of patients with positive ADA	n (%)	66 (45.8)	0	Anti-inotersen ABs: 16 (66.7) Anti-eplontersen ABs: 14 (58.3) Anti-inotersen or anti-eplontersen ABs: 18 (75.0)	34 (30.4)	Very high ADA titers after switching from inotersen to eplontersen are not expected to change the safety profile.	(3), (4)

Notes: (1) up to Week 66 data of ION-682884-CS3 (NEURO-TTRansform) and ISIS 420915-CS2 (NEURO-TTR); (2) Eplontersen Treated Set (ION-682884-CS3 and -CS13); (3) Eplontersen 45 mg q4w group of ION-682884-CS3 (Week 85+); (4) ISIS 420915-CS2

[a] 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. The numbers represent treatment difference in serum TTR concentration percent change from baseline and mNIS+7 Composite Score, and Norfolk QoL-DN Total Score change from baseline up to Week 66 using Copy Increment from Reference Analyses (CIR) in CSR (ION-682884-CS3) with all on-study (ie, both on-treatment and post-treatment) measurements (Full Analysis Set). The results of the CIR analysis were applied to only those missing data following treatment discontinuation

[b] 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.

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

[d] Patients with a missing mNIS+7 composite score or Norfolk QoL-DN total score at Week 35 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.

* These values are from the ISIS 420915-CS2 Clinical Study Report, submitted with the eplontersen MAA

These values are from the ION-682884-CS3 Report Body Section 14.2 (Week 35 Interim Analysis Update).

§ These values are from the ION-682884-CS3 Report Body Section 14.1, W85 EOT study report (Week 85 Analysis).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

A pivotal study (CS3) including a small group of concurrent inotersen is used to support this MAA. The main comparison was between eplontersen in CS3 study and external placebo group from CS2 study (a well-conducted pivotal study supporting the approval of inotersen).

In the Week 66 final analysis, the 3 co-primary endpoints (percent change in serum TTR concentration from baseline to Week 65, change in mNIS+7 composite score from baseline to Week 66, and change in Norfolk QoL-DN total score from baseline to Week 66) were analysed and showed a large effect in TTR reduction, the neurological index and the quality of life for eplontersen treatment. Comparable results, albeit to a lesser extent, were shown for the concurrent inotersen group, providing reassurance for the large effects observed with eplontersen.

It is believed that achieving significant reductions in TTR protein through a targeted mechanism of action will lead to clinical benefit for patients suffering from ATTRv-PN. Based on the evidence gathered in recent years, one could even argue that the observed large effect on TTR levels alone is sufficient to justify the use of eplontersen in these patients.

The secondary endpoints and subgroup analyses supported the favourable results obtained with the primary analysis. Sensitivity analyses showed similar large effects.

The clinically relevant and statistically significant results in the reduction of serum TTR concentration and the reductions in mNIS+7 composite score and Norfolk QoL-DN score across all prespecified subgroups (Disease stage 1 or 2 and PND score I, II or IIIa/IIIb) are noted. Efficacy could be extrapolated to patients with stage 3 polyneuropathy, based on target engagement and mechanism of action. However, there were no clinical data available for ATTRv patients with stage 3 polyneuropathy. The applicant clarified that 3 patients progressed to stage 3 (PND score IV) polyneuropathy during the course of the CS3 study and 2 of them improved again.

The data from the applicant and relevant publications are very limited and the CHMP took into account the input of the SAG-N experts who did not favour extrapolation of results from stage 1 or 2 to stage 3 PN patients.

The wording of the indication was therefore discussed at CHMP and during the oral explanation of the applicant with the Committee.

Following the discussion at the oral explanation, the CHMP considered that extrapolation from stage 1 or 2 patients to stage 3 cannot be justified based only on the mechanism of action and the target engagement of eplontersen. However, patients who progress to stage 3 should be allowed to continue treatment.

Safety:

Overall, the safety issues with eplontersen 45 mg q4w in the clinical studies point towards an acceptable risk in the studied patient population. The safety profile compares similar to external placebo and moreover, it compares favourably to inotersen 300 mg q1w. Based on the open-label experience in study CS3 and its long-term extension study CS13 up to the data cut-off, a majority of TEAEs were mild to moderate in severity, while serious AEs have been reported in single patients only without being rated as causally related to eplontersen, and TEAEs/ SAEs rarely led to discontinuation of

treatment.

Taking into consideration the nature of the disease, the size of the safety database with patients having at least 12 or 24 months exposure to eplontersen is considered adequate at the time of potential marketing authorisation, while long-term safety will be further addressed by the ongoing CS13 study and followed-up in the PSURs. The limitation of the clinical programme deriving from the open-label design of study CS3 with indirect comparison to external placebo and historical inotersen from the CS2 study can mostly be compensated by the long-term experience with the precursor product inotersen. At the same time, the GalNAc conjugation aims to reduce the dose and administration frequency required for effective TTR inhibition, while the mixed phosphorothioate and phosphodiester linkages in the backbone are thought to additionally lower pro-inflammatory side effects reported with inotersen.

So far, TEAEs were not found to increase with long-term eplontersen treatment, except those which might be explained by progression of the underlying disease (e.g., cardiac related TEAEs in patients with ATTRv-CM and baseline cardiac conditions).

Although, the kidneys have been identified as one of the major organs for distribution and accumulation (in the proximal renal tubular epithelium) as well as excretion of 2'MOE ASOs like eplontersen and inotersen, renal function parameters and TEAEs of renal impairment OAEI also need to be interpreted against the background of the underlying disease including recurrent infections, fluid shifts and cardiomyopathy leading to a variability in renal function.

Clinical consequences related to thrombocytopenia (i.e. haemorrhages) and renal abnormalities (i.e. glomerulonephritis) have been defined as AESI/ OAEI for eplontersen (based on the experience with the unconjugated parent AON inotersen). No such events have been observed in the clinical programme, which is considered to be a consequence of a more efficient hepatic uptake and lower systemic bioavailability mitigating the immunological and pro-inflammatory effects that have been observed with inotersen and other 2'-MOE AONs.

Appropriate labelling in the product information has been discussed including patients at risk, i.e. for those with medical conditions and/ or concomitant treatment known to trigger platelet count decreases or renal function decline and as a result, additional risk mitigation measures are not considered to be needed.

Reduction in vitamin A serum levels with eplontersen is slightly higher compared to inotersen, entailing a theoretically increased risk for ocular toxicities (e.g. higher incidence of vision blurred), while no clear signal could be identified. Moreover, ocular involvement in ATTRv-PN is frequent and its prevalence seems to increase with disease duration. Symptoms related to amyloid deposits resemble symptoms following vitamin A deficiency and therefore, it is important to assess if these changes could potentially be related to vitamin A deficiency caused by eplontersen. In order to address this issue, a warning statement regarding ocular signs and symptoms of vitamin A deficiency and recommendation for ophthalmological assessment if such symptoms occur, as well as recommendation for vitamin A supplementation is included in the proposed product information, in line with other TTR-lowering treatments.

3.7.2. Balance of benefits and risks

A large pharmacodynamic effect reflected in clear and robust reductions of TTR has been achieved with eplontersen, a ligand-conjugated ASO administered by subcutaneous injection every 4 weeks. These significant reductions in TTR protein through a targeted mechanism of action have led to clinical benefit for patients suffering from ATTRv-PN as measured by neurological indices (mainly mNIS+7) and

quality of life (Norfolk QoL-DN). The observed large effect on the TTR levels alone may be sufficient to justify the use of eplontersen treatment. The observed large differences in pharmacodynamic and clinical endpoints observed with eplontersen compared to external placebo, as well as clear differences compared to concurrent inotersen, (both of which comparators were in a better neurological condition) can support the efficacy of eplontersen in ATTRv patients with stage 1 or 2 polyneuropathy.

After the input from the SAG-N experts, the final wording of the indication was discussed at CHMP.

Taking into account all available information and the Oral Explanation, extrapolation to stage 3 patients was not considered justified based only on the mechanism of action and target engagement of eplontersen. However, the following phrase was agreed to be included in the section 4.2 Posology: "*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*".

The convenient way of administration (subcutaneously) and the longer time intervals between administrations (every 4 weeks) are considered advantageous and less burdensome for patients and their caregivers.

The safety of eplontersen in patients with ATTRv-PN based on the open-label experience generally presents findings qualitatively similar to inotersen, but with quantitative differences clearly in favour of eplontersen. The identified safety issues are considered to be manageable with appropriate labelling in the product information and routine risk minimisation measures in the RMP. Approval is recommended from a clinical safety perspective. The long-term experience with inotersen is considered supportive for the eplontersen safety database at the time of potential marketing authorisation, while additional long-term data are further evaluated in Study 51.

3.7.3. Additional considerations on the benefit-risk balance

Patients' perception of benefits and risks of a medicine may be different from the view of medical experts. That is why EMA engages with patients and their representatives at multiple stages of its activities and the added value of including their perspectives in the evaluation of medicines has been well demonstrated. To that effect, CHMP invited the Association Française contre l'Amylose to share patients' perspectives on behalf of its patient/carer members with respect to eplontersen in the treatment of patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv). The following points are noted from the response from the Association Française contre l'Amylose:

- Rare, serious and disabling disease that affects around 700 patients in France; quantitative survey shows that more than 65% of patients are limited in their daily activities to a degree that changes over time. Patients gradually lose their independence, and the impact on carers is extremely heavy.
- The burden of the disease is highlighted including severe impairment of daily activities requiring assistance throughout the day; mobility and walking are severely impaired and require external support (e.g. cane and/ or wheelchair); more than half of the patients have to stop work (51.61%); many (38.71%) have taken more time off work in the last 12 months than previously (19.35%). Long periods off work: 134 days on average per year for patients with cardiac TTR mutation (4 to 5 months/year).

- The hereditary nature of the disease and its severity mean that the whole family is affected, which is related to feeling of guilt leading to additional stress; caring for patients is heavy and emotionally exhausting.
- More than 70% of patients reported a significant reduction in sexual desire.
- Social life is extremely impaired by loss of mobility; feeling of loneliness; digestive problems lead to apprehension, and contributes to isolation.
- The impact of the disease is completely linked to the severity of the disease, and patients who carry the mutation and are followed up early and treated very early can maintain a near-normal quality of life for several years. The physical burden of the disease is completely linked to the progression of the disease and the appearance of disorders of the autonomic nervous system. Digestive disorders in particular have an enormous physical and psychological impact.
- Tafamidis, Onpattro and Inotersen are the treatments used for patients suffering from hereditary amyloidosis with stage 1 and 2 polyneuropathy in France, as recommended in the PNDS. Early access availability of vutrisiran.
- Experience with Tafamidis is limited to early-stage patients. Administration is straightforward, but patients are treated very quickly with Patisiran if their condition worsens. Patisiran is presumed to be more effective, even though it is more cumbersome to administer than the other treatments available (Tafamidis and inotersen); those who had access to the treatment were satisfied with its effectiveness, while over time, however, frequency and complexity of the treatment is an additional burden. The latter has been supported by statements of patients, who question the impact of the infusions on working ability; infusions were stated to have bad tolerability, including infusion-site pain and haematomas; worries around long-term corticosteroid pre-treatment medication.
- Overall statement: disease affects all organs, senses, and all aspects of life, and its continual progression generates an enormous, constant and deleterious burden and anxiety for patients and their families. Effective treatments are in place that need to be administered throughout the patient's life. The method and frequency of administration must not add to the already heavy daily burden on patients and their carer givers. Adjuvant premedication can have adverse effects that should be avoided as part of a long-term therapeutic strategy. Patients want to maintain a quality of life and a time for living that is not solely dedicated to care and illness. Importance of having different treatments is stressed enabling a therapeutic strategy that is tailored to each patient and to the different stages of the disease. Patients' life expectancy is increasing, requiring effective and tolerable treatments over the long-term. The administration and frequency of treatment have a fundamental impact on the effectiveness of the treatment and on the QoL of patients and their care givers.

The description of the difficulties that patients with ATTRv face provides a clear patients’ perspective and certain issues which are important to them. For them it is very important to have different treatments, which will enable a therapeutic strategy to be put in place that is tailored to each patient and to the different stages of the disease. The main issues raised were the posology and the method and frequency of administration as well as the need for hospital visits. These issues can impose a burden to patients or to their carers. The absence of hospital visits, the ease of administration (e.g. subcutaneous) and the longer time intervals between administrations are major factors towards improvement of the quality of life of patients and maintenance of a time for living that is not solely dedicated to care and illness.

The CHMP have always considered potential benefits with different routes of administration with the subcutaneous being the less invasive and less troublesome for patients compared to intravenous

infusion. In addition, the absence of hospital visits and the longer the interval between administrations, the larger the benefit perceived by the patients. These have been considered in previous MA applications as additional points for the benefit risk discussions.

Moreover, input from two healthcare professionals' organisations, the European Academy of Neurology (EAN) and the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD) has been received, which is based on the opinion of a single expert with conflict of interests (past/ present local PI for clinical trials conducted by Alnylam and Ionis/Akcea, including the pivotal eplontersen trial; participation in Advisory Board Meetings for both companies and Pfizer). The following points were taken into consideration:

- Subcutaneous administration every 4 weeks at a much lower dose (45 mg); no risk of platelet reduction or nephrotoxicity; eplontersen seems to be well tolerated and as effective as the other silencers. Therefore, it could constitute a valuable alternative to currently available therapies, especially, regarding the ease of use, efficacy and tolerability (like with vutrisiran);
- Frequency and relevance of side effects of the approved gene silencers, with the exception of inotersen, which requires careful monitoring, are limited; any new drug should be comparable in terms of side effects if not superior in efficacy;
- TTR stabilisers or gene silencers are currently standard of care and treatment should be started as soon as possible in diagnosed patients with polyneuropathy. The choice is based on several considerations including patients' stage, type of mutation, disease course, and also costs and availability. All these drugs need to be administered chronically and interruption means inevitable rapid worsening. Symptomatic treatment is also important and aims at alleviating neuropathic pain, symptoms related to dysautonomia, and treating cardiomyopathy.

The HCP organisations also addressed the unmet medical need, which can be summarised as such:

- Availability of new drugs is needed in case of switching the treatment with gene silencers is needed (due to efficacy or tolerability issues).
- Lack of availability of an approved drug for patients diagnosed while in stage FAP 3.
- Tafamidis is a small molecule potentially reaching the eye and brain but it is not known whether it has an effect at the administered doses on brain and eye manifestations. Gene silencers address the liver but not the eye and brain.

There were also other issues mentioned, which, however, were not relevant in the case of eplontersen.

Conditional marketing authorisation

Not applicable

Marketing authorisation under exceptional circumstances

Not applicable

3.8. Conclusions

The wording of the indication was discussed at CHMP and it has been ultimately restricted to the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.

The overall benefit /risk balance of Wainzua (eplontersen), formerly Eplontersen AstraZeneca AB, is therefore positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Wainzua (eplontersen) is not similar to Vyndaqel (tafamidis), Tegsedi (inotersen sodium), Onpattro (patisiran) and Amvuttra (vutrisiran) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Revised Similarity assessment.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Wainzua is favourable in the following indication(s):

> Treatment of *hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that eplontersen is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric data

Not applicable.