CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217388Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217388
Priority or standard	Standard
Submit date(s)	12/22/2022
Received date(s)	12/22/2022
PDUFA goal date	12/22/2023
Division/office	Division of Neurology I (DNI)
Review completion date	12/20/2023
Established/proper name	eplontersen
(Proposed) proprietary name	Wainua
Pharmacologic class	Antisense oligonucleotide
Other product name(s)	Eplontersen
Applicant	Ionis Pharmaceuticals
Dosage form(s)/formulation(s)	Injection, solution
Dosing regimen	45 mg by subcutaneous injection once a month
Applicant-proposed indication(s)/ population(s)	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)
SNOMED CT code for proposed indication disease term(s)[1]	442012008
Regulatory action	Approval
Approved dosage (if applicable)	45 mg once monthly
Approved indication(s)/ population(s) (if applicable)	polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
SNOMED CT code for approved indication disease term(s)[1]	442012008

[1] For internal tracking purposes only.
Abbreviations: hATTR, hereditary transthyretin-mediated amyloidosis with polyneuropathy; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	atrioventricular
BE	bioequivalence
CDRH	Center for Devices and Radiological Health
CK	creatine phosphokinase
C_{max}	maximum plasma concentration
CMML	chronic myelomonocytic leukemia
COVID-19	coronavirus disease 2019
CSR	clinical study report
ECG	electrocardiogram
ECL	electrochemiluminescence
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
FAS	full analysis set
FDA	Food and Drug Administration
hATTR-PN	hereditary transthyretin amyloidosis polyneuropathy
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IND	investigational new drug
INR	international normalized ratio
LLN	lower limit of normal
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model with repeated measures
mNIS+7	modified neurological impairment score +7
MSD	Meso Scale Discovery
NDA	new drug application
NIS	neurological impairment score
Norfolk QOL-DN	Norfolk Quality of Life-Diabetic Neuropathy Questionnaire
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	pharmacodynamic
PFS	prefilled syringe
PFS-AI	prefilled syringe-autoinjector
PI	Prescribing Information
PK	pharmacokinetic

PMR	postmarketing requirement
PT	preferred term
Q1M	once every month
Q4W	once every four weeks
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SC	subcutaneous
TEAE	treatment-emergent adverse event
TQT	thorough QT
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urinary protein to creatinine ratio

I. Executive Summary

1. Summary of Regulatory Action

Ionis Pharmaceuticals (Applicant) submitted a new drug application (NDA) 217388 for eplontersen. Eplontersen is an antisense oligonucleotide GalNAc conjugate for the treatment of hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN).

NDA 217388 was reviewed by a multidisciplinary team that did not identify any issues that preclude approval. Each discipline has recommended approval. The signatory authority for this application concurs with those recommendations and agrees that the benefit-risk assessment supports approval.

The Applicant submitted results from a single adequate and well-controlled study (Study ION-682884-CS3), with confirmatory evidence from pharmacodynamic/mechanistic data (i.e., reduction in serum TTR) and knowledge of other drugs in class (i.e., inotersen for the treatment of hATTR-PN), that provide substantial evidence of effectiveness of eplontersen for the indication and supports approval for the treatment of adults with hATTR-PN. Study ION-682884-CS3 is an ongoing multicenter, externally controlled, open-label study that provided reliable and highly statistically significant ($p<0.001$) evidence of clinical benefit on an acceptable outcome (change from baseline to week 35 on the modified neurological impairment score +7 [mNIS+7])), and reliable and highly statistically significant ($p<0.001$) evidence of patient-reported impact on an acceptable additional outcome (change from baseline to week 35 on the Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QOL-DN] score). Overall, the highly persuasive results on an acceptable endpoint (mNIS+7), with support from a clinically meaningful endpoint (Norfolk QOL-DN), make reliance on a single efficacy study in this rare disease, with confirmatory evidence from relevant pharmacodynamic/mechanistic data and knowledge of other drugs in the class, appropriate to support approval.

The available safety data show that risks of eplontersen are acceptable for its intended use. Identified risks can be mitigated through labeling and further evaluated during routine and enhanced pharmacovigilance. The overall benefit-risk is favorable as described in the benefit-risk framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document and the product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Hereditary transthyretin amyloidosis (hATTR amyloidosis) is an autosomal dominant disease that causes slowly progressive buildup of amyloid protein in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract. Patients with hATTR polyneuropathy typically develop a progressive sensorimotor polyneuropathy with numbness, pain, and weakness, as well focal nerve lesions (e.g., carpal tunnel syndrome) and autonomic dysfunction. • It is caused by mutations in the transthyretin (TTR) gene. Wild-type TTR protein is primarily synthesized in the liver and exists in a tetrameric state transporting thyroxine (T4) and vitamin A (retinol) in association with retinol binding protein (RBP). More than 120 different point mutations in the TTR gene have been identified that lead to hATTR amyloidosis. A replacement of valine by methionine at position 30 (V30M) is the most common mutation causing hATTR amyloidosis. • Death usually occurs within 5 to 12 years after symptom onset, most often due to cardiac dysfunction, infection, or cachexia. The incidence of hATTR amyloidosis is 1/100,000 in U.S. Caucasians. • The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons, with the highest rates occurring in certain endemic countries such as Portugal and Sweden (Schmidt et al. 2018).	Hereditary ATTR is a serious and life-threatening disease that can lead to disability and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Patisiran, vutrisiran, and inotersen are approved for the same indication. • Inotersen is available only through a restricted distribution program because of the risks of thrombocytopenia and glomerulonephritis. • Patisiran must be given by intravenous infusion every three weeks and carries a warning for infusion-related reactions. • Vutrisiran must be injected by a healthcare professional only. • Tafamidis is approved for treatment of the cardiomyopathy of hATTR amyloidosis but not polyneuropathy. • Other treatment options for hATTR amyloidosis include liver transplant and medical management of associated symptoms. • Diflunisal, a nonsteroidal anti-inflammatory drug, is sometimes used off-label to treat the disease.	There remains a clinical need for safe and effective treatments for hATTR polyneuropathy that are also convenient to administer for patients. Not all patients are able to receive or tolerate the currently available treatments.
Benefit	• Eplontersen is an antisense oligonucleotide GalNAc conjugate that leads to hepatic-targeted degradation of TTR mRNA, leading to reduction in serum TTR protein concentrations. • The Applicant has provided data from ION-682884-CS3. The study evaluated the efficacy of a 45 mg dose of eplontersen given subcutaneously every 4 weeks, with the primary and key secondary endpoints evaluating efficacy at week 35, the prespecified interim analysis. Placebo-treated subjects from the ISIS-420915-CS2 study of inotersen in hATTR-PN served as the external control. In ION-682884-CS3 there was a statistically significant greater mean reduction in the change in the mNIS+7, an objective evaluation of a range of signs and symptoms related to polyneuropathy where a decrease in score indicates improvement, from baseline to week 35 compared with	The results of ION-682884-CS3 of eplontersen in adults with hATTR-PN provided reliable, clinically meaningful, and stastically significant evidence that eplontersen is effective for the treatment of polyneuropathy in hATTR and helped subjects achieve a clinically meaningful improvement or stability in symptoms of their disease. Confirmatory evidence is provided by pharmacodynamic/mechanistic data and scientific knowledge about the effectiveness of other drugs in the same class (i.e., inotersen for the treatment of hATTR-PN).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo. At week 35, placebo-treated subjects declined by 9 points while eplontersen-treated subjects remained stable. The difference in least squares mean (LSM) was −9.01 for eplontersen versus placebo (p<0.0001). - There was a statistically significant greater mean reduction in the change in the Norfolk QOL-DN score, a subject reported assessment of the impact of polyneuropathy where a decrease in score indicates improvement, from baseline to week 35, for subjects in the eplontersen group compared to external placebo. At week 35, eplontersen-treated subjects improved by 3.1 points while placebo-treated subjects declined by 8.7 points. The difference in LSM was -11.79 for eplontersen versus placebo (p<0.0001).	
Risk and risk management	• The safety database for eplontersen includes all subjects from the Phase 3 externally controlled study and the open-label extension study. In total, at the time of the 120-day safety update, 178 subjects had been exposed to eplontersen ≥ 3 months, 171 subjects for ≥ 6 months, and 137 subjects ≥ 12 months. - The most commonly observed (≥5%) adverse events were vitamin A deficiency, vomiting, proteinuria, injection site reactions, vision blurred, and cataract. - There were two cardiac deaths (one each in ION-682884-CS3 and its open-label extension study ION-682884-CS13), both in subjects with a history of hATTR related cardiomyopathy. Overall, there were four deaths total, (2.4% of 167 subjects exposed to eplontersen). - Eplontersen reduced vitamin A levels. All subjects received the daily recommended amount of vitamin A as a supplement. • Other uncertainties: - Although glomerulonephritis and thrombocytopenia were not identified as risks in this small database, they are	The safety profile of eplontersen is acceptable to support an approval. WARNINGS AND PRECAUTIONS should be inlcuded in labeling to describe the need for vitamin A supplementation to avoid possible vitamin A deficiency. Because of the potential risks of glomerulonephritis, thrombocytopenia observed with this class of drugs and because of an observation of AV block, a postmarketing requirement will evaluate the incidence and provide analyses of glomerulonephritis, thrombocytopenia, and atrioventricular block observed in the ongoing placebo-controlled study ION-682884-CST of eplontersen in adult hereditary and wild-type ATTR cardiomyopathy patients. The potential risks of glomerulonephritis, thromobocytopenia, and ocular toxicity consistent with vitamin A deficiency will be monitored with enhanced pharmacovigilance. Because the risk of adverse outcomes in pregnancy has not been characterized, and because eplontersen will be used in women of childbearing potential, a pregnancy outcomes study and a lactation study will be postmarketing requirements.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	known risks of drugs of this class. Whether they will be observed in a larger population is not known. - AV block was observed in the database. Whether this was disease related or caused by eplontersen has not been determined. - Potential for fetal harm: the risk of adverse outcomes in pregnancy has not been characterized.	

Source: Generated by the FDA review team.
Abbreviations: AV, atrioventricular; ATTR, transthyretin amyloidosis; hATTR, hereditary transthyretin amyloidosis; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; LSM, least squares mean; mNIS+7, modified neuropathy impairment score +7; U.S., United States of America

2.2. Conclusions Regarding Benefit-Risk

Hereditary transthyretin amyloidosis with polyneuropathy is a serious disease that can result in significant morbidity and when accompanied by other organ system involvement such as cardiomyopathy, can lead to mortality as well. Although there are several treatments approved to treat patients with hATTR-PN, there remains a need for effective treatments because not all hATTR-PN patients are able to receive, tolerate, or adequately benefit from the currently available clinical treatments. Currently there are three FDA approved treatments for hATTR-PN: one antisense oligonucleotide product (inotersen, supplied in a prefilled syringe), and two siRNA products (patisiran [intravenous infusion] and vutisiran [prefilled syringe]). Eplontersen is an antisense oligonucelotide GalNAc conjugate that directly binds the TTR mRNA, thus leading to a reduction of serum TTR protein and protein deposits in tissues.

Study ION-682884-CS3 is a randomized, open-label study of eplontersen (45 mg given every 4 weeks) in adult patients with hATTR-PN using inotersen as an active control. The inclusion of the active control arm was recommended by the Agency to assess the relative efficacy and safety of eplontersen to approved therapy.

The Applicant has demonstrated efficacy of eplontersen for the treatment of hATTR-PN in Study ION-682884-CS3. This is an ongoing, multinational, study that has provided reliable, clinically meaningful, and statistically strong evidence of an effect of eplontersen on polyneuropathy in subjects with hATTR. The placebo group from the approved inotersen NDA 211172 Phase 3 study, ISIS-420915-CS2, was used as an external control group for the efficacy analyses of eplontersen due to a similar subject population and endpoints. The Agency was open to the use of an external control given the availability of highly effective therapies as standard of care, and based on experience in prior trials of TTR-lowering that suggested that the effect sizes would be anticipated to be large enough to overcome the biases inherent to the use of an external control. The Applicant conducted a prespecified interim analysis utilizing the week 35 data from Study CS-3. Because the three endpoints (mNIS+7, Norfolk QOL-DN, and change in TTR) all reached statistical significance, the Applicant submitted the NDA with these analyses serving as the final efficacy analyses.

Study CS3 included 144 subjects randomized to the eplontersen arm, 24 to the concurrent inotersen arm, and 60 in the external placebo group. The efficacy endpoints (Norkfolk QOL-DN and mNIS+7) were used in labeling for the three other products approved for the same indication. The mean scores on the primary efficacy endpoint (mNIS+7) in Study ION-682884-CS3 of the mNIS+7 score) in eplontersen-treated subjects were notably stable from baseline at week 35, which is inconsistent with the known course of the condition. The results of the primary analysis from this study were also supported by highly statistically significant positive results on the prespecified secondary efficacy endpoint (change from baseline to week 35 in the Norfolk QOL-DN score) at week 35.

The observed stability of neuropathy as evidenced by the stability in the primary endpoint of the mNIS+7 score is inconsistent with the natural history of hATTR-PN and supports the efficacy of eplontersen. Although there was an imbalance in baseline disease severity between eplontersen and external placebo groups (the baseline mNIS+7 scores indicated less disease severity in the external placebo group), the magnitude of difference between the eplontersen group and external

placebo control, with stability in the eplontersen group and worsening in the placebo group, supports the efficacy of eplontersen.

The observed improvement in symptoms, as evidenced by the key secondary endpoint of Norfolk QOL-DN score, supports the clinical meaningfulness of the efficacy of eplontersen.

The statistically significant percent reduction in serum TTR protein concentration from baseline in the eplontersen-treated group is supportive of the mechanism of action of eplontersen.

ION-682884-CS3 is an adequate and well-controlled, multicenter study that provides reliable and persuasive evidence that eplontersen benefits adult patients with hATTR-PN to achieve a clinically meaningful improvement in the symptoms of their disease that affect their quality of life. No single site provided an unusually large proportion of subjects, and no site was disproportionately responsible for the observed treatment effect. Additionally, pharmacodynamic and mechanistic data relevant to the pathophysiology of hATTR-PN (reduction of serum TTR protein concentration) provide confirmatory evidence to support approval. There is also existing evidence for the effectiveness of using antisense oligonucleotides to degrade TTR mRNA and subsequently reduce serum protein concentrations with the approval of inotersen for the treatment of adults with hATTR-PN (FDA approved in 2018). The effect sizes on the clinical endpoints were large and supported by the objective finding of reduction in TTR protein, and were adequate to overcome potential biases from the use of an external control. Therefore, the study is capable of serving as a single, adequate and well-controlled clinical study plus confirmatory evidence to establish substantial evidence of effectiveness of eplontersen treatment in adult patients with hATTR-PN.

The safety database for eplontersen was adequate for the intended population and proposed dosing regimen. The safety database for hATTR-PN was characterized in a single, randomized, externally controlled, open-label study (ION-682884-CS3) and one open-label extension study (ION-682884-CS13). The most common adverse events (≥5%) were vitamin A deficiency, vomiting, proteinuria, injection site reactions, vision blurred, and cataract. Serious adverse events included atrioventricular block, sepsis, urinary tract infection, and vomiting. There were two cardiac deaths (one each in ION-682884-CS3 and its open-label extension study ION-682884-CS13), both in subjects with a history of hATTR related cardiomyopathy. Safety findings observed during the study can be adequately addressed through labeling and routine and enhanced pharmacovigilance. The Warnings and Precautions statement notes reduced serum vitamin A levels and recommended daily allowance of vitamin A supplementation. Enhanced pharmacovigilance will be requested for serious adverse events related to thrombocytopenia, serious bleeding with thrombocytopenia, glomerulonephritis and serious renal toxicity events, and ocular toxicity consistent with vitamin A deficiency. A pregnancy outcomes study and lactation study will be postmarketing requirements.

Based on the positive results of a single adequate and well-controlled study (Study ION-682884-CS3) and support from pharmacodynamic/mechanistic data of transthyretin reduction, the effectiveness of eplontersen has been established for the treatment of adults with hATTR-PN. The conclusion of this review is that substantial evidence of clinical effectiveness and an acceptable safety profile have been established to support an approval of eplontersen for the treatment of polyneuropathy in adults with hATTR. The availability of eplontersen will provide a new and effective treatment option via a patient-administered subcutaneous injection with an autoinjector for ease of use.

II. Interdisciplinary Assessment

3. Introduction

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disorder (>120 TTR gene mutations known) that is characterized by the slowly progressive buildup of amyloid protein in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract. Death usually occurs within 5 to 12 years after onset, most often due to cardiac dysfunction, infection, or cachexia. The exact incidence of hATTR amyloidosis is unknown and varies geographically but is estimated to be 1/100,000 in U.S. Caucasians. Approximately 100 to 2,500 individuals are estimated to have hATTR-PN in the United States. These subjects typically develop sensorimotor polyneuropathy with numbness, pain, and weakness, as well as focal nerve lesions (e.g., carpal tunnel syndrome) and autonomic dysfunction (e.g., orthostatic hypotension).

There are three general forms of the disease, although patients can have overlapping symptoms from all three forms. The neuropathic form (hereditary TTR amyloidosis polyneuropathy [hATTR-PN], also known as transthyretin familial amyloid polyneuropathy), is defined by the presence of sensorimotor peripheral neuropathy (with symptoms of numbness, pain, and weakness), focal nerve lesions (e.g., carpal tunnel syndrome), autonomic dysfunction (e.g., orthostatic hypotension, gastrointestinal dysfunction), vitreous opacity of the eye, and glaucoma. The leptomeningeal form is defined by the presence of stroke, intracranial hemorrhage, hydrocephalus, ataxia, spastic paralysis, seizures, dementia, psychosis, and vision impairment. The cardiac form is defined by the presence of arrhythmia, cardiomegaly, heart failure, and death.

Eplontersen is an antisense oligonucleotide N-acetylgalactosamine (GalNAc) conjugate that causes hepatic-targeted degradation of TTR mRNA (for mutant variants and wild-type TTR) through direct binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. It is related to inotersen, approved for the same indication in 2018, but has been modified for targeted liver delivery and less frequent dosing (once a month) compared to dosing every week for inotersen.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

There were no key efficacy issues identified.

3.1.2. Key Safety Review Issues

3.1.2.1. Safety of Autoinjector

The proposed commercial formulation for eplontersen is a prefilled syringe-autoinjector (PFS-AI). However, this formulation was not used in the pivotal study of ION-682884-CS3. Study CS-3 primarily used the vial and syringe formulation. The PFS-AI was evaluated in one bioequivalence study (ION-682884-CS21) has been used in the open-label extension study ION-682884-CS13. Administration of eplontersen with the PFS-AI showed comparable area under the concentration-time curve (AUC) but higher maximum plasma concentration (C_{max}) compared to the vial with syringe (clinical trial formulation). A potential key safety review issue was to determine whether the Applicant had adequate safety data to support the administration of eplontersen with the PFS-AI.

3.1.2.2. Vitamin A Deficiency

TTR (transthyretin) is a transport protein, and one of its major functions is to transport retinol (vitamin A). The mechanism of action of eplontersen involves reduction in serum TTR levels, and thus potentially reductions in serum vitamin A levels. Serum reduction in vitamin A levels have also been seen in other approved treatments targeting TTR. Given the mechanism of action of eplontersen in targeting reduction of serum TTR, vitamin A deficiency was identified as a potential key safety review issue.

3.1.2.3. Thrombocytopenia and Glomerulonephritis

Thrombocytopenia and glomerulonephritis were observed during clinical trials of inotersen, are included in boxed warnings for inotersen, and are the reason for its risk evaluation and mitigation strategy (REMS). The Applicant noted that inotersen is an antisense oligonucleotide (ASO) with the same sequence as eplontersen, but also suggested that the mechanism of action of eplontersen and targeted hepatic delivery with the N-acetyl galactosamine (GalNAc)-ligand-conjugation, offers improved safety over inotersen. Given the clinical experience with inotersen, thrombocytopenia and glomerulonephritis were identified as potential key safety review issues.

3.2. Approach to the Clinical Review

Effectiveness and safety were assessed by evaluating the results from the Phase 3, randomized, open-label, active comparator, and externally controlled ION-682884-CS3 study in adult subjects with hATTR-PN. The effectiveness assessment focused on the clinical interpretability of the trial endpoints and the Applicant's reported results. Confirmation of the efficacy analyses was provided by the biometrics reviewer for this application. The safety assessment was based on the Applicant's reports and data analyst and clinical reviewer analysis of the submitted data.

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determination[a] for Eplontersen

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
ION-682884-CS3	Subjects with stage 1 or stage 2 hATTR-PN with documented genetic mutation in the TTR gene and NIS of 10 to 130 at baseline	Control Type: External placebo control Randomization: Standard randomization (6:1 ratio) Blinding: Open-label	Drug (established name): eplontersen Dose: • Eplontersen treatment arm: 45 mg eplontersen Q4W through Week 81 • Inotersen treatment arm: 300 mg inotersen sodium Q1W through Week 34[b], then 45 mg eplontersen Q4W from Week 37 through Week 81 Number treated: 168 • Eplontersen 45 mg Q4W SC: 144 • Inotersen 300 mg Q1W SC prior to switch: 24 • Eplontersen 45 mg Q4W SC after switch: 20 Duration (Quantity and Units): • Screening: ≤10 weeks • Treatment: 84 weeks • Post-treatment evaluation period or enrollment into OLE study: 20 weeks	• Percent change from baseline in serum TTR concentration at Week 35 • Change from baseline in mNIS+7 at Week 35 • Change from baseline in Norfolk-QOL-DN at Week 35	Planned: 140 Actual: 168	Centers: 52 Countries: 16

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
ISIS-420915-CS2	Subjects with stage 1 or stage 2 hATTR-PN with NIS of 10 to 130 at baseline	Control Type: Placebo concurrent Randomization: Stratified randomization (2:1 ratio) Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): inotersen Dose: • 300 mg inotersen sodium or placebo on Days 1, 3, and 5 of Week 1, then Q1W from Week 2 through Week 65 (total of 67 doses) Number treated: 172 • Inotersen 300 mg: 112 • Placebo: 60 Duration (quantity and units): • Screening: ≤6 weeks • Treatment: 65 weeks • Post-treatment evaluation period: 6 months	Primary: • Change from baseline to Week 66 in the mNIS+7 score, and in the Norfolk QOL-DN questionnaire total score Secondary: • Change from baseline to Week 66 in the Norfolk QOL-DN questionnaire symptoms domain score (stage 1 subjects only) and the Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score (stage 2 subjects only) • Change from baseline to Week 65 in the mBMI • Change from baseline to Week 65 in the BMI • Change from baseline to Week 66 in the NIS • Change from baseline to Week 66 in the mNIS+7 • Change from baseline to Week 66 in the NIS +7 • Change in GLS by ECHO from baseline to Week 65 in the ECHO subgroup and in the CM-ECHO set	Planned: 135 Actual: 173	Centers: 25 Countries: 10

Source: Clinical Study Report and adsl.xpt
[a.] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[b.] Some subjects may continue to receive inotersen sodium 300 mg beyond Week 34 and switch to eplontersen later than the protocol specified time.
Abbreviations: BMI, body mass index; CM, cardiomyopathy; ECHO, echocardiogram; GLS, global longitudinal strain; hATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score +7; NSC, neuropathy symptom and change; NIS, neuropathy impairment score; Norfolk QoL-DN, Norfolk quality of life-diabetic neuropathy; OLE, open-label extension; PCS, physical component summary; PND, polyneuropathy disability; Q1W, once weekly; Q4W, once every 4 weeks; SC, subcutaneous(ly); SF-36, 36-item short form survey; TTR, transthyretin

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6.2
☒	Performance outcome	Section 6.2
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Eplontersen (ION-682884) is a 20-mer chimeric 2′-MOE mixed (PS/PO) backbone ASO conjugated to a triantennary N-acetyl galactosamine (GalNAc3) ligand, which is intended to promote uptake by hepatocytes through recognition by the asialoglycoprotein receptors (ASGPR). Eplontersen is designed to target the 3′-untranslated region of human TTR mRNA and suppress transcription of normal and mutant human TTR. The ASO portion of eplontersen has the same nucleotide sequence as inotersen, which is a 2′-MOE modified full PS ASO and was approved by FDA for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in 2018.

In in vitro studies in human hepatocytes, eplontersen suppressed human TTR mRNA, with an IC_{50} of 59 nM. The binding sequence of eplontersen is complimentary to human and monkey TTR mRNA but not rodent. In vivo pharmacology studies in transgenic mice carrying the Ile84Ser human TTR mutant demonstrated eplontersen-induced reduction of hepatic hTTR mRNA and plasma hTTR protein levels, with ED_{50} values of 0.5 and 1.5 mg/kg/week, respectively.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Transthyretin-directed antisense oligonucleotide
Mechanism of action	Eplontersen is an antisense oligonucleotide-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein deposits in tissues
Active moieties	Unconjugated ASO of ION-682884 (eplontersen)
QT prolongation	At a dose 2.7 times the recommended eplontersen dose, clinically significant QTc interval prolongation was not observed.
General Information	
Bioanalysis	A validated hybridization electrochemiluminescence (ECL) method was used to measure plasma concentrations of full length ASOs (conjugated, partially conjugated, and unconjugated eplontersen). 70% to 100% of the incurred sample reanalysis met the acceptance criteria. Refer to Section 14.3 for more details.
Healthy subjects versus patients	PK is not different in healthy volunteers and patients with hATTR-PN.
Drug exposure at steady state following the therapeutic dosing regimen	**Table 6. PK Parameters at Steady State** **Parameter** / **Mean ± SD** $AUC_{tau,ss}$ 2190±689 ng*h/mL $C_{max,ss}$ 283±152 ng/mL Source: FDA review team. Abbreviations: AUC, area under the concentration-time curve; max, maximum; PK, pharmacokinetic; SD, standard deviation; ss, steady state
Range of effective dose(s) or exposure	Not available. A single dose level of 45 mg given SC Q4W demonstrated efficacy and safety in the pivotal Phase 3 study
Maximally tolerated dose or exposure	Not available. 45 mg given SC Q4W is the highest dose tested in the Phase 3 study
Dose proportionality	Following a single subcutaneous dose of eplontersen, plasma exposures (C_{max} and AUC_t) increased more than dose proportional over 45 mg to 120 mg.
Accumulation	No accumulation in C_{max} and AUC with 45 mg SC Q4W dosing.
Time to achieve steady-state	Steady-state is achieved immediately since there is no accumulation in C_{max} and AUC.
Bridge between to-be-marketed and clinical trial/study formulations	Clinical trial formulation was presented as vial and syringe and the to-be-marketed formulation is proposed as prefilled syringe with auto injector (PFS-AI). Although the administration with PFS-AI was found to result in similar AUC but 13% higher C_{max} comparing to that with vial and syringe, the clinical safety evaluation suggests no clinical impact from the administration with PFS-AI (Refer to Section 14.2 for details).

Characteristic	Drug Information
Absorption	
Bioavailability	Absolute/relative bioavailability after SC administration of eplontersen has not been determined.
T_{max}	2 hours
Injection sites	Eplontersen can be administered in the back of the arm or in the abdomen. Refer to Section 8.2 for details.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable.
Distribution	
Volume of distribution	• Central compartment volume (Vc/F) is 12.2 L. • Peripheral compartment volume (Vp/F) is 11,100 L.
Plasma protein binding	• ~98% of eplontersen binds to plasm proteins, and it is independent of concentration within the range of 0.1 to 5 µg/mL. • No plasma protein binding displacement interaction between eplontersen and warfarin or ibuprofen.
Drug as substrate of transporters	Not a substrate of P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K, and BSEP.
Elimination	
Mass balance results	Human mass balance study was not conducted
Clearance	CL/F is 6.19 L/h
Half-life	Terminal elimination half-life is 3 weeks.
Metabolic pathway(s)	Eplontersen is not metabolized by CYP450 enzymes. The primary route of metabolism is initial rapid hydrolysis of GalNAc conjugate in tissues, and the unconjugated ASO is slowly metabolized by endo- and exonucleases.
Primary excretion pathways (% dose)	<1% of the administered dose excreted in urine as unchanged drug within 24 hours.
Intrinsic Factors and Specific Populations	
Body weight	Based on the population PK analysis eplontersen plasma PK exposures are unlikely affected by body weight.
Age	Age does not affect the PK of eplontersen based on results from population PK analysis
Renal impairment	Based on population PK analysis mild or moderate renal impairment does not affect PK significantly. Eplontersen was not studied in patients with severe renal impairment or with ESRD.
Hepatic impairment	Mild hepatic impairment does not affect the PK of eplontersen based on population PK analysis. Eplontersen was not studied in subjects with moderate or severe hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	• Not an inducer of CYP1A2, CYP2B6, or CYP3A4 in vitro. • Not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzymes in vitro.
Inhibition/induction of transporter systems	Not an inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K, and BSEP transporters in vitro.

Characteristic	Drug Information
Immunogenicity (if Applicable)	
Bioanalysis	A multitiered anti-drug antibodies (ADAs) assay based on ELISA was used to detect ADAs in subjects with hATTR-PN.
Incidence	36.8% of patients developed treatment-emergent ADAs
Clinical impact	The presence of ADAs did not affect steady state plasma C_{max} and total AUC, but increased C_{trough}. The presence of ADAs did not affect pharmacodynamic activity, reduction in mean percent change in TTR from baseline. ADAs did not appear to affect safety and efficacy, though the available data are too limited to make definitive conclusions.

Source: FDA review team.
Abbreviations: ADA, antidrug antibody; ASO, antisense oligonucleotides; AUC, area under the concentration-time curve; BSEP, bile salt export pump; ECL, electrochemiluminescence; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; C_{trough}, lowest plasma concentration at steady-state; CYP, cytochrome P450; ECP, established pharmaceutical class; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; GalNAc, N-Acetylgalactosamine; hATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; MATE, multidrug and toxin extrusion protein; OAT, organic anion transporter; OCT, organic cation transporter; PFS-AI, prefilled syringe with auto injector; PK, pharmacokinetic; Q4W, once every four weeks; SC, subcutaneous(ly); TTR, transthyretin; Vc/F, central compartment volume; Vp/F, peripheral compartment volume

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The proposed dosing regimen for eplontersen is 45 mg given subcutaneously (SC) once every month (Q1M). The proposed dosing regimen is slightly different from that used in the pivotal ongoing Phase 3 efficacy study, ION-682884-CS3, where the dosing regimen was 45 mg once every four weeks (Q4W) given SC. The Applicant has provided modeling and simulation demonstrating the proposed dosing regimen of Q1M results in similar pharmacokinetics (PK), and pharmacodynamics (PD) compared to the dosing regimen of Q4W evaluated in Study ION-682884-CS3.

Dosage regimen of 45 mg Q4W for the Phase 3 study was selected based on TTR reduction and safety data from the Phase1 study, ION-682884-CS1. The mean percent change from baseline in serum TTR protein 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 percent change from baseline in TTR at day 99 (2 weeks after the 4th dose of Q4W) was -81.3%, -90.8%, and -93.3% for eplontersen 45, 60, and 90 mg, respectively (refer to Section 14.2 for details). The Applicant noted dose-dependent reversible elevation of alanine aminotransferase was in the 60 mg and 90-mg dose cohort in a small number of subjects. The dose of 45 mg Q4W was selected by targeting a desired TTR reduction of at least 80% and a favorable benefit/risk profile.

The results from the Phase 3 clinical study, ION-682884-CS3 provided primary evidence of efficacy for eplontersen 45 mg given SC Q4W. The interim analysis findings showed statistically significant improvement in primary and key secondary efficacy endpoints for hATTR-PN patients treated with eplontersen compared to the external control of the placebo cohort in study ISIS-420915-CS2 at Week 35.

The steady-state PK exposure metrics (C_{max},ss, C_{trough},ss, and AUC_{tau},ss) and TTR reduction was comparable between 45 mg SC Q4W and 45 mg SC Q1M dosing based on PK/PD modeling and simulation. Therefore, the review team concluded that the proposed dose of 45 mg Q1M given SC is considered appropriate (refer to Section 14.5 for details).

6.1.1. Mechanistic Evidence of Support

Consistent with the proposed mechanism of action, 81% reduction in the TTR levels by week 35 was observed in the CS-3 study in hATTR-PN subjects treated with eplontersen 45 mg Q4W given SC (refer to Sections 14.2 and 14.5 for details). This magnitude of TTR reduction was similar to the magnitude of reduction observed by inotersen which also inhibits TTR production. In addition, established association between mutant TTR levels and pathophysiology of the disease along with the understanding of the mechanism of action of eplontersen as a targeted therapy inhibiting the production of TTR, including the mutant TTR, provide mechanistic support for approval of this product.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Study ION-682884-CS3

6.2.1.1. Design, Study ION-682884-CS3

Study ION-682884-CS3 is an ongoing, multinational (16 countries), multicenter (52 centers), Phase 3, open-label study with an external control and an active reference arm (inotersen) which enrolled adult subjects with stage 1 and stage 2 hATTR-PN.

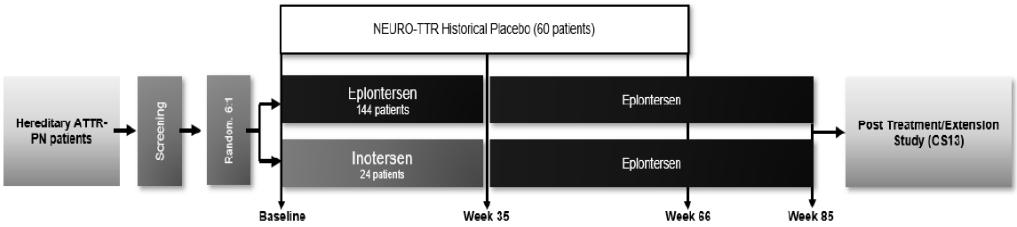
The primary efficacy objective was to study the efficacy of eplontersen as compared with the external control of the placebo cohort in the ISIS-420915-CS2 study, evaluating change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and change from baseline in serum TTR concentration. The secondary efficacy objective was to evaluate the change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) in subjects with hATTR-PN. An interim analysis was conducted when all ongoing subjects completed week 35 of the study, which was the basis for this submission.

The safety objectives were to evaluate safety and tolerability in hATTR-PN subjects treated with eplontersen.

This NDA submission includes the results of the prespecified interim analysis of efficacy at week 35 (data cutoff of April 18, 2022) and cumulative safety data through the data cutoff date of July 19, 2022, as well as the 120-day safety update with a data cutoff date of October 19, 2022. Because the Applicant achieved statistical significance on all three endpoints (mNIS+7, Norfolk-QOL-DN, and change in serum TTR concentration), the interim analysis is considered the final efficacy analysis.

Basic Study Design

Figure 1. ION-682884-CS3 Study Design



Source: ION-682884-CS3 Report Body.
Abbreviations: ATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; NEURO-TTR, Study ISIS-420915-CS2

Study ION-682884-CS3 consists of a ≤10-week screening period, an 84-week treatment period, and a 20-week post-treatment evaluation period or enrollment into the open-label extension study.

Subjects were randomized 6:1 to receive subcutaneous injections of either 45 mg eplontersen Q4W or 300 mg inotersen Q1W up to and including week 34, followed by dosing with 45 mg eplontersen Q4W through the end-of-treatment (EOT) period. Subjects randomized to the inotersen reference arm switched to eplontersen at week 37. All subjects are to continue dosing with eplontersen until week 81, with EOT assessments at week 85, four weeks after the last dose.

Following treatment and the EOT assessments, eligible subjects could elect to enroll in an open-label extension study (ION-682884-CS13). Subjects not participating in the open-label extension study could enter a 20-week post-treatment evaluation period that consisted of visits for safety monitoring, after completing the EOT assessments.

Choice of Control Group

The placebo group of the ISIS-420915-CS2 study was used as an external control for the primary and secondary efficacy analyses. Study ISIS-420915-CS2 served as the primary evidence of effectiveness of inotersen for the treatment of hATTR-PN. This external placebo group consists of subjects with hATTR-PN with comparable eligibility criteria to the hATTR-PN subjects enrolled in the ION-682884-CS3 study (disease stage, age range, gender, exclusions of certain comorbidities, restriction of concomitant medications, and functional status). The incidence of all three stratification factors (Val30Met TTR mutation, previous treatment, and disease stage) were well balanced. This external placebo group also had proportionally similar baseline characteristics detailed in Table 7. However, subjects in the external placebo group had less disease severity as measured by the mNIS+7 scores compared to the eplontersen group in ION-682884-CS3. The majority of subjects in ISIS-420915-CS2 were white (88.3%), as was the case in ION-682884-CS3 (78.3% in the eplontersen group, 82.6% in the inotersen-eplontersen group). The ION-682884-CS3 study also included an active control group receiving the approved treatment inotersen.

The treatment period of ISIS-420915-CS2 was 65 weeks (i.e., up to week 66), therefore the placebo group from this study that is being used as an external placebo control in

ION-682884-CS3 only extends for 66 weeks, compared to the treatment period of ION-682884-CS3 up to 85 weeks.

Table 7. Demographics and Baseline Disease Characteristics (Safety Set)

Characteristic	ISIS-420915-CS2 Placebo (N=60)	ION-682884-CS3 Inotersen-Eplontersen (N=24)	ION-682884-CS3 Eplontersen (N=144)
Age (mean (SD))	59.5 (14.05)	51.1 (14.38)	53.0 (15.00)
Male	41 (68.3%)	16 (66.7%)	100 (69.4%)
Female	19 (31.7%)	8 (33.3%)	44 (30.6%)
Disease Stage 1	42 (70.0%)	18 (75%)	115 (79.9%)
Disease Stage 2	18 (30.0%)	6 (25.0%)	29 (20.1%)
mNIS+7 Composite Score (mean (SD))	74.75 (39.003)	65.06 (33.515)	81.28 (43.401)
mNIS+7 Composite Score Median	74.89	58.44	78.08
Duration of disease from hATTR-PN Diagnosis (months, mean)	39.3	45.7	46.8
Subjects with Clinical Diagnosis of hATTR-CM	22 (36.7%)	7 (29.2%)	39 (27.1%)
Subjects with V30M TTR Mutation	33 (55.0%)	16 (66.7%)	85 (59.0%)
Subjects with Previous Treatment (Vyndaqel or Diflunisal)	36 (60.0%)	15 (62.5%)	100 (69.4%)

Source: ION-682884-CS3 Report Body.
Abbreviations: hATTR-CM, hereditary transthyretin-mediated amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; mNIS+7, modified Neuropathy Impairment Score +7; N, number of subjects in treatment group; SD, standard deviation; TTR, transthyretin

The open-label design with an external placebo control is potentially subject to bias. This was mitigated by using an external placebo group in the same disease population collected by the same Applicant within the last 8 years, using similar eligibility criteria, sites/regions, and staff, blinding the primary endpoints to the Applicant's team, and utilizing endpoints that are largely objective such as mNIS+7. At the pre-IND meeting on February 29, 2019, the Division agreed to the use of an external control given the availability of highly effective therapies as standard of care, with the expectation that there would be a large magnitude of effect that could overcome the biases inherent to the use of an external control. The Division also recommended the inclusion of the active control arm in order to understand whether eplontersen provides comparable efficacy and safety to inotersen.

All subjects (regardless of the treatment arm to which they are randomized) get the recommended daily allowance of vitamin A.

Please see Section 15 for additional information regarding trial design – including dosing selection and concomitant therapies.

Primary Efficacy Endpoint

The primary efficacy endpoint for Study ION-682884-CS3 at week 35 was the change in baseline in mNIS+7 at week 35 as compared to the external placebo control from Study ISIS-420915-CS2.

The mNIS+7 is a composite measure of neurologic impairment that includes the following measures and components. The range of possible total scores is -22.3 to 346.3. Note that higher scores indicate greater impairment.

- Physical exam of lower limbs, upper limbs and cranial nerves in order to assess motor strength/weakness and determine the following component scores:
  - neuropathy impairment score (NIS)-weakness
  - NIS-reflexes
- Electrophysiologic measures of small and large nerve fiber function in order to determine the sum of five nerve conduction studies component scores that included assessment of the ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, and peroneal CMAP
- Sensory testing to determine the quantitative sensory testing score included assessing touch pressure by body surface area and heat pain by body surface area
- Postural blood pressure was measured to assess autonomic function.

Table 8. mNIS+7

Test	Component	Minimum Score	Maximum Score
NIS	Cranial Nerves	0	40
	Muscle Weakness	0	152
	Reflexes	0	20
	Sensation	0	32
Modified +7	Heart Rate Deep Breathing†	-3.72	3.72
	Nerve Conduction†	-18.6	18.6
	Touch Pressure	0	40
	Heat-Pain	0	40
mNIS+7*	**Composite**	**-22.3**	**346.3**

Source: Supplement to: Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22-31 (Benson et al. 2018).
Abbreviations: mNIS+7, modified Neuropathy Impairment Score +7; NIS, neurological impairment score

The primary endpoint, mNIS+7, is composed of a clinical exam-based NIS combined with electrophysiologic measures of small and large nerve fiber function (+7) such as nerve conduction studies, quantitative sensory testing, and measurement of autonomic function (postural blood pressure). Many of the individual components of the score, such as nerve conduction studies, are clearly biomarkers that do not, of themselves, represent direct clinical benefit. Other components of the score, such as motor and sensory function by neurological exam, also are not direct measures of clinical benefit, as differences detected by the physician might not be perceptible to the subject or result in improved function in daily activities. The mNIS+7 is an acceptable endpoint, but the results should be considered in the context of the results of the secondary endpoints, particularly the Norfolk QOL-DN. Note that the mNIS+7 and Norfolk QOL-DN were also the efficacy endpoints for the ISIS-420915-CS2 clinical study of inotersen, which was approved for the treatment of hATTR amyloidosis in 2018, for the

APOLLO clinical study of patisiran, which was approved for the treatment of hATTR amyloidosis in 2018, and for the HELIOS-A clinical study of vutisiran, which was approved for the treatment of hATTR amyloidosis in 2022 (Vinik et al. 2005; Suanprasert et al. 2014; Vinik et al. 2014).

Coprimary Efficacy Endpoint

The Applicant also used percent change from baseline in serum TTR protein concentration at week 35 as a primary efficacy endpoint, given the mechanism of action of eplontersen in reducing serum TTR protein levels. The Agency had recommended that the Applicant not utilize serum TTR reduction as a primary endpoint for their Phase 3 study in a pre-IND meeting on February 21, 2019, as stated below:

> *"We do not agree with your proposal to use TTR reduction as a primary endpoint for your Phase 3 study. Although we note the importance of TTR reduction based on the mechanism of the drug, clinical outcomes should be assessed as the primary endpoints for the study. We strongly recommended the use of the Norfolk-QOL-DN and mNIS+7 as coprimary endpoints. TTR reduction would be most appropriate as a secondary endpoint, with adjustment for multiplicity."*

For this reason, this clinical review will not refer to percent change from baseline in serum TTR protein concentration as a primary efficacy endpoint and will instead be evaluated as an additional endpoint.

Secondary Efficacy Endpoints

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

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that is sensitive to the different features of diabetic neuropathy: small fiber, large fiber, and autonomic nerve function. There are 35 questions divided into 5 domains. The range of possible total scores is -4 to 136. Higher scores indicate a worse quality of life. A negative score is possible because in Question 31, "Very Good" is scored as –1, and "Excellent" is scored as –2. In Question 32, "Somewhat better" is scored as –1 and "Much better" is scored as -2.

Table 9. Norfolk QoL-DN

Domain	Items[1,2]	Minimum Score	Maximum Score
Symptoms	Σ (1-7, 9)	0	32
Physical Functioning/Large Fiber Neuropathy	Σ (8, 11, 13-15, 24, 27-35)	-4	56
Small Fiber Neuropathy	Σ (10, 16-18)	0	16
Large Fiber Neuropathy	Σ (19-21)	0	12
Activities of Daily Living	Σ (12, 22, 23, 25, 26)	0	20
Norfolk QoL-DN*	**Total**	**-4**	**136**

Source: Supplement to: Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22-31 (Benson et al. 2018).
Abbreviations: Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire

The Norfolk QOL-DN is a clinically meaningful endpoint that is appropriate for use in this study.

6.2.1.2. Eligibility Criteria, Study ION-682884-CS3

Key Inclusion Criteria

To participate in this study, patients were required to meet the following eligibility criteria at screening:

1. Aged 18 to 82 years at the time of informed consent.
2. hATTR-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 (Coutinho et al. 1980).
   - Documented genetic mutation in the TTR gene.
   - Symptoms and signs consistent with neuropathy associated with transthyretin-mediated amyloidosis (ATTR), including NIS ≥10 and ≤130. The NIS assessment is a 244-point composite measure of neurologic impairment which includes a physical exam of lower limbs, upper limbs and cranial nerves to assess motor strength/weakness, reflexes, and sensation.
3. Willingness to adhere to vitamin A supplementation per protocol.

Key Exclusion Criteria

Patients meeting any of the following criteria were not eligible for the study:

1. Clinically significant (CS) 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.

2. Screening laboratory results as follows, or any other CS abnormalities in screening laboratory values that would render a subject unsuitable for inclusion:
   - Urine protein to creatinine ratio (UPCR) ≥1,000 mg/g
   - Renal insufficiency as defined by eGFR <45 mL/min/1.73 m^2 at screening
   - Positive test for blood (including trace) on urinalysis that is subsequently confirmed with urine microscopy showing >5 red blood cells per high power field and is related to glomerulopathies
   - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 × upper limit of normal (ULN)
   - Bilirubin ≥1.5 × ULN (subjects with bilirubin ≥1.5 × ULN could be allowed on study if only indirect bilirubin is elevated, ALT/AST is not more than the ULN, and the subject is known to have Gilbert's disease)
   - Platelets <125 × 109/L
   - Hemoglobin A1C ≥7%
   - Abnormal thyroid function tests with clinical significance per Investigator judgement.
3. Active infection requiring systemic antiviral or antimicrobial therapy that is not completed prior to day 1.
4. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B.
5. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin, melanoma in situ, prostate carcinoma grade group 1, breast ductal carcinoma in situ, or carcinoma in situ of the cervix.
6. Current treatment with any approved drug for hATTR such as Vyndaqel/Vyndamax (tafamidis), Tegsedi (inotersen), Onpattro (patisiran), off-label use of diflunisal or doxycycline, and tauroursodeoxycholic acid. If previously treated with Vyndaqel/Vyndamax, diflunisal or doxycycline, and tauroursodeoxycholic acid, must have discontinued treatment for 2 weeks prior to Day 1.
7. Current or previous treatment with Tegsedi (inotersen) or Onpattro (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA). This exclusion criterion does not apply to COVID-19 messenger ribonucleic acid vaccinations.
8. History of bleeding, diathesis or coagulopathy (e.g., liver cirrhosis, hematologic malignancy, antiphospholipid antibody syndrome, congenital disorders such as hemophilia A, B, and Von Willebrand disease).
9. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, diabetic neuropathy).
10. Prior liver transplant or anticipated liver transplant within one (1) year of screening.
11. New York Heart Association functional classification of ≥3.
12. Known immunoglobulin (Ig) light chain amyloidosis (AL amyloidosis), known leptomeningeal amyloidosis, known multiple myeloma, or monoclonal gammopathy of undetermined significance and/or alterations in Ig-free light chain ratio.

6.2.1.3. Statistical Analysis Plan, Study ION-682884-CS3

Study CS-3 utilized two coprimary endpoints: serum TTR and the mNIS+7 score for the analysis at week 35.

The percent change in serum TTR from baseline to week 35 was analyzed using the mixed effects model with repeated measures (MMRM) model adjusted by propensity score weights. The MMRM model will also include the effects of treatment (eplontersen or external placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with tafamidis or diflunisal (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score was calculated for each external placebo or eplontersen-treated subject using a logistic regression model with covariates including disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with tafamidis or diflunisal (Yes/No).

The primary endpoint of mNIS+7 score (change from baseline at week 35) was analyzed using an ANCOVA model adjusted by propensity score, because only one post-baseline assessment was available at week 35. The ANCOVA model included treatment group, disease stage (Stage 1 or Stage 2), V30M mutation (Yes/No), previous treatment with tafamidis or diflunisal (Yes/No), and mNIS+7 score at baseline. Missing mNIS+7 at week 35 were imputed using an imputation model that was based on missing at random assumption with the following variables: disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment with tafamidis or diflunisal (Yes/No), and the baseline value of the endpoint, stratified by treatment group. If the Shapiro-Wilks test assessing normality of the ANCOVA residuals were statistically significant at the 0.01 level, a stratified Wilcoxon rank sum test would be provided.

Efficacy analyses were based on the full analysis set (FAS) population defined as all randomized subjects who received at least one dose of study drug grouped by randomized treatment group (for reporting efficacy data). Subjects were grouped based on the assigned treatment.

At the week 35 analysis, the same analysis of mNIS+7 was applied for the Norfolk QOL-DN.

The two coprimary endpoints were analyzed at the 0.025 level. If both the coprimary endpoints (TTR and mNIS+7) were significant at alpha level of two-sided 0.025, then the secondary endpoint Norfolk QOL-DN would be tested at the 0.025 level at the analysis at week 35.

Secondary Endpoint: Comparison of change from baseline to week 35 in the Norfolk QOL-DN total score between eplontersen and the external placebo group in the FAS.

The TTR level from the external placebo arm will be converted using the following formula to match data generated by the current assay y=0.0057x^2+0.5843x-0.3819. The converted value would then be used in the primary analysis.

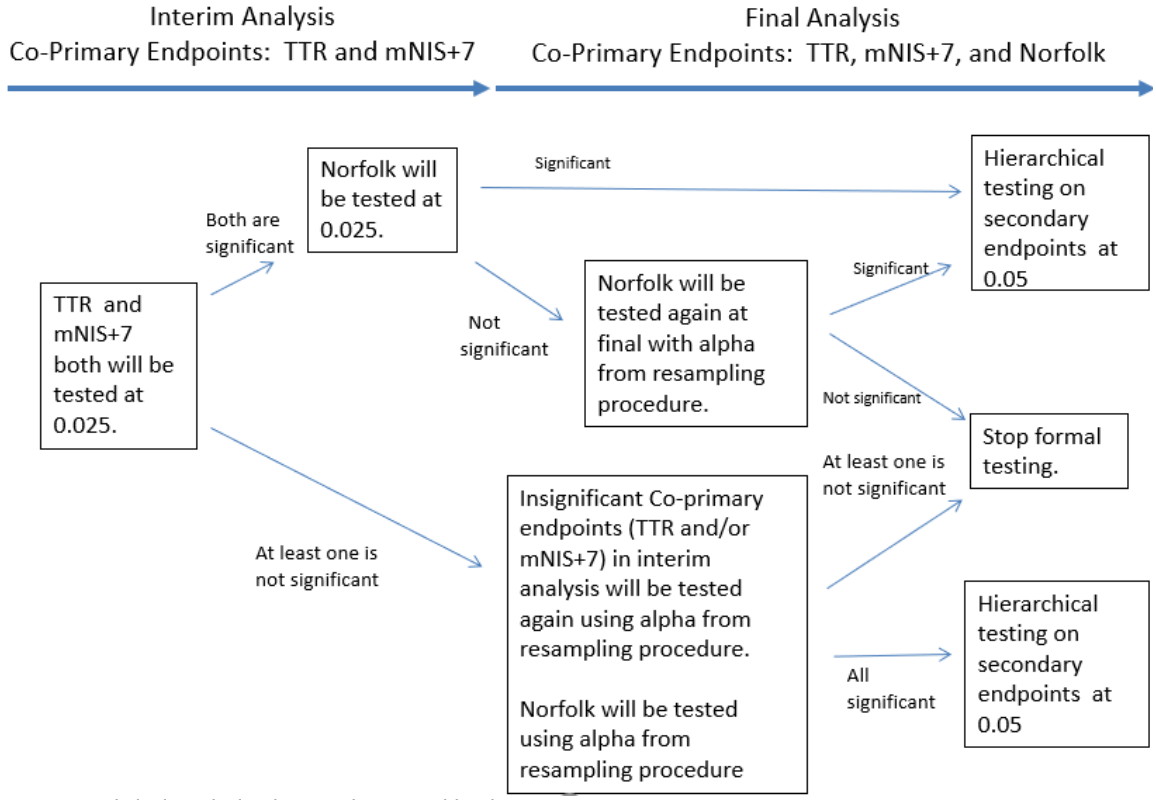
SAP Version 2.1 states that the mNIS+7 and TTR level will be tested at the week 35 interim analysis (See Figure 2). If significant, the testing procedure allows for the testing of the Norfolk QOL-DN at week 35. If all three endpoints were found to be statistically significant, the corresponding week 66 ‘final analyses’ would not be conducted for these endpoints, and the week 35 endpoint analysis would be considered the final analysis for these endpoints.

Because all three endpoints were in fact statistically significant at the week 35 analysis, the interim analyses of these three endpoints are considered the final analyses for these three endpoints. Additional secondary endpoints could be tested with alpha of 0.05, but those analyses

were not reviewed as part of this NDA. The additional secondary analyses were primarily analyses of week 66 data and were not completed at the time of this submission.

In addition, because the study results produced very small p values being <0.0001 for all three endpoints, such changes in the order of importance had no impact on the statistical significance of the two preferred endpoints of the Norfolk QOL-DN and mNIS+7 score.

Figure 2. Testing Procedure for Study CS-3



Source: Statistical Analysis Plan Version 2.1 Addendum.
Abbreviations: mNIS+7, modified neurological impairment score +7; TTR, transthyretin

6.2.1.4. Results of Analyses, Study ION-682884-CS3

6.2.1.4.1. Subject Disposition, Demographic and Baseline Characteristics

The first subject was screened on (b) (6) first subject dosed on (b) (6) and efficacy interim data cutoff date on April 18, 2022. The study report was created on the date of November 22, 2022.

Of the 217 screened subjects, 49 subjects were screen failures. In total, 168 subjects were randomized and treated (inotersen: N=24; eplontersen: N=144).

Table 10. Subject Dispositions – Study ION-682884-CS3 and Study ISIS-420915-CS2

	Study ION-682884-CS3			Study ISIS-420915-CS2		
Subject Counts	**Eplontersen[a]**	**Inotersen[b]**	**Total**	**Inotersen[c]**	**Placebo[d]**	**Total**
Randomized	144	24	168	113	60	173
Treated	144	24	168	112	60	172
Completed Week 35	140	20	160	95	57	152
FAS	140	20	160	106	59	165
Per protocol	138	15	153	84	52	136

Source: Table 7 and Table 9 in CS-3 study report under NDA 217388 and Table 6 in CS-2 study report under NDA 211172.
[a.] investigational new drug.
[b.] concurrent reference group.
[c.] approved drug.
[d.] external control group.
Abbreviations: FAS, full analysis set

FAS was defined as randomized and treated with a baseline and at least one post-baseline assessment for the efficacy endpoint. This definition of FAS is consistent with the modified intent-to-treat population and is acceptable.

The efficacy evaluation compared the eplontersen arm in Study CS-3 to the placebo arm in Study CS-2, therefore the review includes baseline tables and results for these two arms, one from each study.

There were two subjects in the eplontersen group who died; both deaths were not related to study drug as assessed by the investigator. Subject (b) (6) died on Day 100, and therefore was missing the week 35 or day 245 visit and was not included in the FAS population for the primary analysis. Subject (b) (6) died on day 282 and was included in the FAS and primary analysis. More detailed analyses about these two subjects are in Section 6.2.1.4.3.

Demographic variables were balanced between the drug and placebo groups.

Table 11. Subject Baseline Demographics – FAS – Study ION-682884-CS3

Demographic	**Eplontersen (N=140)**	**Placebo (N=59)**
Age (years)		
Mean (SD)	52.80 (15.05)	59.39 (14.14)
Median	51.00	63.00
Minimum, Maximum	24, 82	28, 81
Age Group, n (%)		
<65 years	97 (69.29)	34 (57.63)
65 to 74 years	36 (25.71)	16 (27.12)
≥75 years	7 (5.00)	9 (15.25)
Gender, n (%)		
Female	43 (30.71)	18 (30.51)
Male	97 (69.29)	41 (69.49)
Region, n (%)		
Europe	51 (36.43)	22 (37.29)
North America	21 (15)	26 (44.07)
South America/Australia/Asia	68 (48.57)	11 (18.64)
Race, n (%)	**(N=139)**	**(N=59)**
American Indian or Alaska Native	0	0
Asian	22 (15.83)	3 (5.08)
Black or Africa American	5 (3.6)	1 (1.69)
Native Hawaiian or Other Pacific Islander	0	0

Demographic	Eplontersen (N=140)	Placebo (N=59)
White	108 (77.7)	52 (88.14)
Other	3 (2.16)	2 (3.39)
Multiple	1 (0.72)	1 (1.69)

Source: Reviewer's own analysis using ADSL and Table 10 in the Applicant's study report, verified by the statistical reviewer.
Note: Some categories have lower number of subjects, due to missing data for those subjects.
Abbreviations: N, number of subjects in treatment group; n, number of subjects in category; SD, standard deviation

Baseline disease characteristics were consistent with an hATTR-PN population and balanced across the treatment groups.

Table 12. Subject Baseline Disease Characteristics – FAS – Study ION-682884-CS3

Characteristic	Eplontersen (N=140)	Placebo (N=59)
Disease Stage, n (%)		
Stage 1	112 (80)	42 (71.19)
Stage 2	28 (20)	17 (28.81)
V30M TTR Mutation, n (%)		
Yes	82 (58.57)	33 (55.93)
No	58 (41.43)	26 (44.07)
Previous treatment (42rogram42s or diflunisal), n (%)		
Yes	98 (70)	35 (59.32)
No	42 (30)	24 (40.68)
Duration of disease from hATTR-PN diagnosis (months)		
Mean (SD)	46.91 (57.96)	39.76 (40.45)
Median	30.0	24.0
Min, Max	0, 379	1, 159
Duration from onset of hATTR-PN symptoms (months)	**(N=139)**	**(N=59)**
Mean (SD)	67.53 (50.91)	64.41 (52.70)
Median	54.0	48.0
Min, Max	5, 354	8, 277
mNIS+7 composite score	**(N=140)**	**(N=59)**
Mean (SD)	79.59 (42.32)	74.12 (39.03)
Median	76.59	74.66
Min, Max	7.91, 205.62	13.16, 156.68
Norfolk QOL-DN total score	**(N=133)**	**(N=58)**
Mean (SD)	43.48 (26.25)	48.60 (26.97)
Median	41.00	47.56
Min, Max	1.0, 106.0	-1.0, 111.0
BMI (kg/m^2)	**(N=134)**	**(N=59)**
Mean (SD)	24.41 (4.92)	24.25 (4.89)
Median	24.12	23.87
Min, Max	15.39, 35.36	14.54, 39.77

Source: Reviewer's analysis using ADSL and Table 11 in the Applicant's study report, verified by the statistical reviewer.
Note:

- Some categories have lower number of subjects due to missing data for those subjects.
- V30M includes the following genotypes: Val30Met, Val50Met, Val50Met MUTATION, Val50Met, and P.Val50Met. V30 was also written as V50 due to alternative nomenclature used by the testing laboratory.

Abbreviations: BMI, body mass index; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; mNIS+7, modified Neuropathy Impairment Score +7; N, number of subjects in treatment group; n, number of subjects in group; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy.

6.2.1.4.2. Efficacy Results of the Primary Clinical Endpoint

The results reported by the Applicant were confirmed.

The primary analysis of mNIS+7 included 199 subjects: 140 from the drug arm and 59 the from placebo arm. There was a statistically significant greater mean reduction in the change in mNIS+7 total score from baseline to week 35 of the treatment phase for eplontersen compared with placebo. The difference in least squares mean (LSM) (95% CI) was −9.01 (−13.48, −4.54) for eplontersen versus placebo (p<0.0001).

Table 13. Primary Endpoint Analyses of mNIS+7 – FAS – Study ION-682884-CS3

mNIS+7 Score	Eplontersen (N=140)	Placebo (N=59)
Baseline		
n	140	59
Mean (SD)	79.59 (42.318)	74.12 (39.029)
Median	76.59	74.66
Q1, Q3	43.19, 106.90	40.29, 106.28
Minimum, Maximum	7.9, 205.6	13.2, 156.7
Change from baseline at week 35		
n	137	55
Mean (SD)	-0.03 (16.281)	9.76 (14.199)
Median	0.05	9.85
Q1, Q3	-6.30, 7.65	-2.07, 19.32
Minimum, Maximum	-80.6, 47.4	-19.4, 40.6
Adjusted analysis		
n	140	59
LSM	0.2150	9.2247
(95% CI of LSM)	(-3.4589, 3.8888)	(5.5380, 12.9115)
Difference in LSM		-9.0097
(95% CI of difference)		(-13.4827, -4.5368)
p-value		<0.0001

Source: Reviewer's analysis and Applicant's analysis Table 14 verified by the reviewer.
Abbreviations: CI, confidence interval; LSM, least square mean; modified Neuropathy Impairment Score +7; N, number of subjects in treatment group; n, number of subjects in analysis; SD, standard deviation

The ANCOVA model included treatment group (drug or placebo), disease stage (1 or 2), V30M mutation (Yes or No), previous treatment (Yes or No), propensity score and the baseline value. P-value was for the comparison of treatment groups in change from baseline at week 35.

Subjects with a missing mNIS+7 at week 35 had values multiply imputed using an imputation model. Each of 500 imputed data sets was analyzed using a simple ANCOVA model, and the results were combined using Rubin's rules. During the review, descriptive counts including subject counts at baseline and week 35 were replicated as well as the same p-value; however, the estimate of the effect was -9.03, slightly larger than Applicant's result of -9.01. This may be due to the imputation codes not producing the exact same random numbers for the 500 runs on different computing platforms. Because the results are very close and the Agency's estimated effect size is slightly larger, the Applicant's result in the study report is considered confirmed.

There were two subjects in the eplontersen group who died. Subject (b) (6) was included in the FAS and primary analysis. This subject had a baseline score of 151.439 and a week 35 score of 152.131, with a change of 0.6915 points measured by mNIS+7. Removing this subject from the analysis of almost 200 subjects had almost no effect on the estimate for treatment effect nor p-value. This subject also had baseline serum TTR value 0.123, and 0.046, 0.031, 0.022, 0.012, 0.011 at week 5, 9, 13, 25, and 35 respectively, which showed a change of about -91% from

baseline. This subject appears to have consistent efficacy either by mNIS+7 or serum TTR from baseline to week 35.

The study statistical analysis plan did prespecify a rule to check for normality as follows: if the Shapiro-Wilks test assessing normality of the ANCOVA residuals is significant at the 0.01 level, i.e., <0.01, then a stratified Wilcoxon rank sum test would be performed. The Shapiro-Wilks test did produce a p <0.01, so the Applicant provided a stratified Wilcoxon rank sum test which showed a result of "rank diff = -9.48 with p<0.0001." The underlying reason for this result was that subject (b) (6) from the drug arm had a change from baseline score of -80.5591. Removing this one subject from the analysis in the same ANCOVA model produced a result of "mNIS+7 score diff = -8.6522 with p<0.0001" and the Shapiro-Wilks test p-value 0.0457, higher than 0.01. The normality of the ANCOVA model residuals passed the check by removing just one subject. In addition, well defined clinical endpoints are preferred to report effect size, instead of ranks in nonparametric methods such as the rank difference, which is difficult to interpret in clinical settings.

In summary, the Agency considers the ANCOVA model result "mNIS+7 score diff = -9.0 with p<0.0001" from the Applicant confirmed.

6.2.1.4.3. Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and slightly higher in the placebo group.

Table 14. Subject Counts at Baseline and Week 35 for mNIS+7 – FAS – Study ION-682884- CS3

Subject Counts	Week 0	Week 35	Week 35 Missing	Missing %
Eplontersen	140	137	3	2.14%
External Placebo	59	55	4	6.78%
Total	199	192	7	3.52%

Source: Reviewer's own analysis.
Abbreviations: FAS, full analysis set; mNIS+7, modified Neuropathy Impairment Score +7

In the sensitivity analyses presented by the Applicant, observed data only without imputation and a per-protocol analysis were performed. In the Agency's sensitivity analyses, a worst-case scenario imputing for missing data was performed where the missing from the placebo arm was assigned a change of -20 points while the missing from drug arm had a change of +20 points. Twenty points was used as effect size at the planning stage. The primary endpoint was analyzed using the same ANCOVA model after the imputation. The result of the sensitivity analyses was consistent with those of the primary analysis. Under the "worst case scenario", the p-value was still less than 0.05, although larger than the p-value in the primary analysis.

Table 15. Sensitivity Analysis of mNIS+7 for Missing Data -FAS – Study ION-682884-CS3

Change From Baseline mNIS+7 at Week 35	Observed Data Only (N=192)		Per Protocol (N=190)		"Worst-Case" Imputation (N=199)	
	Drug (n=137)	Placebo (n=55)	Drug (n=138)	Placebo (n=52)	Drug (n=140)	Placebo (n=59)
LSM	0.29	9.35	0.51	8.08	0.81	7.33
(95% CI)	(-3.42, 3.99)	(5.75, 12.96)	(-3.22, 4.24)	(4.39, 11.77)	(-3.01, 4.64)	(3.62, 11.03)
Difference in LSM		-9.07		-7.56		-6.51
(95% CI)		(-13.45, -4.68)		(-11.96, -3.17)		(-11.07, -1.95)
p-value		<0.0001		0.0007		0.0053

Source: Table 15 from CSR and reviewer's analysis.
Abbreviations: CI, confidence interval; LSM, least square mean; mNIS+7, modified Neuropathy Impairment Score +7; N, number of subjects in analysis set; n, number of subjects in treatment group

6.2.1.4.4. Efficacy Results of Additional Endpoints

The analysis of serum TTR included 199 subjects: 140 from the drug arm and 59 from the placebo arm. There was a statistically significant greater mean percentage change (reduction) in serum TTR level from baseline to week 35 of the treatment phase for eplontersen compared with the external placebo. The difference in least squares mean (LSM) (95% CI) was −66.43 (−71.39, −61.47) for eplontersen versus placebo (p<0.0001).

Table 16. Analyses of Serum TTR – FAS – Study ION-682884-CS3

Serum TTR	Eplontersen (N=140)	External Placebo (N=59)
Baseline		
n	140	59
Mean (SD)	0.2269 (0.0755)	0.1541 (0.0375)
Median	0.2220	0.1560
Q1, Q3	0.1790, 0.2695	0.1290, 0.1830
Minimum, Maximum	0.064, 0.448	0.074, 0.228
Percent Change from baseline at Week 35		
n	136	57
Mean (SD)	-81.98 (11.702)	-11.13 (19.604)
Median	-84.17	-9.45
Q1, Q3	-90.06, -77.11	-25.69, -0.64
Minimum, Maximum	-97.2, -33.0	-47.8, 35.7
Adjusted analysis		
n	140	59
LSM	-81.20	-14.76
(95% CI of LSM)	(-84.55, -77.84)	(-18.73, -10.80)
Difference in LSM		-66.43
(95% CI of difference)		(-71.39, -61.47)
p-value		<0.0001

Source: Reviewer's own analysis and Applicant's analysis Table 12 verified by the reviewer.
Note: Unit for serum TTR concentration is g/L.
Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least square mean; N, number of subjects in treatment group; n, number of subjects in analysis; Q1, first quantile; Q3, third quantile; SD, standard deviation; TTR, transthyretin

The MMRM model included treatment group (drug or placebo), disease stage (1 or 2), V30M mutation (Yes or No), previous treatment (Yes or No), propensity score weight and the baseline value, time (5 visit numbers) and the baseline by time interaction. With no imputation for missing data in the MMRM model, we were able to get the exact same numbers not only for the

descriptive including subject counts at baseline and week 35 but also the estimate for effect size and p-value as in Applicant's report.

We note that the drug arm in Study CS-3 had 5 visits: week 5, 9, 13, 25 and 35; while the external placebo arm from Study CS-2 had 5 visits: week 5, 8, 13, 23, and 35. The visit numbers were aligned to be the same five visit numbers.

Because both serum TTR and mNIS+7 were significant at an alpha level of two-sided 0.025, the secondary endpoint Norfolk QOL-DN was tested at the 0.025 level. At the week 35 analysis, the same analysis of mNIS+7 was applied for Norfolk QOL-DN. The result reported by the Applicant was confirmed.

Table 17. Secondary Endpoint of Norfolk QOL-DN at Week 35 – FAS – Study ION-682884-CS3

Norfolk QOL-DN score	Eplontersen (N=140)	External Placebo (N=59)
Baseline		
n	133	58
Mean (SD)	43.48 (26.251)	48.60 (26.974)
Median	41.00	47.56
Q1, Q3	21.100, 61.00	31.00, 70.00
Minimum, Maximum	1.0, 106.0	-1.0, 111.0
Change from baseline at Week 35		
n	130	57
Mean (SD)	-4.79 (16.514)	5.51 (20.178)
Median	-2.50	5.00
Q1, Q3	-13.00, 2.00	-8.00, 17.00
Minimum, Maximum	-65.0, 41.0	-62.0, 52.0
Adjusted analysis		
n	133	58
LSM	-3.1173	8.6725
(95% CI of LSM)	(-7.1900, 0.9554)	(4.5314, 12.8135)
Difference in LSM		-11.7897
(95% CI of difference)		(-16.8171, -6.7625)
p-value		<0.0001

Source: Reviewer's own analysis and Applicant's analysis Table 17 verified by the reviewer.
Abbreviations: CI, Confidence Interval; LSM, Least Square Mean; Q1, first quantile; Q3, third quantile; SD, Standard Deviation.

The ANCOVA model included treatment group (drug or placebo), disease stage (1 or 2), V30M mutation (Yes or No), previous treatment (Yes or No), propensity score weight and the baseline value. P-value was for the comparison of treatment groups in change from baseline at week 35.

Subjects with a missing Norfolk QOL-DN at Week 35 had values multiply imputed using an imputation model. Each of 500 imputed data sets was analyzed using simple ANCOVA model, and the 500 ANCOVA model results were combined using Rubin's rules.

During the review, descriptive counts including subject counts at baseline and week 35 were confirmed. The same p-value was calculated by the Agency, but the estimate of the effect was calculated as -11.80 being slightly larger than the Applicant's number of -11.79. This may be due to the imputation codes not producing the same random numbers for the 500 runs on different computing platforms. Because the results were very close and the Agency's estimated effect size was slightly larger, the Applicant's result in study report is considered confirmed.

6.2.1.4.5. Findings in Subgroups – Age, Gender, and Race

Analyses for the treatment effect across subgroups such as age, gender, and race were performed. The trend in treatment success appears to be similar across subgroups.

Table 18. Age, Gender, and Race Summaries by Treatment Group – FAS – Study ION-682884-CS3

Treatment Group	Age (>=65)	Gender (Female)	Race (White)	Race (Asian)	Race (Black)	Race (Multiple)	Race (Other)	Race (Missing)
Drug (n=140)	43	43	108	22	5	1	3	1
Placebo (n=59)	25	18	52	3	1	1	2	0
Overall (n=199)	68	61	160	25	6	2	5	1

Source: Reviewer's result.
Abbreviations: FAS, full analysis set; n, number of subjects in treatment group

Table 19. Findings in Subgroup Populations: Age Gender and Race – FAS – Study ION-682884-CS3

mNIS +7	N	Baseline Mean (SD)	CFB Week 35 (95% CI)	Diff (95% CI)
Age >=65				
Drug	43	86.61 (42.08)	-0.45 (-6.13, 5.24)	-13.73 (-21.23, -6.23)
Placebo	25	80.19 (37.68)	13.28 (8.16, 18.40)	
Age <65				
Drug	97	76.47 (42.27)	0.18 (-4.36, 4.73)	-6.21 (-11.61, -0.81)
Placebo	34	69.66 (39.95)	6.39 (1.78, 11.00)	
Gender = Female				
Drug	43	76.38 (42.43)	-4.07 (-9.81, 1.67)	-9.25 (-17.35, -1.16)
Placebo	18	64.06 (36.04)	5.18 (-0.98, 11.357	
Gender = Male				
Drug	97	81.01 (42.41)	2.70 (-1.57, 6.97)	-8.46 (-13.59, -3.34)
Placebo	41	78.55 (39.89)	11.16 (7.06, 15.25)	
Race = White (White and Multiple)				
Drug	109	79.85 (40.01)	0.73 (-3.58, 5.04)	-8.87 (-13.71, -4.04)
Placebo	53	76.22 (38.91)	9.60 (5.77, 13.43)	
Race = ALL OTHER (Black, Asian, Other, Missing)				
Drug	30	79.75 (50.83)	-0.88 (-8.00, 6.23)	-8.32 (-21.97, 5.33)
Placebo	6	55.65 (38.30)	7.43 (-4.33, 19.19)	

Source: Table 2.27, 2.28 and 2.29, study report.
Abbreviations: CFB, change from baseline; CI, confidence interval; Diff, difference; FAS, full analysis set; N, number of subjects in treatment subgroup; mNIS+7, modified Neuropathy Impairment Score +7; SD, standard deviation

Race collected as "multiple" in dataset ADSL was counted together in "White" for subgroup results. There was only one such subject in each arm in FAS population. The Applicant's table is considered confirmed.

6.2.1.4.6. Findings in Other Special Subgroups

Evaluation of efficacy in subgroups is limited by the small population size.

However, based on the characteristics in the above demographics tables, the development program is deemed to provide generally adequate representation across the disease population. The course of the disease is not known to differ importantly in minority populations, and there are no known factors that would predispose these populations to drug-induced toxicity. The subject exposure appears generalizable to the U.S. patient population.

6.3. Key Efficacy Review Issues

There were no key efficacy issues identified. Refer to Section 3.1.1.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical studies of eplontersen submitted to the NDA included general toxicology studies of up to 26 weeks (mouse) and 9 months (monkey) in duration, a standard battery of in vitro (Ames, clastogenicity in Chinese hamster lung cells) and in vivo (mouse micronucleus) genetic toxicology assays, a combined fertility and embryofetal development study in mouse; and a 13-week impurity qualification study in mouse. All pivotal studies were conducted in accordance with Good Laboratory Practice. Eplontersen is pharmacologically active in monkey but not mouse.

In the 13-week subcutaneous (SC) toxicity study in mouse, eplontersen was administered weekly at doses of 0, 5, 25, and 75 mg/kg). The primary findings were cytoplasmic alternation in the liver (mid and high doses), basophilic granules in multiple tissues (consistent with uptake and accumulation of drug and commonly observed with ASOs), including liver Kupffer and renal tubule cells, and vacuolated/granular macrophages at the injection site. In the 26-week SC toxicity study in mouse, eplontersen was administered biweekly at doses of 0, 10, 50, and 150 mg/kg). The primary findings were related to accumulation of basophilic granules in multiple tissues, including liver, kidney, injection site, skin, and testes, and inflammatory responses. The no-adverse-effect level (NOAEL) in the 26-week study in mouse was 150 mg/kg.

In the 13-week SC study in monkey (0, 2, 6, and 24 mg/kg/week), findings consisted of thrombocytopenia, with secondary hemorrhage, in one high-dose (HD) female (recovered following corticosteroid treatment and a dosing holiday), basophilic granules in liver Kupffer cells (mid (MD) and HD), and granular macrophages in lymph nodes (all doses). In the 9-month SC toxicity study in monkey (0, 5, 10, and 25 mg/kg/month), findings included accumulation of basophilic granules in liver, kidney, and lymph nodes. A transient increase in complement Bb was observed at the HD. Decreases in TTR mRNA levels in liver (52, 59, and 62%, respectively) and in plasma TTR protein levels (37, 46, and 52%, respectively) and retinol-binding protein 4 (RBP4) protein levels (8, 9, and 29%, respectively) were observed at all doses. The NOAEL in the 39-week study in monkey was 25 mg/kg.

Eplontersen was negative for genotoxicity in adequately conducted in vitro and in vivo genetic toxicology assays.

The potential for adverse effects on fertility and embryofetal development (EFD) was assessed in a combined fertility and EFD study in mouse (0, 1.42, 7.16, and 21.45 mg/kg every other day; 0, 5, 25, and 75 mg/kg/week); separate groups were administered a mouse-specific surrogate (ION-1184986; 7.16 mg/kg every other day; 25 mg/kg/week). No adverse effects were observed with eplontersen or ION-1184986. Unconjugated eplontersen levels were increased in a dose-

dependent manner in maternal and paternal liver but was undetectable in placenta and fetal liver. The mouse-specific surrogate resulted in decreases in hepatic TTR mRNA levels by 93-97%.

To assess the potential toxicity of eplontersen impurities, eplontersen (200 mg/kg/week SC), in the presence or absence of Test Article Mixture (TAM)#1 (b) (4) TAM#2 (b) (4) (b) (4) or TAM #3 (b) (4) was administered to mice for 13 weeks. Toxicities were similar among groups and included accumulation of vacuolated histiocytes in lymph nodes, testes, and epididymides, and mononuclear cell infiltration at the injection site.

Based on plasma exposure, the NOAEL in monkey will provide safety margins of 134 ($AUC_{0\text{-}24h}$) and 112 (C_{max}) compared to the proposed human dose of 45 mg.

Table 20. Safety Margins Based on Plasma Exposure With Respect to Recommended Human Dose

Proposed Human Dose*	Exposure Margin	
mg	9-month Monkey NOAEL (25 mg/kg)+	
	$AUC_{0\text{-}24h}$ (µg*h/mL)	C_{max} (µg/mL)
45	134	112

Source: Reviewer generated
* $AUC_{0\text{-}24h}$ (1.4 µg*h/mL) and C_{max} (0.215 µg/mL) in human at MRHD (45 mg) SC Q4W eplontersen (Study #: ION-682884-CS1)
+ $AUC_{0\text{-}24h}$ (187 µg*h/mL) and C_{max} (24 µg/mL) in monkey at NOAEL (25 mg/kg) SC Q4W eplontersen (Study #: 682884-AS05)
Abbreviations: $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours postdose; C_{max}, maximum plasma concentration; NOAEL, no observed adverse effect level; MRHD, maximum recommended human dose; Q4W, once every four weeks; SC, subcutaneous(ly)

The completed nonclinical studies are adequate to support the NDA for eplontersen.

The carcinogenic potential of eplontersen has not been assessed. A 26-week carcinogenicity study in the tg.ratH2 mouse will be a post-marketing requirement.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Eplontersen is an antisense oligonucleotide GalNAc conjugate that causes hepatic-targeted degradation of TTR mRNA (for mutant variants and wild-type TTR) through direct binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. TTR (transthyretin) is a transport protein that transports thyroxine and retinol to the liver.

Potential safety concerns for eplontersen based on the route of administration and therapeutic class (including information from the previously approved hATTR drug inotersen) were thrombocytopenia, glomerulonephritis, renal impairment, abnormal liver function, injection site reactions, flu-like symptoms, central nervous system disorders, hemorrhages, and coagulation abnormalities. Potential safety concerns based on the mechanism of action of eplontersen included vitamin A deficiency and reduced thyroxine. Other disease-related pathophysiology of hATTR amyloidosis included evaluation of cardiac disorders. Inotersen, the unconjugated parent form of eplontersen, has a boxed warning for thrombocytopenia and for glomerulonephritis and is available only through the Tegsedi REMS restricted distribution program.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Eplontersen is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for eplontersen.

7.3.1. Expectations on Safety

The clinical study findings may not fully represent the clinical safety of eplontersen in the setting of more advanced hATTR-PN because ION-682884-CS3 and ION-682884-CS13 did not include subjects with Stage 3 hATTR-PN.

The safety of eplontersen in women who are pregnant or breast-feeding, and in infants who are breastfeeding, has not been characterized in clinical trials. Because eplontersen will be used in women of childbearing potential, a pregnancy outcomes study and a lactation pharmacokinetic study will be requested postmarketing requirements.

Eplontersen is intended to be administered subcutaneously by non-health professionals (e.g., patients, caregivers). Because its mechanism of action is specific to the treatment of hATTR-PN, we do not anticipate significant off-label use of eplontersen.

7.4. FDA Approach to the Safety Review

The eplontersen clinical development program consists of three Phase 1 studies in healthy volunteers (ION-682884-CS1, ION-682884-CS20, and ION-682884-CS21) and two Phase 3 studies in hATTR-PN (ION-682884-CS3 and the open-label extension ION-682884-CS13) and two Phase 3 studies in ATTR-CM (ION-682884-CS2 and ION-682884-CS12). The cardiomyopathy studies ION-682884-CS2 and ION-682884-CS12 are ongoing, CS-2 remains blinded, and neither are included as part of this application.

Eplontersen Phase 1 Studies

ION-682884-CS1 was a Phase 1/2 study that evaluated the safety, tolerability, PK, and pharmacodynamics of eplontersen in healthy volunteers. A total of 39 subjects received eplontersen in Study CS-1 (10 subjects each in the 45-, 60-, and 90-mg multidose cohorts, and 9 subjects in a 120 mg single-dose cohort). For the multidose cohorts, the treatment period was 13 weeks followed by a post treatment evaluation period of 13 weeks.

ION-682884-CS20 was a Phase 1, randomized, double-blinded, placebo-controlled study that assessed the safety, tolerability, PK, and pharmacodynamics of single-ascending doses of eplontersen in healthy subjects of Japanese descent. A total of 18 subjects received eplontersen in the study (45, 60, and 90 mg) and 6 received placebo. Post-treatment evaluations were conducted through 92 days following dosing.

ION-682884-CS21 was a Phase 1, single-dose, randomized, open-label, 3-period, crossover, bioequivalence study in 57 healthy adult subjects comparing 3 different means of SC administration.

Eplontersen Phase 3 Studies

ION-682884-CS3 is an open-label, external-control, randomized (6:1 eplontersen: concurrent inotersen reference) study with an 84-week treatment period evaluating if eplontersen 45 mg Q4W is superior to an external placebo group from the inotersen pivotal study, ISIS-420915-CS2. A concurrent inotersen reference group (n=20) was also included in ION-682884-CS3. This inotersen/eplontersen treatment group received inotersen from weeks 1 to 37 before switching to eplontersen. The treatment period was followed by a 20-week post-treatment evaluation period or enrollment into a long-term treatment extension study, ION-682884-CS13. Data from the pivotal study ION-682884-CS3 and the open-label extension study ION-682884-CS13 formed the basis of the majority of the clinical safety evaluation. Information submitted as part of NDA 217388, as well as published information related to antisense oligonucleotides, hATTR, and other relevant published literature, are discussed in this review.

The assessment of frequency of adverse events was based on analyses of studies ION-682884-CS3 and the open-label extension ION-682884-CS13. Additional data from the Phase 1 studies described above informed the key safety review issues of thrombocytopenia and glomerulonephritis.

Clinical study data analyses were provided by the FDA clinical data analysts. Safety data were independently analyzed using JMP software. No major data quality or integrity issues were identified that would preclude a safety review of this NDA. There were no major issues identified with respect to recording, coding, and categorizing adverse events (AEs). The Applicant's translations of verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in studies ION-682884-CS3 and ION-682884-CS13 were found to be acceptable. The Applicant used MedDRA version 25.0.

A treatment-emergent AE (TEAE) was defined as adverse events that occurred or worsened after the first dose of eplontersen. An AE with a completely missing start date was assumed to be treatment-emergent. The severity of AEs was graded as mild, moderate, or severe by the investigator based on clinical judgement.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for a comprehensive safety assessment of eplontersen for the proposed indication, patient population, dosage regimen, and duration. The data submitted with the initial submission included safety data for 100 subjects treated for 1 year with eplontersen. This data was in line with the expectation stated in the August 23, 2022, pre-NDA meeting for investigational new drug (IND) 139521, given the potential safety concerns for drugs in this class. The number of subjects exposed for ≥1 year exceeds the ICH E1A (March 1995) recommendation (see Table 21 and Table 22).

The safety population is representative of, and thus applicable to, the population of interest. The overall subject exposure in the clinical development program was found to be adequate.

Notably, given the underlying risk of cardiac abnormalities at baseline for hATTR patients, subjects with New York Heart Association functional classification of ≥3 were excluded.

Table 21. Eplontersen Safety Set Exposure Prior to 120-Day Safety Update (Data Cutoff: July 19, 2022)

Trial Name	≥3 months	≥6 months	≥12 months
Total No. Exposed to Eplontersen (ION-682884-CS3)	164	150	107

Source: ION-682884-CS3 Study Report.

Table 22. Eplontersen Safety Set Exposure After 120-Day Safety Update (Data Cutoff: October 19, 2022)

Trial Name	≥3 months	≥6 months	≥12 months
Total No. Exposed to Eplontersen (ION-682884-CS3)	164	161	137
Trial Name	**≥1 month**	**≥3 months**	**≥6 months**
Total No. Exposed to Eplontersen (ION-682884-CS13)	42	14	10

Source: 120-Day Safety Update.

The NDA submission was well-organized. The submission quality with respect to the Applicant's clinical safety assessments was acceptable. The FDA analysis reviewed AE coding to assess the accuracy of the translation from the verbatim to the preferred terms and found the translation adequate.

The Applicant designated the following adverse events of adverse events of significant interest (AESI) based on the therapeutic class, mechanism of action of eplontersen, route of administration, disease-related pathophysiology of hATTR amyloidosis, or general interest: thrombocytopenia, glomerulonephritis, and vitamin A deficiency. Other adverse events of interest include coagulation abnormalities, renal impairment, abnormal liver function, injection site reactions, flu-like symptoms, central nervous system disorders, hemorrhages, cardiac disorders, and reduced thyroxine. Safety assessments of these events are discussed in Section 7.6.2.1.

In addition to queries for adverse events, assessments of vital signs and laboratory monitoring were performed in the pivotal safety/efficacy study ION-682884-CS3. Laboratory monitoring included assessments of serum chemistry, hematology, urinalysis, coagulation, viral hepatitis, liver function testing, follicle-stimulating hormone testing (FSH), pregnancy testing, cardiac biomarkers (NT-proBNP, troponin T, and troponin I), TTR protein, vitamin A, electrocardiogram (ECG), and anti-drug antibodies.

The schedule of key safety assessments for ION-682884-CS3 is presented in Table 23, based on the submitted protocol. Given the half-life of eplontersen, the timing of assessments and monitoring, including after the last dose, are appropriate.

Table 23. ION-682884-CS3 Schedule of Key Safety Assessments

Safety Assessment	To Week 35	Weeks 35-85	Post Treatment Evaluation Period
Physical Exam	Weeks 1, 13, 25, 35	Weeks 49, 57, 65, 73, 81, 85	Weeks 93, 105
Vital Signs	Weeks 1, 13, 25, 35	Weeks 37, 49, 57, 65, 73, 81, 85	Weeks 93, 105

Safety Assessment	To Week 35	Weeks 35-85	Post Treatment Evaluation Period
Electrocardiogram	Weeks 13, 35	Weeks 65, 85	Week 105
Blood Chemistry	Weeks 1, 13, 25	Weeks 37, 49, 57, 65, 73, 81, 85	Weeks 89, 93, 97, 105
Hematology	Weeks 1, 13, 25	Weeks 37, 49, 57, 65, 73, 81, 85	Weeks 89, 93, 97, 105
Vitamin A	Weeks 1, 13, 25	Weeks 37, 49, 65, 85	Weeks 93, 105

Source: ION-682884-CS3 Study Report.

7.6. Safety Results

Overall, the safety profile of eplontersen in subjects with polyneuropathy of hereditary transthyretin-mediated amyloidosis is acceptable at the recommended dose.

7.6.1. Safety Results, Pooled Analyses, Trials ION-682884-CS3 and ION-682884-CS13

7.6.1.1. Immunogenicity, Pooled Analyses, Trials ION-682884-CS3 and ION-682884-CS13

Demographics and baseline characteristics were balanced between anti-drug antibody (ADA) positive and negative subjects. TEAEs were observed in a similar frequency between both groups. TEAEs of diarrhea, vitamin A deficiency, vomiting, hypotension, and dehydration had a ≥5% higher incidence in ADA-positive subjects versus ADA-negative subjects. However, these did not lead to drug interruption/discontinuation and there was no difference in the incidence of subjects with these TEAEs by ADA titer.

Table 24. TEAEs With an Incidence of at Least 5% by Overall Subject Immunogenicity Status as of the 120-Day Safety Update (Eplontersen Treated Set, Including ION-682884-CS3 and ION-682884-CS13, Data Cutoff: October 19, 2022)

Preferred Term	Positive (N = 78)		Negative (N = 88)	
	Subjects, n (%)	Events	Subjects, n (%)	Events
Subjects with at least one (1) TEAE	74 (94.9)	644	85 (96.6)	654
COVID-19	25 (32.1)	26	25 (28.4)	27
Diarrhoea	18 (23.1)	21	13 (14.8)	15
Urinary tract infection	15 (19.2)	32	16 (18.2)	27
Vitamin A deficiency	12 (15.4)	12	6 (6.8)	6
Nausea	10 (12.8)	13	7 (8.0)	9
Vomiting	9 (11.5)	21	5 (5.7)	5
Oedema peripheral	8 (10.3)	9	6 (6.8)	7
Proteinuria	6 (7.7)	6	9 (10.2)	11
Headache	7 (9.0)	7	5 (5.7)	6
Immunisation reaction	6 (7.7)	6	7 (8.0)	13
Fatigue	5 (6.4)	10	6 (6.8)	6
Pain in extremity	5 (6.4)	5	5 (5.7)	7
Vision blurred	5 (6.4)	8	3 (3.4)	4
Hypotension	6 (7.7)	6	1 (1.1)	1

Source: 120-day safety update.
Abbreviations: COVID-19, coronavirus disease of 2019; N, number of subjects by immunogenicity status; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

Overall, there does not appear to be a clinically meaningful difference between the safety of ADA+ and ADA- subjects treated with eplontersen.

7.6.2. Safety Results, Trial ION-682884-CS3

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial ION-682884-CS3

Discussions of safety for this trial will be split into its randomized period and its extension period (during which all subjects are placed on eplontersen). Please note this extension period differs from the separate open-label extension study, ION-682884-CS13. The primary safety evaluation compares eplontersen in CS-3 to the placebo arm in CS-2. Results from the inotersen active comparator arm will also be provided. The placebo arm from study CS-2 and the active control arm from CS-3 were utilized to make relative safety comparisons. However, there were some limitations in making direct comparisons. Study CS-3 was conducted during the COVID-19 pandemic while CS-2 was completed prior to the pandemic.

It is important to note that the active comparator arm drug, inotersen, is administered once weekly, as opposed to eplontersen which is administered once every 4 weeks which could affect the frequency of adverse event reporting. In addition, it should be noted that ISIS-420915-CS2, the study from which the external placebo group is taken, lasted 65 weeks (i.e., up to week 66), as compared to ION-682884-CS3 which has a treatment period lasting to 85 weeks.

The initial data cutoff date for ION-682884-CS3 (both randomized and extension periods) was July 19, 2022. Reference to safety data from the 120-day safety update utilizes a data cutoff of October 19, 2022.

In the randomized period of ION-682884-CS3, the frequency of any TEAEs in the eplontersen group (87.5%) was lower than the external placebo group (100%). The majority of TEAEs were mild in the eplontersen group. There were two life-threatening serious adverse events (SAEs) in the eplontersen group and none in the inotersen active comparator and external placebo groups. There was one SAE with a fatal outcome in the eplontersen-treated group, and none in the active comparator and external placebo groups.

Table 25. Overview of Treatment-Emergent Adverse Events, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
TEAE Event Category	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
SAE	14 (9.7)	3 (12.5)	-2.8 (-16.9, 11.3)	13 (21.7)
SAEs with fatal outcome	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Life-threatening SAEs	2 (1.4)	0	1.4 (-0.5, 3.3)	0
AE leading to permanent discontinuation of study drug	3 (2.1)	3 (12.5)	-10.4 (-23.9, 3.0)	2 (3.3)
AE leading to dose modification of study drug	6 (4.2)	9 (37.5)	-33.3 (-53.0, -13.7)[a]	3 (5.0)
AE leading to interruption of study drug	6 (4.2)	9 (37.5)	-33.3 (-53.0, -13.7)[a]	3 (5.0)
AE leading to reduction of study drug	0	0	0 (0, 0)	0
AE leading to dose delay of study drug	0	0	0 (0, 0)	0
Other	0	0	0 (0, 0)	0
Any AE	126 (87.5)	24 (100)	-12.5 (-17.9, -7.1)[a]	60 (100)
Severe and worse	10 (6.9)	3 (12.5)	-5.6 (-19.4, 8.3)	14 (23.3)
Moderate	37 (25.7)	14 (58.3)	-32.6 (-53.6, -11.7)[a]	39 (65.0)
Mild	79 (54.9)	7 (29.2)	25.7 (5.8, 45.6)[a]	7 (11.7)

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

In the extension period, 78.3% of subjects receiving eplontersen reported any TEAE. There was one life-threatening SAE and one fatal SAE.

Table 26. Overview of Treatment-Emergent Adverse Events, Safety Population, Trial ION-682884-CS3 Extension Period

TEAE Event Category	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
SAE	16 (11.3)	1 (5.0)	17 (10.6)
SAEs with fatal outcome	1 (0.7)	0	1 (0.6)
Life-threatening SAEs	1 (0.7)	1 (5.0)	2 (1.2)
AE leading to permanent discontinuation of study drug	2 (1.4)	0	2 (1.2)
AE leading to dose modification of study drug	6 (4.3)	1 (5.0)	7 (4.3)
AE leading to interruption of study drug	6 (4.3)	1 (5.0)	7 (4.3)
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Other	0	0	0
Any AE	111 (78.7)	15 (75.0)	126 (78.3)
Severe and worse	7 (5.0)	3 (15.0)	10 (6.2)
Moderate	33 (23.4)	4 (20.0)	37 (23.0)
Mild	71 (50.4)	8 (40.0)	79 (49.1)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Severity as assessed by the investigator.

Abbreviations: AE, adverse event; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with at least one event; Rnd., randomized; SAE, serious adverse event; TEAE, treatment-emergent adverse event

There were no notable differences in the incidence of subjects with at least 1 TEAE or new drug discontinuations in the 120-day safety update for ION-682884-CS3.

7.6.2.2. Deaths, Trial ION-682884-CS3

In the randomized period, there was one death in the eplontersen group due to arrhythmia, and there were no deaths in the inotersen active comparator group or external placebo group. The subject who died was Subject (b) (6), a 56-year-old male with a history of hATTR with cardiomyopathy with baseline abnormal ECG and echocardiogram, who experienced sudden loss of consciousness on day 100 and could not be resuscitated. The subject had received four doses of eplontersen prior to his death.

In the extension period, there was one death in subjects receiving eplontersen, Subject (b) (6) (b) (6) a 69-year-old male with a history of hATTR with cardiomyopathy with two previous ECGs demonstrating atrial fibrillation. The subject had normal laboratory parameters (including platelet and coagulation parameters) throughout the study (last platelet count prior to this event was 154 x 10^9/L). He had received 10 doses of eplontersen prior to his death. On an unknown date the subject had a fall caused by sudden dizziness with left-sided weakness. The subject was hospitalized and on admission had normal labs except for mildly reduced platelet count (136 x 10^9/L; normal range 140-400 x 10^9/L). A CT scan demonstrated an intracerebral hemorrhage (ICH). Following a complex 2-week hospital stay, the subject died from complications related to the ICH.

There were no new deaths noted in the 120-day safety update for ION-682884-CS3 (please see Section 7.6.3.2 on ION-682884-CS13 for updated deaths in that trial).

Hereditary ATTR is a complex, chronic multisystem disease with known complications due to amyloid deposition in multiple organ systems such as in the brain (leading to increased susceptibility to intracerebral hemorrhage) and in the heart (cardiomyopathy and arrhythmias). Although the deaths were likely related to the underlying disease, a role for eplontersen cannot be ruled out.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial ION-682884-CS3

In the randomized period, the frequency of SAEs in the eplontersen group (9.7%) was lower than that in the external placebo group (21.7%) and the inotersen active comparator group (12.5%). The most frequent SAEs in the eplontersen group include gastrointestinal (vomiting), cardiac disorders, and infections (though none had a frequency of ≥5%), and the frequency of these SAEs was similar to that seen in the external placebo group.

Please see Section 7.6.2.6 for detailed information about cardiac SAEs.

There was one designated medical event of rhabdomyolysis, the case narrative of which is described below.

- Subject (b) (6) A 68-year-old male with a baseline elevated CK (369 U/L) and baseline mildly elevated ALT of 55 U/L and normal AST of 34 U/L, had on study day 509 an ALT of 121 U/L, AST of 248 U/L, and CK of 13,537 U/L; study drug continued without interruption

and the event of rhabdomyolysis was resolved by study day 561. Notably the subject had been on atorvastatin, which is known to cause elevated CK. It should also be noted that elevated CK was a known ongoing medical condition for this subject prior to enrollment in the study. The subject had mildly elevated CKs throughout the study. He also had elevated troponin levels throughout the study (0.02 ng/mL on study day 1 prior to starting study drug to a peak of 0.023 ng/mL, normal value: <0.014 ng/mL).

Given the risk factors for elevated CK (such as atorvastatin use and elevated CK at baseline) and given that the event resolved without a de-challenge, it is unlikely that this event was caused by study drug, although a role for eplontersen cannot be ruled out.

Per the 120-day safety update, the incidence of subjects with CK > ULN at any time postbaseline was 68.3% (n=114) in the eplontersen safety set, compared with 61.7% (n=37) in the external placebo group, and 58.6% (n=65) in the historical inotersen group. Muscle wasting in peripheral neuropathies may cause elevated CK levels at baseline.

However, it should be noted that in ION-682884-CS1, the Phase 1 study evaluating eplontersen in healthy subjects, there were four healthy subjects with CK elevations (all of these subjects were receiving 90 mg of eplontersen every 4 weeks, which is double the dose proposed for marketing of 45 mg every 4 weeks). These elevations included:

- Subject (b) (6) with a peak CK of 1484 U/L
- Subject (b) (6) with a peak CK of 1149 U/L
- Subject (b) (6) with a peak CK of 2571 U/L
- Subject (b) (6) with a peak CK of 2982 U/L

All resolved without intervention. These subjects had normal CK levels at baseline except for Subject (b) (6) who had a mildly elevated baseline CK of 227 U/L. In this study, subjects were required to abstain from heavy exercise for 72 hours prior to study visits.

Table 27. Subjects With Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
System Organ Class Preferred Term	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
Any SAE	14 (9.7)	3 (12.5)	-2.8 (-16.9, 11.3)	13 (21.7)
Blood and lymphatic system disorders (SOC)	0	0	0 (0, 0)	0
Thrombocytopenia	0	0	0 (0, 0)	0
Cardiac disorders (SOC)	4 (2.8)	0	2.8 (0.1, 5.5)[a]	2 (3.3)
Angina unstable	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Arrhythmia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Atrioventricular block	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Atrioventricular block second degree	1 (0.7)	0	0.7 (-0.7, 2.1)	0

System Organ Class Preferred Term	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	 Inotersen N=24 n (%)	 Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Gastrointestinal disorders (SOC)	6 (4.2)	0	4.2 (0.9, 7.4)[a]	1 (1.7)
Vomiting	4 (2.8)	0	2.8 (0.1, 5.5)[a]	1 (1.7)
Nausea	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Gastric hemorrhage	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Gastritis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Impaired gastric emptying	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Infections and infestations (SOC)	6 (4.2)	1 (4.2)	0 (-8.6, 8.6)	5 (8.3)
Urinary tract infection	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Cellulitis	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
COVID-19	1 (0.7)	0	0.7 (-0.7, 2.1)	0
COVID-19 pneumonia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Gastroenteritis	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Streptococcal sepsis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Urosepsis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Soft tissue infection	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	0
Injury, poisoning, and procedural complications (SOC)	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	3 (5.0)
Burns third degree	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Nervous system disorders (SOC)	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Metabolic encephalopathy	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Syncope	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Renal and urinary disorders (SOC)	2 (1.4)	1 (4.2)	-2.8 (-11.0, 5.4)	0
Hematuria	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Renal impairment	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Urinary retention	1 (0.7)	0	0.7 (-0.7, 2.1)	0

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease of 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

In the extension period, the frequency of SAEs in subjects receiving eplontersen was 10.6%. The majority of these SAEs include gastrointestinal disorders and infections (neither with a frequency ≥5%). One subject in the eplontersen group had complete atrioventricular block.

Subject (b) (6) a 24-year-old female, had pyelonephritis on study day 276; then later while enrolled in the open-label extension Study ION-682884-CS13 she had two hospitalizations for urosepsis (study days 659 and 793, respectively).

Table 28. Subjects With Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial ION-682884-CS3 Extension Period

System Organ Class Preferred Term	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Any SAE	16 (11.3)	1 (5.0)	17 (10.6)
Cardiac disorders (SOC)	1 (0.7)	1 (5.0)	2 (1.2)
Atrioventricular block complete	1 (0.7)	1 (5.0)	2 (1.2)
Atrial flutter	0	1 (5.0)	1 (0.6)
Ear and labyrinth disorders (SOC)	1 (0.7)	0	1 (0.6)
Vertigo	1 (0.7)	0	1 (0.6)
Gastrointestinal disorders (SOC)	5 (3.5)	0	5 (3.1)
Vomiting	3 (2.1)	0	3 (1.9)
Ileus	1 (0.7)	0	1 (0.6)
Impaired gastric emptying	1 (0.7)	0	1 (0.6)
General disorders and administration site conditions (SOC)	1 (0.7)	0	1 (0.6)
Asthenia	1 (0.7)	0	1 (0.6)
Infections and infestations (SOC)	6 (4.3)	0	6 (3.7)
COVID-19 pneumonia	1 (0.7)	0	1 (0.6)
Nasopharyngitis	1 (0.7)	0	1 (0.6)
Pneumonia	1 (0.7)	0	1 (0.6)
Pyelonephritis	1 (0.7)	0	1 (0.6)
Skin infection	1 (0.7)	0	1 (0.6)
Urinary tract infection	1 (0.7)	0	1 (0.6)
Injury, poisoning and procedural complications (SOC)	1 (0.7)	0	1 (0.6)
Foot fracture	1 (0.7)	0	1 (0.6)
Investigations (SOC)	2 (1.4)	0	2 (1.2)
Clostridium test positive	1 (0.7)	0	1 (0.6)
Glomerular filtration rate decreased	1 (0.7)	0	1 (0.6)
Metabolism and nutrition disorders (SOC)	2 (1.4)	0	2 (1.2)
Dehydration	1 (0.7)	0	1 (0.6)
Hypokalemia	1 (0.7)	0	1 (0.6)
Hyponatremia	1 (0.7)	0	1 (0.6)
Nervous system disorders (SOC)	2 (1.4)	0	2 (1.2)
Cerebral hemorrhage	1 (0.7)	0	1 (0.6)
Syncope	1 (0.7)	0	1 (0.6)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
- Duration is 84 weeks.

Abbreviations: AE, adverse event; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; Rnd., randomized; SAE, serious adverse event; SOC, system organ class

In the 120-day safety update for ION-682884-CS3, the most common serious TEAEs in eplontersen-treated subjects were noted to be vomiting (5 subjects), nausea, urinary tract infection, pneumonia (2 subjects each), and syncope (3 subjects).

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, ION-682884-CS3

In the randomized period, the frequency of AEs leading to eplontersen discontinuation was 2.1%, which is less than the that of the external placebo group (3.3%) and the inotersen active comparator group (12.5%). The causes of discontinuation in the three subjects who discontinued eplontersen were urinary sepsis, cardiac arrhythmia (one of the deaths listed in Section 7.6.2.2), and renal dysfunction.

The subject with urinary sepsis, (b) (6) a 49-year-old male, developed a urinary tract infection on study day 141 and was hospitalized and discharged on Study Day 151, then re-hospitalized on study day 156 for urosepsis and had significant sequelae of status epilepticus and decreased mental alertness. The last dose of eplontersen received was on Study Day 113. This event was likely unrelated to the study drug.

The subject with renal dysfunction, (b) (6) is a 76-year-old female with baseline estimated glomerular filtration rate (eGFR) below normal limits (52 mL/min/1.73m^2, normal >60). On study day 13, she experienced further decreased eGFR to 45 mL/min/1.73 m^2, and an increased urine protein/creatinine ratio of 259 mg/g (normal <200). On study day 36, she developed mild peripheral edema and eGFR further dropped to 39 mL/min/1.73m^2. Between study days 55 and 112, she also received furosemide. Her last dose of eplontersen was on study day 57. On study day 71, the subject's eGFR worsened further to 30 mL/min/1.73m^2 and then 27 mL/min/1.73m^2 (the nadir) on study day 113. The subject continued to have peripheral edema. Eplontersen was permanently discontinued on study day 127, with her last dose having been on study day 57. Her last eGFR reading was 43 mL/min/1.73m^2 on study day 155.

Given the subject's baseline low eGFR, her renal function changes were likely due to her underlying disease, complicated by concomitant furosemide use. However, a role for eplontersen cannot be ruled out. Glomerulonephritis is a risk identified for other antisense oligonucleotides and will be addressed in Section 7.7.3.

Table 29. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
System Organ Class Preferred Term	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
Any AE leading to Discontinuation	3 (2.1)	3 (12.5)	-10.4 (-23.9, 3.0)	2 (3.3)
Blood and lymphatic system disorders (SOC)	0	0	0 (0, 0)	0
Thrombocytopenia	0	0	0 (0, 0)	0
Cardiac disorders (SOC)	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Arrhythmia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Infections and infestations (SOC)	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Urosepsis	1 (0.7)	0	0.7 (-0.7, 2.1)	0

System Organ Class Preferred Term	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	 Inotersen N=24 n (%)	 Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Renal and urinary disorders (SOC)	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	1 (1.7)
Renal impairment	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Glomerulonephritis	0	1 (4.2)	-4.2 (-12.2, 3.8)	0

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

In the extension period, there were two subjects who discontinued eplontersen, one because of intracerebral hemorrhage (one of the deaths discussed in Section 7.6.2.2) and one because of proteinuria.

The subject with proteinuria, (b) (6) is a 56-year-old male with normal renal function at baseline who at highest reading had a urine protein/creatinine (P/C) ratio of 2388 mg/g (study day 225) while on eplontersen (normal <200). Throughout his course in the study, he had several elevated readings of urine P/C ratio. Serum creatinine and eGFR remained normal. His last dose of eplontersen was on study day 283.

Table 30. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial ION-682884-CS3 Extension Period

System Organ Class Preferred Term	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Any AE leading to Discontinuation	2 (1.4)	0	2 (1.2)
Nervous system disorders (SOC)	1 (0.7)	0	1 (0.6)
Cerebral hemorrhage	1 (0.7)	0	1 (0.6)
Renal and urinary disorders (SOC)	1 (0.7)	0	1 (0.6)
Proteinuria	1 (0.7)	0	1 (0.6)

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.

Abbreviations: AE, adverse event; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; Rnd., randomized; SOC, system organ class

In the 120-day safety update for ION-682884-CS3, one new TEAE (cardiac failure) led to withdrawal from the study. Subject (b) (6) a 69-year-old male with baseline hATTR cardiomyopathy since (b) (6) (concentric hypertrophy, diastolic dysfunction), had completed his last dose of eplontersen and had a post-treatment follow-up visit scheduled for Study Day 669. However, that same day the subject was hospitalized on the advice of his treating cardiologist for cardiac failure and supraventricular tachycardia. The subject missed the post-treatment follow-up visits and did not complete this portion but consented to continue into the survival status follow-up phase of the study. As of the 120-day safety update, these events were still ongoing.

A role for eplontersen for the adverse events of the above subjects cannot be ruled out.

7.6.2.5. Treatment-Emergent Adverse Events, ION-682884-CS3

Table 31 provides an overview of TEAEs that occurred during the randomized period. In the randomized period, the most frequent AEs in the eplontersen group were diarrhea and urinary tract infections. This frequency is less than the frequency seen in the external placebo group for both AEs. The AE of vision blurring had a higher frequency (4.2%) than the external placebo group (1.7%) but lower than that of the inotersen active comparator group (8.3%).

At the time of ISIS-420915-CS2, COVID-19 did not exist, so the external placebo group from this trial cannot be used to compare this adverse event.

Table 31. Subjects With Common Treatment-Emergent Adverse Events, Safety Population, ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Preferred Term	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
Any AE	126 (87.5)	24 (100)	-12.5 (-18.9, 1.6)	60 (100)
Diarrhea	19 (13.2)	1 (4.2)	9.0 (-7.6, 16.9)	12 (20.0)
COVID-19	14 (9.7)	1 (4.2)	5.6 (-11.0, 12.9)	0
Edema peripheral	8 (5.6)	0	5.6 (-8.4, 10.6)	6 (10.0)
Urinary tract infection	18 (12.5)	2 (8.3)	4.2 (-14.0, 13.4)	11 (18.3)
Dyspnea	5 (3.5)	0	3.5 (-10.5, 7.9)	5 (8.3)
Urinary retention	5 (3.5)	0	3.5 (-10.5, 7.9)	4 (6.7)
Dizziness	4 (2.8)	0	2.8 (-11.2, 6.9)	7 (11.7)
Dyspepsia	4 (2.8)	0	2.8 (-11.2, 6.9)	3 (5.0)
Dysuria	4 (2.8)	0	2.8 (-11.2, 6.9)	3 (5.0)
Orthostatic hypotension	4 (2.8)	0	2.8 (-11.2, 6.9)	0
Thermal burn	4 (2.8)	0	2.8 (-11.2, 6.9)	6 (10.0)
Asthenia	3 (2.1)	0	2.1 (-11.8, 6.0)	8 (13.3)
Constipation	3 (2.1)	0	2.1 (-11.8, 6.0)	6 (10.0)
Hypotension	3 (2.1)	0	2.1 (-11.8, 6.0)	2 (3.3)
Neuralgia	3 (2.1)	0	2.1 (-11.8, 6.0)	9 (15.0)
Weight decreased	3 (2.1)	0	2.1 (-11.8, 6.0)	5 (8.3)
Erythema	2 (1.4)	0	1.4 (-12.5, 4.9)	3 (5.0)
Hematuria	2 (1.4)	0	1.4 (-12.5, 4.9)	5 (8.3)
Immunization reaction	8 (5.6)	1 (4.2)	1.4 (-15.0, 7.8)	0
Peripheral swelling	2 (1.4)	0	1.4 (-12.5, 4.9)	1 (1.7)
Syncope	2 (1.4)	0	1.4 (-12.5, 4.9)	2 (3.3)
Conjunctival hemorrhage	1 (0.7)	0	0.7 (-13.2, 3.8)	3 (5.0)
Depression	1 (0.7)	0	0.7 (-13.2, 3.8)	5 (8.3)
Dry mouth	1 (0.7)	0	0.7 (-13.2, 3.8)	1 (1.7)
Dysphagia	1 (0.7)	0	0.7 (-13.2, 3.8)	3 (5.0)
Hypoesthesia	1 (0.7)	0	0.7 (-13.2, 3.8)	6 (10.0)
Influenza like illness	1 (0.7)	0	0.7 (-13.2, 3.8)	3 (5.0)
Muscular weakness	1 (0.7)	0	0.7 (-13.2, 3.8)	6 (10.0)
Neuropathy peripheral	1 (0.7)	0	0.7 (-13.2, 3.8)	4 (6.7)
Oropharyngeal pain	1 (0.7)	0	0.7 (-13.2, 3.8)	2 (3.3)
Seasonal allergy	1 (0.7)	0	0.7 (-13.2, 3.8)	4 (6.7)
Ankle fracture	0	0	0.0 (-13.9, 2.6)	3 (5.0)
Anxiety	0	0	0.0 (-13.9, 2.6)	4 (6.7)
Atrial fibrillation	0	0	0.0 (-13.9, 2.6)	1 (1.7)

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Preferred Term	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
Blepharitis	0	0	0.0 (-13.9, 2.6)	4 (6.7)
Cardiac failure congestive	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Ecchymosis	0	0	0.0 (-13.9, 2.6)	4 (6.7)
Ligament sprain	0	0	0.0 (-13.9, 2.6)	3 (5.0)
Edema	0	0	0.0 (-13.9, 2.6)	3 (5.0)
Rhinitis	0	0	0.0 (-13.9, 2.6)	4 (6.7)
Upper respiratory tract infection	6 (4.2)	1 (4.2)	-0.0 (-16.3, 6.0)	3 (5.0)
Insomnia	5 (3.5)	1 (4.2)	-0.7 (-17.0, 5.1)	3 (5.0)
Anemia	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	2 (3.3)
Back pain	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	5 (8.3)
Muscle spasms	3 (2.1)	1 (4.2)	-2.1 (-18.3, 3.1)	4 (6.7)
Paresthesia	3 (2.1)	1 (4.2)	-2.1 (-18.3, 3.1)	2 (3.3)
Proteinuria	3 (2.1)	1 (4.2)	-2.1 (-18.3, 3.1)	2 (3.3)
Influenza	2 (1.4)	1 (4.2)	-2.8 (-19.0, 2.0)	4 (6.7)
Abdominal pain	1 (0.7)	1 (4.2)	-3.5 (-19.6, 0.9)	4 (6.7)
Gait disturbance	1 (0.7)	1 (4.2)	-3.5 (-19.6, 0.9)	5 (8.3)
Nasopharyngitis	7 (4.9)	2 (8.3)	-3.5 (-21.3, 4.4)	6 (10.0)
Vision blurred	6 (4.2)	2 (8.3)	-4.2 (-21.9, 3.5)	1 (1.7)
Alanine aminotransferase increased	4 (2.8)	2 (8.3)	-5.6 (-23.3, 1.7)	2 (3.3)
Fall	3 (2.1)	2 (8.3)	-6.3 (-23.9, 0.7)	13 (21.7)
Rash	3 (2.1)	2 (8.3)	-6.3 (-23.9, 0.7)	1 (1.7)
Skin ulcer	3 (2.1)	2 (8.3)	-6.3 (-23.9, 0.7)	0
Pain in extremity	8 (5.6)	3 (12.5)	-6.9 (-25.8, 2.7)	8 (13.3)
Contusion	1 (0.7)	2 (8.3)	-7.6 (-25.3, -1.2)[a]	1 (1.7)
Pain	1 (0.7)	2 (8.3)	-7.6 (-25.3, -1.2)[a]	8 (13.3)
Platelet count decreased	1 (0.7)	2 (8.3)	-7.6 (-25.3, -1.2)[a]	0
Sinusitis	0	2 (8.3)	-8.3 (-25.9, -2.3)[a]	2 (3.3)
Cough	4 (2.8)	3 (12.5)	-9.7 (-28.4, -0.7)[a]	8 (13.3)
Vomiting	10 (6.9)	4 (16.7)	-9.7 (-29.3, 1.6)	3 (5.0)
Nausea	12 (8.3)	5 (20.8)	-12.5 (-32.6, 0.4)	7 (11.7)
Arthralgia	4 (2.8)	4 (16.7)	-13.9 (-33.3, -3.2)[a]	5 (8.3)
Headache	8 (5.6)	5 (20.8)	-15.3 (-35.3, -2.7)[a]	7 (11.7)
Glomerular filtration rate decreased	1 (0.7)	4 (16.7)	-16.0 (-35.3, -5.8)[a]	2 (3.3)
Thrombocytopenia	1 (0.7)	4 (16.7)	-16.0 (-35.3, -5.8)[a]	1 (1.7)
Myalgia	3 (2.1)	5 (20.8)	-18.8 (-38.6, -6.7)[a]	1 (1.7)
Decreased appetite	1 (0.7)	5 (20.8)	-20.1 (-39.9, -8.4)[a]	0
Chills	0	5 (20.8)	-20.8 (-40.5, -9.2)[a]	2 (3.3)
Fatigue	4 (2.8)	6 (25.0)	-22.2 (-42.3, -8.8)[a]	12 (20.0)
Pyrexia	1 (0.7)	7 (29.2)	-28.5 (-48.6, -14.1)[a]	5 (8.3)
Injection site reaction	12 (8.3)	12 (50.0)	-41.7 (-60.8, -22.4)[a]	7 (11.7)

Source: adae.xpt; Software: R.

[a.] Rows where the 95% confidence interval excludes zero.

Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Coded as MedDRA preferred terms.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

In the extension period, the most common AEs in subjects receiving eplontersen were COVID-19, urinary tract infection, and vitamin A deficiency.

Table 32. Subjects With Common Treatment-Emergent Adverse Events Occurring at ≥1% Frequency, Safety Population, ION-682884-CS3 Extension Period and ISIS-420915-CS2

Preferred Term	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Any AE	111 (78.7)	15 (75.0)	126 (78.3)
COVID-19	28 (19.9)	1 (5.0)	29 (18.0)
Urinary tract infection	12 (8.5)	3 (15.0)	15 (9.3)
Vitamin A deficiency	11 (7.8)	2 (10.0)	13 (8.1)
Diarrhea	7 (5.0)	1 (5.0)	8 (5.0)
Proteinuria	7 (5.0)	1 (5.0)	8 (5.0)
Dizziness	6 (4.3)	0	6 (3.7)
Vomiting	6 (4.3)	1 (5.0)	7 (4.3)
Arthralgia	5 (3.5)	0	5 (3.1)
Fall	5 (3.5)	1 (5.0)	6 (3.7)
Syncope	5 (3.5)	0	5 (3.1)
Back pain	4 (2.8)	0	4 (2.5)
Depression	4 (2.8)	1 (5.0)	5 (3.1)
Fatigue	4 (2.8)	2 (10.0)	6 (3.7)
Immunization reaction	4 (2.8)	0	4 (2.5)
Nasopharyngitis	4 (2.8)	0	4 (2.5)
Nausea	4 (2.8)	0	4 (2.5)
Edema peripheral	4 (2.8)	2 (10.0)	6 (3.7)
Thermal burn	4 (2.8)	1 (5.0)	5 (3.1)
Vision blurred	4 (2.8)	0	4 (2.5)
Anemia	3 (2.1)	0	3 (1.9)
Anxiety	3 (2.1)	1 (5.0)	4 (2.5)
Cataract	3 (2.1)	1 (5.0)	4 (2.5)
Cough	3 (2.1)	0	3 (1.9)
Cystitis	3 (2.1)	0	3 (1.9)
Gamma-glutamyl transferase increased	3 (2.1)	0	3 (1.9)
Influenza	3 (2.1)	0	3 (1.9)
Leukopenia	3 (2.1)	0	3 (1.9)
Myalgia	3 (2.1)	0	3 (1.9)
Noncardiac chest pain	3 (2.1)	0	3 (1.9)
Rash	3 (2.1)	1 (5.0)	4 (2.5)
Skin lesion	3 (2.1)	0	3 (1.9)
Upper respiratory tract infection	3 (2.1)	0	3 (1.9)
Vertigo	3 (2.1)	0	3 (1.9)
Abdominal pain	2 (1.4)	0	2 (1.2)
Alanine aminotransferase increased	2 (1.4)	0	2 (1.2)
Aspartate aminotransferase increased	2 (1.4)	0	2 (1.2)
Dermatitis	2 (1.4)	0	2 (1.2)
Dry eye	2 (1.4)	0	2 (1.2)
Early satiety	2 (1.4)	0	2 (1.2)
Gastritis	2 (1.4)	0	2 (1.2)
Glomerular filtration rate decreased	2 (1.4)	2 (10.0)	4 (2.5)
Hematoma	2 (1.4)	0	2 (1.2)
Hypertension	2 (1.4)	1 (5.0)	3 (1.9)
Hypoglycemia	2 (1.4)	0	2 (1.2)
Hypotension	2 (1.4)	1 (5.0)	3 (1.9)
Limb injury	2 (1.4)	0	2 (1.2)
Lymphopenia	2 (1.4)	0	2 (1.2)
Muscle spasms	2 (1.4)	2 (10.0)	4 (2.5)
Esophagitis	2 (1.4)	0	2 (1.2)

Preferred Term	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Osteoarthritis	2 (1.4)	0	2 (1.2)
Pneumonia	2 (1.4)	0	2 (1.2)
Renal impairment	2 (1.4)	0	2 (1.2)
Respiratory tract infection	2 (1.4)	0	2 (1.2)
Skin papilloma	2 (1.4)	0	2 (1.2)
Skin ulcer	2 (1.4)	0	2 (1.2)
Tinnitus	2 (1.4)	0	2 (1.2)
Transaminases increased	2 (1.4)	0	2 (1.2)
Troponin T increased	2 (1.4)	0	2 (1.2)
Albuminuria	1 (0.7)	1 (5.0)	2 (1.2)
Alopecia	1 (0.7)	1 (5.0)	2 (1.2)
Atrial flutter	1 (0.7)	1 (5.0)	2 (1.2)
Atrioventricular block complete	1 (0.7)	1 (5.0)	2 (1.2)
Hemorrhoids	1 (0.7)	1 (5.0)	2 (1.2)
Headache	1 (0.7)	1 (5.0)	2 (1.2)
Localized infection	1 (0.7)	1 (5.0)	2 (1.2)
Pain in extremity	1 (0.7)	1 (5.0)	2 (1.2)
Skin infection	1 (0.7)	1 (5.0)	2 (1.2)

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; Ext., extension; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; Rnd., randomized

In the 120-day safety update, proteinuria was noted as a TEAE seen with an incidence of greater than 5% in the eplontersen group and seen ≥2% more frequently than in the external placebo (8.3% versus 3.3%, respectively).

Injection site reactions were reported in 7% of subjects treated with eplontersen. Reported symptoms included erythema, pain, and pruritis.

Of note, the observed immunization reactions are all related to COVID-19 vaccination and include symptoms such as fever and body aches. These reactions are attributable to the COVID-19 vaccination and not due to eplontersen.

Table 33. Treatment-Emergent Adverse Events With an Incidence of ≥5% (Without Rounding) in the Eplontersen Group and ≥2% Greater Than in the ISIS-420915-CS2 External Placebo Group as of the 120DSU Cutoff Date of October 19, 2022 (ION-682884-CS3 Safety Set)

	ISIS 420915-CS2 Placebo (N = 60)		Eplontersen (N = 144)	
Preferred Term	Subjects, n (%)	Events	Subjects, n (%)	Events
COVID-19	0	0	46 (31.9)	49
Vitamin A deficiency	0	0	16 (11.1)	16
Vomiting	3 (5.0)	3	13 (9.0)	25
Immunization reaction	0	0	13 (9.0)	19
Proteinuria	2 (3.3)	2	12 (8.3)	14
Vision blurred	1 (1.7)	1	8 (5.6)	11
Cataract	1 (1.7)	1	8 (5.6)	8

Source: Applicant's 120-day safety update.
Note: For each treatment group, a subject is counted only once within each preferred term.
Abbreviations: 120DSU, 120-Day safety update; COVID-19, coronavirus disease of 2019; N, total number of subjects in treatment arm; n, number of subjects with adverse event

For the purposes of labeling, Table 33 from the 120-day safety update data will be used to inform the adverse reactions of vitamin A deficiency, vision blurring, and proteinuria.

Table 34. Adverse Reactions Reported in at Least 5% of Subjects Treated With Eplontersen (ION-682884-CS3 Safety Set)

Adverse Reaction	Eplontersen N=144 %
Vitamin A decreased[a]	11
Vomiting	9
Proteinuria	8
Injection site reactions[b]	7
Vision blurred	6
Cataract	6

Source: 120-day safety update.
[a.] Vitamin A decreased includes vitamin A deficiency and vitamin A decrease
[b.] Includes erythema, pain, pruritis
Abbreviations: N, total number of subjects in treatment arm

Hypersensitivity

The proportion of subjects experiencing hypersensitivity TEAEs were lower in the eplontersen group (17.4%) compared to the external placebo group (26.7%). There were no serious TEAEs or events of anaphylaxis. There was one TEAE of throat tightness. The most common hypersensitivity TEAEs were in the skin and subcutaneous disorders system organ class (17 subjects, or 11.8%); these included rash, pruritis, eczema, erythema, dermatitis, and urticaria. Most events resolved. Overall, there were no significant hypersensitivity safety events in the eplontersen group.

Table 35. Adverse Events Related to Hypersensitivity Reactions, Safety Population, Trials ION-682884-CS3, Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Hypersensitivity **AESI** **Statistic**	**Eplontersen N=144 n (%)**	**Inotersen N=24 n (%)**	**Risk Difference (%) (95% CI)**	**Placebo N=60 n (%)**
AE grouping related to AESI	16 (11.1)	8 (33.3)	-22.2 (-42.8, -5.7)[a]	16 (26.7)
Asthma	0	0	0.0 (-13.9, 2.6)	0
Blister	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Blood immunoglobulin M increased	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Conjunctivitis	1 (0.7)	0	0.7 (-13.2, 3.8)	2 (3.3)
Conjunctivitis allergic	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Dermatitis	0	0	0.0 (-13.9, 2.6)	0
Dermatitis contact	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Dermatitis herpetiformis	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Drug eruption	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Drug hypersensitivity	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Eczema	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Eosinophil count increased	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Eosinophilia	0	0	0.0 (-13.9, 2.6)	0
Erythema	2 (1.4)	0	1.4 (-12.5, 4.9)	3 (5.0)
Face edema	0	0	0.0 (-13.9, 2.6)	0
Flushing	0	0	0.0 (-13.9, 2.6)	0
Generalized edema	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Hypersensitivity	0	0	0.0 (-13.9, 2.6)	0
Infusion related reaction	0	0	0.0 (-13.9, 2.6)	0
Injection site rash	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Injection site urticaria	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Interstitial lung disease	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Lip edema	0	0	0.0 (-13.9, 2.6)	0
Localized edema	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Mouth ulceration	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Periorbital swelling	0	0	0.0 (-13.9, 2.6)	0
Pruritus	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	2 (3.3)
Rash	3 (2.1)	2 (8.3)	-6.3 (-23.9, 0.7)	1 (1.7)
Rash macular	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Rash pruritic	0	0	0.0 (-13.9, 2.6)	0
Rash vesicular	0	0	0.0 (-13.9, 2.6)	0
Rhinitis allergic	0	0	0.0 (-13.9, 2.6)	0

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Hypersensitivity **AESI** **Statistic**	**Eplontersen N=144 n (%)**	**Inotersen N=24 n (%)**	**Risk Difference (%) (95% CI)**	**Placebo N=60 n (%)**
Seasonal allergy	1 (0.7)	0	0.7 (-13.2, 3.8)	4 (6.7)
Stomatitis	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Swelling face	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Throat tightness	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Tongue edema	0	0	0.0 (-13.9, 2.6)	1 (1.7)
Urticaria	1 (0.7)	1 (4.2)	-3.5 (-19.6, 0.9)	1 (1.7)
Maximum severity				
Death	0	0	0.0 (-13.9, 2.6)	0
Life-threatening	0	0	0.0 (-13.9, 2.6)	0
Severe	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Moderate	2 (1.4)	1 (4.2)	-2.8 (-19.0, 2.0)	8 (13.3)
Mild	14 (9.7)	6 (25.0)	-15.3 (-35.7, -1.0)a	8 (13.3)
Serious	0	0	0.0 (-13.9, 2.6)	0
Deaths	0	0	0.0 (-13.9, 2.6)	0
Resulting in discontinuation	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Relatedness	2 (1.4)	0	1.4 (-12.5, 4.9)	0
Number of subjects with adverse events with end dates on or before treatment end dates	8/16 (50.0)	4/8 (50.0)	0.0 (-39.1, 39.1)	10/16 (62.5)
Duration, days (from AE start date to AE end date)				
Mean (SD)	18.8 (27.1)	17.8 (8.4)	NA	33.8 (52.6)
Median (Q1, Q3)	6.5 (4, 18)	18 (12.5, 23.2)	NA	16.5 (8.8, 21.8)
Min, Max	3, 82	8, 27	NA	2, 176
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	6/16 (37.5)	1/8 (12.5)	25.0 (-16.3, 53.9)	5/16 (31.2)

AE Group Related to Hypersensitivity AESI Statistic	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	 Inotersen N=24 n (%)	 Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	3/16 (18.8)	3/8 (37.5)	-18.8 (-55.6, 17.1)	0/16 (0)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	80 (56.3)	21.3 (30)	NA	NA
Median (Q1, Q3)	112 (63.5, 112.5)	4 (4, 30)	NA	NA
Min, Max	15, 113	4, 56	NA	NA, NA

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 36. Adverse Events Related to Hypersensitivity Reactions, Safety Population, Trials ION-682884-CS3, Nonrandomized Extension Period

AE Group Related to Hypersensitivity AESI Statistic	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
AE grouping related to AESI	10 (7.1)	1 (5.0)	11 (6.8)
Dermatitis	2 (1.4)	0	2 (1.2)
Eczema	1 (0.7)	0	1 (0.6)
Eosinophil count increased	1 (0.7)	0	1 (0.6)
Pruritus	1 (0.7)	0	1 (0.6)
Rash	3 (2.1)	1 (5.0)	4 (2.5)
Throat tightness	1 (0.7)	0	1 (0.6)
Urticaria	1 (0.7)	0	1 (0.6)
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	0	0
Moderate	0	0	0
Mild	10 (7.1)	1 (5.0)	11 (6.8)

AE Group Related to Hypersensitivity AESI Statistic	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	0	0
Relatedness	2 (1.4)	1 (5.0)	3 (1.9)
Number of subjects with adverse events with end dates on or before treatment end dates	7/10 (70.0)	1/1 (100)	8/11 (72.7)
Duration, days (from AE start date to AE end date)			
Mean (SD)	48.6 (55.6)	2 (NA)	42.8 (54)
Median (Q1, Q3)	18 (9.5, 75.5)	2 (2, 2)	16.5 (3.5, 69.8)
Min, Max	1, 151	2, 2	1, 151
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	3/10 (30.0)	0/1 (0)	3/11 (27.3)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/10 (0)	0/1 (0)	0/11 (0)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; Rnd., randomized; SD, standard deviation

7.6.2.6. Other Adverse Events of Interest

Further in-depth analyses of safety events of interest include renal impairment, abnormal liver function, injection site reactions, flu-like symptoms, central nervous system disorders, hemorrhages, cardiac disorders, and reduced thyroxine. For discussions on liver function, please see Sections 7.6.2.7 and 7.6.2.8.

The currently approved hATTR drug, inotersen (in the same pharmacologic class as eplontersen) also has a warning in its label regarding "inflammatory and immune" events, particularly vasculitis. Per the 120-day safety update, a lower frequency of subjects with hs-CRP > ULN at postbaseline was observed in the eplontersen group (38.7%) compared with the external placebo (53.3%) group. No events of vasculitis or other inflammatory processes were noted in this submission for eplontersen.

Cardiac Disorders

An evaluation of cardiac disorders in the randomized period of ION-682884-CS3 is shown in the Table 37. There were no significant changes in the frequency of cardiac disorders at the 120-day safety update. Per the 120-Day safety update, the proportion of subjects experiencing cardiac disorders was 16.7% in the eplontersen group compared to 21.7% in the external placebo group. There were four events meeting criteria for major adverse cardiovascular events in subjects receiving eplontersen: intracerebral hemorrhage, cardiovascular death (both described in 7.6.2.2), hospitalization for unstable angina (7.6.3.2), and nonfatal myocardial infarction.

By the 120-Day safety update, there were four subjects who had had pacemaker implantation for atrioventricular (AV) block, all with a history of cardiomyopathy at baseline:

- Subject (b) (6) (complete AV block)
- Subject (b) (6) (complete AV block)
- Subject (b) (6) (second degree AV block)
- Subject (b) (6) (death in ION-682884-CS13, described further in Section 7.6.3.2)

Another subject, (b) (6) also with cardiomyopathy at baseline, received a pacemaker for "sinus pauses." Subject (b) (6) also with a diagnosis of hATTR related cardiomyopathy at baseline, had to withdraw from the post-treatment follow-up phase (study day 672) due to hospitalization of SAEs of supraventricular tachycardia and cardiac failure.

Three subjects experienced mild TEAEs of troponin T increased by the 120-day safety update, with no associated myocardial infarction. The incidence of subjects with troponin T > ULN at any time postbaseline was 67.7% (n=113). Troponin T was not evaluated in the external placebo group, so there are no data for comparison. Mean troponin values remained within a normal range over time.

Overall, hATTR-PN is a complex, chronic multisystem disease with significant cardiovascular symptoms, including arrhythmias and AV block. Approximately 25%-35% of hATTR patients receive pacemakers (John 2018). It appears unlikely that cardiac disorders noted in subjects receiving eplontersen were caused by the investigational drug, especially given the higher frequency of occurrence in the external placebo group (it should be noted that there was a higher

frequency of subjects with diagnosed hATTR-CM in the external placebo group than the eplontersen group (36.7% versus 27.1%). However, a role for eplontersen cannot be ruled out. To further evaluate AV block, a PMR will be issued to evaluate the incidence and provide analysis of AV block observed in the ongoing placebo-controlled Study ION-682884-CST of eplontersen in adult hereditary and wild-type ATTR cardiomyopathy patients. Although the number of cases of AV block were low, and occurred in subjects who were at risk, these cases are nevertheless concerning. In a 2019 paper in Circulation, the cardiac effects of patisiran were explored. While patisiran is a small interfering RNA (siRNA) and eplontersen is an antisense oligonucleotide (ASO), the final mechanism of action is the same (degradation of mutant and wild type TTR mRNA, reducing serum TTR protein and TTR protein deposits). In this paper, it is noted that patisiran can lead to intraventricular septal thinning. Given this finding, it is plausible that there is remodeling and/or inflammation within the septum, in turn affecting atrioventricular conduction. For this reason, a statement regarding the serious adverse reactions of AV block will be included in the label (Solomon et al. 2019).

Table 37. Other Adverse Events of Interest Assessment Related to Cardiac Disorders, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Cardiac Disorders OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	14 (9.7)	0	9.7 (4.9, 14.6)[a]	13 (21.7)
Angina pectoris	0	0	0 (0, 0)	0
Angina unstable	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Aortic valve thickening	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Arrhythmia	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Atrioventricular block	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Atrioventricular block second degree	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Cardiac amyloidosis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Cardiac failure	1 (0.7)	0	0.7 (-0.7, 2.1)	2 (3.3)
Cardiomyopathy	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Left ventricular dysfunction	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Left ventricular hypertrophy	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Tachyarrhythmia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Ventricular extrasystoles	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Maximum severity				
Death	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Moderate	4 (2.8)	0	2.8 (0.1, 5.5)[a]	7 (11.7)
Mild	7 (4.9)	0	4.9 (1.3, 8.4)[a]	5 (8.3)

AE Group Related to Cardiac Disorders OAEI	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Serious	4 (2.8)	0	2.8 (0.1, 5.5)[a]	2 (3.3)
Deaths	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Resulting in discontinuation	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Relatedness	0	0	0 (0, 0)	0

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Acute Kidney Injury

There was no clinically meaningful difference between the eplontersen group and the external placebo group in terms of acute kidney injury in either the randomized or extension periods.

Table 38. Adverse Events Assessment of Acute Kidney Injury, FDA Medical Query (Narrow), Safety Population, Trials ION-682884-CS3 Randomized Period

FMQ (Narrow) Preferred Term	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Acute kidney injury (FMQ)	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	0
Acute kidney injury	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Tubulointerstitial nephritis	0	1 (4.2)	-4.2 (-12.2, 3.8)	0
Urine output decreased	0	0	0 (0, 0)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	0
Mild	0	0	0 (0, 0)	0
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	0	0	0 (0, 0)	0

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event query

Table 39. Adverse Events Assessment of Acute Kidney Injury, FDA Medical Query (Narrow), Safety Population, Trial ION-682884-CS3 Extension Period

FMQ (Narrow) Preferred Term	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Acute kidney injury (FMQ)	1 (0.7)	0	1 (0.6)
Acute kidney injury	1 (0.7)	0	1 (0.6)
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	0	0
Moderate	1 (0.7)	0	1 (0.6)
Mild	0	0	0
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	0	0
Relatedness	0	0	0

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; Ext., extension; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; Rnd., randomized

Renal Impairment

There were eleven cases of TEAEs of renal impairment in the eplontersen group during the randomized period (most mild to moderate, one leading to discontinuation), five cases in the concurrent inotersen comparator arm, and six in the historical placebo group. In the 120-day safety update, there were 14 total cases of proteinuria in 12 subjects noted in total in the eplontersen treated safety set, and proteinuria was seen more frequently than in the external placebo group (8.3% versus 3.3%). See Section 7.6.2.5 for further discussion. Refer to Section 7.7.3 for further information on renal safety with eplontersen.

Table 40. Other Adverse Events of Interest Assessment Related to Renal Impairment, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Renal Impairment OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	11 (7.6)	5 (20.8)	-13.2 (-30.0, 3.6)	6 (10.0)
Acute kidney injury	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Albuminuria	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Blood creatinine increased	0	0	0 (0, 0)	1 (1.7)
Blood urea increased	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Creatinine renal clearance decreased	0	0	0 (0, 0)	0
Glomerular filtration rate decreased	1 (0.7)	4 (16.7)	-16.0 (-30.9, -1.0)[a]	2 (3.3)
Protein urine present	0	0	0 (0, 0)	0
Proteinuria	3 (2.1)	1 (4.2)	-2.1 (-10.4, 6.2)	2 (3.3)
Renal failure	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Renal impairment	3 (2.1)	0	2.1 (-0.2, 4.4)	0
Tubulointerstitial nephritis	0	1 (4.2)	-4.2 (-12.2, 3.8)	0
Urine output decreased	0	0	0 (0, 0)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Moderate	3 (2.1)	2 (8.3)	-6.2 (-17.6, 5.1)	0
Mild	7 (4.9)	3 (12.5)	-7.6 (-21.3, 6.1)	5 (8.3)
Serious	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Relatedness	3 (2.1)	0	2.1 (-0.2, 4.4)	5 (8.3)

Source: adae.xpt; Software: R.

[a.] Rows where the 95% confidence interval excludes zero.

Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Reduced Thyroxine

Below is the evaluation of TEAEs related to reduced thyroxine in the randomized period of ION-682884-CS3. In the 120-day safety update, there have been four events total of reduced thyroxine in three subjects receiving eplontersen, all mild and nonserious. Overall, eplontersen does not appear to have a clinically significant effect on thyroid function.

Table 41. Other Adverse Events of Interest Assessment Related to Reduced Thyroxine, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Reduced Thyroxine OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	1 (0.7)	2 (8.3)	-7.6 (-18.8, 3.5)	3 (5.0)
Autoimmune thyroiditis	0	0	0 (0, 0)	0
Blood thyroid stimulating hormone increased	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	1 (1.7)
Hypothyroidism	0	1 (4.2)	-4.2 (-12.2, 3.8)	1 (1.7)
Thyroxine decreased	0	0	0 (0, 0)	1 (1.7)
Thyroxine free increased	0	0	0 (0, 0)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	0	0	0 (0, 0)	1 (1.7)
Mild	1 (0.7)	2 (8.3)	-7.6 (-18.8, 3.5)	2 (3.3)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	0	0	0 (0, 0)	1 (1.7)

Source: adae.xpt; Software: R.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Hemorrhages

There were no clinically meaningful differences between the eplontersen and placebo group in TEAEs related to the risk of hemorrhage in the randomized period. The subjects with cerebral hemorrhage and gastrointestinal hemorrhage with fatal outcomes were discussed previously in Section 7.6.2.2.

By the 120-day safety update data cutoff, cumulatively there were no clinically meaningful differences in coagulation abnormalities (aPTT, PT and international normalized ratio [INR]) between the eplontersen treated group and the external placebo group (detailed further in the laboratory Section 7.6.2.7).

Table 42. Other Adverse Events of Interest Assessment Related to Hemorrhages, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Hemorrhages OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	14 (9.7)	7 (29.2)	-19.4 (-38.3, -0.6)[a]	20 (33.3)
Conjunctival hemorrhage	1 (0.7)	0	0.7 (-0.7, 2.1)	3 (5.0)
Contusion	1 (0.7)	2 (8.3)	-7.6 (-18.8, 3.5)	1 (1.7)
Epistaxis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Gastric hemorrhage	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Hematocrit decreased	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Hematoma	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Hematuria	2 (1.4)	0	1.4 (-0.5, 3.3)	5 (8.3)
Hemoglobin decreased	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Increased tendency to bruise	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Injection site bruising	1 (0.7)	5 (20.8)	-20.1 (-36.4, -3.8)[a]	2 (3.3)
Injection site hemorrhage	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	1 (1.7)
Muscle contusion	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Occult blood positive	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Rectal hemorrhage	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Vessel puncture site hemorrhage	1 (0.7)	0	0.7 (-0.7, 2.1)	0

AE Group Related to Hemorrhages OAEI	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Moderate	3 (2.1)	2 (8.3)	-6.2 (-17.6, 5.1)	4 (6.7)
Mild	10 (6.9)	5 (20.8)	-13.9 (-30.7, 2.9)	16 (26.7)
Serious	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	2 (1.4)	0	1.4 (-0.5, 3.3)	3 (5.0)

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Flu-Like Symptoms

Overall, there were no clinically significant flu-like symptoms seen in subjects receiving eplontersen.

Table 43. Other Adverse Events of Interest Assessment Related to Flu-Like Symptoms, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Flu-Like Symptoms OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	2 (1.4)	7 (29.2)	-27.8 (-46.1, -9.5)[a]	7 (11.7)
Body temperature increased	0	0	0 (0, 0)	0
Influenza like illness	1 (0.7)	0	0.7 (-0.7, 2.1)	3 (5.0)
Pyrexia	1 (0.7)	7 (29.2)	-28.5 (-46.7, -10.2)[a]	5 (8.3)
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	1 (1.7)
Mild	1 (0.7)	6 (25.0)	-24.3 (-41.7, -6.9)[a]	6 (10.0)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	0	0	0 (0, 0)	2 (3.3)

Source: adae.xpt; Software: R.
[a.] indicates rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Central Nervous System (CNS) Disorders

There were no clinically meaningful differences between the eplontersen and placebo groups in terms in disorders of the CNS in the randomized period.

Table 44. Other Adverse Events of Interest Assessment Related to CNS Disorders, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to CNS Disorders OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	30 (20.8)	8 (33.3)	-12.5 (-32.5, 7.5)	33 (55.0)
Altered state of consciousness	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Balance disorder	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Burning sensation	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Dizziness	4 (2.8)	0	2.8 (0.1, 5.5)[a]	7 (11.7)
Dizziness postural	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Fine motor skill dysfunction	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Headache	8 (5.6)	5 (20.8)	-15.3 (-32.0, 1.4)	7 (11.7)
Hemiparesis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Hypoesthesia	1 (0.7)	0	0.7 (-0.7, 2.1)	6 (10.0)
Lethargy	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Metabolic encephalopathy	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Neuralgia	3 (2.1)	0	2.1 (-0.2, 4.4)	9 (15.0)
Neuropathy peripheral	1 (0.7)	0	0.7 (-0.7, 2.1)	4 (6.7)
Paresthesia	3 (2.1)	1 (4.2)	-2.1 (-10.4, 6.2)	2 (3.3)
Polyneuropathy	2 (1.4)	1 (4.2)	-2.8 (-11.0, 5.4)	0
Presyncope	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Somnolence	1 (0.7)	0	0.7 (-0.7, 2.1)	2 (3.3)
Syncope	2 (1.4)	0	1.4 (-0.5, 3.3)	2 (3.3)
Vocal cord paresis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	4 (6.7)
Moderate	5 (3.5)	4 (16.7)	-13.2 (-28.4, 2.0)	13 (21.7)
Mild	25 (17.4)	4 (16.7)	0.7 (-15.4, 16.8)	16 (26.7)

AE Group Related to CNS Disorders OAEI	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Serious	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	7 (4.9)	0	4.9 (1.3, 8.4)[a]	3 (5.0)

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; CNS, central nervous system; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Injection Site Reactions

There were 13 AEs reported for injection site reactions for eplontersen during the randomized period, with none being serious.

Table 45. Other Adverse Events of Interest Assessment at the Injection Site, Safety Population, Trials ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Injection Site OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	13 (9.0)	12 (50.0)	-41.0 (-61.5, -20.4)[a]	7 (11.7)
Injection site atrophy	0	0	0 (0, 0)	0
Injection site bruising	1 (0.7)	5 (20.8)	-20.1 (-36.4, -3.8)[a]	2 (3.3)
Injection site discoloration	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	0
Injection site erythema	5 (3.5)	8 (33.3)	-29.9 (-49.0, -10.8)[a]	0
Injection site hematoma	0	1 (4.2)	-4.2 (-12.2, 3.8)	1 (1.7)
Injection site hemorrhage	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	1 (1.7)
Injection site pain	5 (3.5)	3 (12.5)	-9.0 (-22.6, 4.5)	5 (8.3)
Injection site pruritus	3 (2.1)	1 (4.2)	-2.1 (-10.4, 6.2)	0
Vessel puncture site hemorrhage	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	1 (0.7)	3 (12.5)	-11.8 (-25.1, 1.5)	0
Mild	12 (8.3)	9 (37.5)	-29.2 (-49.1, -9.3)[a]	7 (11.7)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	1 (4.2)	-4.2 (-12.2, 3.8)	0
Relatedness	9 (6.2)	0	6.2 (2.3, 10.2)[a]	5 (8.3)

Source: adae.xpt; Software: R.

[a.] Rows where the 95% confidence interval excludes zero.

Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

7.6.2.7. Laboratory Findings, ION-682884-CS3

Overall, decreased serum vitamin A levels is the main notable, clinically meaningful, laboratory change in subjects treated with eplontersen (discussed further in Section 7.7.2).

Per the 120-day safety update, there were decreases in eGFR ≥25% in 35 out of 144 subjects (24.3%) in the eplontersen treated set, with most (14 subjects) being single occurrences, and most other subjects returning to baseline while still on treatment The incidence of eGFR decrease in the external placebo group was 11.7%. It is important to note, though, that there were more frequent eGFR assessments in the external placebo group than the eplontersen group. Many of the eplontersen-treated subjects had abnormal screening/baseline renal function testing. There are confounding factors that could affect eGFR such as hATTR affecting renal function, heart failure, and concomitant medications. Please see Section 7.7.3 for further information on renal safety.

In the eplontersen treated set in the 120-day safety update, there were eight subjects with elevated CK levels reported as a TEAE in the eplontersen-treated set (5.6%), which is slightly increased in frequency compared to the external placebo group (3.3%). However, evaluating CK lab values (detailed in Table 46), CK elevations were balanced between the eplontersen group and the external placebo in the randomized period of ION-682884-CS3. Only one case of elevated CK in the eplontersen group met the criteria for rhabdomyolysis, described previously in Section 7.6.2.3.

There were no other clinically meaningful laboratory changes or patterns in subjects treated with eplontersen.

Table 46. Subjects With Chemistry Values Exceeding Specified Levels for General Chemistry, Safety Population, Trial ION-682884-CS3

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Laboratory Parameter Level	Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	Placebo N=60 n/N_w (%)
Sodium, low (mEq/L)				
Level 1 (<132)	8/144 (5.6)	2/24 (8.3)	-2.8 (-14.5, 8.9)	0/60 (0)
Level 2 (<130)	6/144 (4.2)	2/24 (8.3)	-4.2 (-15.7, 7.4)	0/60 (0)
Level 3 (<125)	1/144 (0.7)	0/24 (0)	0.7 (-0.7, 2.1)	0/60 (0)
Glucose, low (mg/dL)				
Level 1 (<70)	17/144 (11.8)	1/24 (4.2)	7.6 (-1.9, 17.2)	7/60 (11.7)
Level 2 (<54)	3/144 (2.1)	0/24 (0)	2.1 (-0.2, 4.4)	0/60 (0)
Level 3 (<40)	2/144 (1.4)	0/24 (0)	1.4 (-0.5, 3.3)	0/60 (0)
Magnesium, high (mg/dL)				
Level 1 (>2.3)	99/144 (68.8)	17/24 (70.8)	-2.1 (-21.8, 17.6)	50/60 (83.3)
Level 2 (>4)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Level 3 (>7)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Protein, total, low (g/dL)				
Level 1 (<6)	10/144 (6.9)	1/24 (4.2)	2.8 (-6.2, 11.8)	7/60 (11.7)
Level 2 (<5.4)	4/144 (2.8)	0/24 (0)	2.8 (0.1, 5.5)[a]	0/60 (0)
Level 3 (<5)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)

Laboratory Parameter Level	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n/N_w (%)
Albumin, low (g/dL)				
Level 1 (<3.1)	3/144 (2.1)	2/24 (8.3)	-6.2 (-17.6, 5.1)	3/60 (5.0)
Level 2 (<2.5)	1/144 (0.7)	0/24 (0)	0.7 (-0.7, 2.1)	0/60 (0)
Level 3 (<2)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Blood urea nitrogen, high (mg/dL)				
Level 1 (>23)	42/144 (29.2)	6/24 (25.0)	4.2 (-14.7, 23.0)	23/60 (38.3)
Level 2 (>27)	20/144 (13.9)	2/24 (8.3)	5.6 (-6.9, 18.0)	10/60 (16.7)
Level 3 (>31)	10/144 (6.9)	1/24 (4.2)	2.8 (-6.2, 11.8)	5/60 (8.3)

Source: adlb.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; CK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; NA, not applicable; ULN, upper limit of normal

Table 47. Subjects With Creatine Phosphokinase Analyte Values Exceeding Specified Levels, Safety Population, Trials ION-682884-CS3, Randomized Period

Laboratory Parameter Level	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n/N_w (%)
CK, high (U/L)				
Level 1 (>3X ULN)	12/144 (8.3)	1/24 (4.2)	4.2 (-12.3, 11.2)	5/60 (8.3)
Level 2 (>5X ULN)	4/144 (2.8)	1/24 (4.2)	-1.4 (-17.6, 4.1)	2/60 (3.3)
Level 3 (>10X ULN)	0/144 (0)	0/24 (0)	0.0 (-13.9, 2.6)	0/60 (0)

Source: adlb.xpt; Software: R.
Note:
- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CK, creatine phosphokinase; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal range

Table 48. Subjects With Creatine Phosphokinase Analyte Values Exceeding Specified Levels, Safety Population, Trial ION-682884-CS3, Nonrandomized Extension Period

Laboratory Parameter Level	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n/N_w (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n/N_w (%)	Combined Eplontersen N=161 n/N_w (%)
CK, high (U/L)			
Level 1 (>3X ULN)	16/141 (11.3)	1/20 (5.0)	17/161 (10.6)
Level 2 (>5X ULN)	7/141 (5.0)	1/20 (5.0)	8/161 (5.0)
Level 3 (>10X ULN)	1/141 (0.7)	0/20 (0)	1/161 (0.6)

Source: adlb.xpt; Software: R.
Note:
- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CK, creatine phosphokinase; Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; Rnd., randomized; ULN, upper limit of normal range

Table 49. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial ION-682884-CS3

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Laboratory Parameter Level	Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	Placebo N=60 n/N_w (%)
Creatinine, high (mg/dL)				
Level 1 (≥1.5X baseline)	6/144 (4.2)	2/24 (8.3)	-4.2 (-15.7, 7.4)	2/60 (3.3)
Level 2 (≥2X baseline)	0/144 (0)	1/24 (4.2)	-4.2 (-12.2, 3.8)	0/60 (0)
Level 3 (≥3X baseline)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
eGFR, low (mL/min/1.73 m^2)				
Level 1 (≥25% decrease)	16/139 (11.5)	5/21 (23.8)	-12.3 (-31.3, 6.7)	5/57 (8.8)
Level 2 (≥50% decrease)	0/139 (0)	1/21 (4.8)	-4.8 (-13.9, 4.3)	0/57 (0)
Level 3 (≥75% decrease)	0/139 (0)	0/21 (0)	0 (0, 0)	0/57 (0)
CrCl, low (mL/min)				
Level 1 (≥25% decrease)	0/0 (NA)	0/0 (NA)	NA	0/6 (0)
Level 2 (≥50% decrease)	0/0 (NA)	0/0 (NA)	NA	0/6 (0)
Level 3 (≥75% decrease)	0/0 (NA)	0/0 (NA)	NA	0/6 (0)

Source: adlb.xpt; Software: R.
Note:
- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; NA, not applicable

Table 50. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial ION-682884-CS3

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Laboratory Parameter Level	**Eplontersen N=144 n/N_w (%)**	**Inotersen N=24 n/N_w (%)**	**Risk Difference (%) (95% CI)**	**Placebo N=60 n/N_w (%)**
Complete Blood Count				
WBC, low (cells/uL)				
Level 1 (<3500)	37/144 (25.7)	7/24 (29.2)	-3.5 (-23.0, 16.1)	5/60 (8.3)
Level 2 (<3000)	18/144 (12.5)	3/24 (12.5)	0 (-14.3, 14.3)	5/60 (8.3)
Level 3 (<1000)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
WBC, high (cells/uL)				
Level 1 (>10800)	15/144 (10.4)	3/24 (12.5)	-2.1 (-16.2, 12.1)	9/60 (15.0)
Level 2 (>13000)	5/144 (3.5)	1/24 (4.2)	-0.7 (-9.2, 7.8)	4/60 (6.7)
Level 3 (>15000)	1/144 (0.7)	0/24 (0)	0.7 (-0.7, 2.1)	2/60 (3.3)
Hemoglobin, low (g/dL)				
Level 2 (>1.5 g/dL dec. from baseline)	31/144 (21.5)	9/24 (37.5)	-16.0 (-36.5, 4.5)	15/60 (25.0)
Level 3 (>2 g/dL dec. from baseline)	11/144 (7.6)	7/24 (29.2)	-21.5 (-40.2, -2.8)[a]	11/60 (18.3)
Hemoglobin, high (g/dL)				
Level 2 (>2 g/dL inc. from baseline)	1/144 (0.7)	1/24 (4.2)	-3.5 (-11.6, 4.6)	2/60 (3.3)
Level 3 (>3 g/dL inc. from baseline)	1/144 (0.7)	0/24 (0)	0.7 (-0.7, 2.1)	0/60 (0)
Platelets, low (cells/uL)				
Level 1 (<140000)	37/144 (25.7)	13/24 (54.2)	-28.5 (-49.6, -7.3)[a]	11/60 (18.3)
Level 2 (<125000)	13/144 (9.0)	11/24 (45.8)	-36.8 (-57.3, -16.3)[a]	2/60 (3.3)
Level 3 (<100000)	2/144 (1.4)	9/24 (37.5)	-36.1 (-55.6, -16.6)[a]	2/60 (3.3)
WBC Differential				
Lymphocytes, low (cells/uL)				
Level 1 (<1000)	56/144 (38.9)	9/24 (37.5)	1.4 (-19.6, 22.3)	17/60 (28.3)
Level 2 (<750)	31/144 (21.5)	4/24 (16.7)	4.9 (-11.5, 21.2)	6/60 (10.0)
Level 3 (<500)	8/144 (5.6)	2/24 (8.3)	-2.8 (-14.5, 8.9)	1/60 (1.7)
Lymphocytes, high (cells/uL)				
Level 1 (>4000)	2/144 (1.4)	1/24 (4.2)	-2.8 (-11.0, 5.4)	4/60 (6.7)
Level 2 (>10000)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Level 3 (>20000)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Neutrophils, low (cells/uL)				
Level 1 (<2000)	61/144 (42.4)	9/24 (37.5)	4.9 (-16.1, 25.8)	16/60 (26.7)
Level 2 (<1000)	11/144 (7.6)	2/24 (8.3)	-0.7 (-12.6, 11.2)	4/60 (6.7)
Level 3 (<500)	2/144 (1.4)	0/24 (0)	1.4 (-0.5, 3.3)	1/60 (1.7)

Laboratory Parameter Level	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n/N_w (%)
Eosinophils, high (cells/uL)				
Level 1 (>650)	12/144 (8.3)	6/24 (25.0)	-16.7 (-34.6, 1.2)	3/60 (5.0)
Level 2 (>1500)	0/144 (0)	1/24 (4.2)	-4.2 (-12.2, 3.8)	0/60 (0)
Level 3 (>5000)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)
Coagulation Studies				
PT, high (sec)				
Level 1 (>1.1X ULN)	0/0 (NA)	0/0 (NA)	NA	11/60 (18.3)
Level 2 (>1.3X ULN)	0/0 (NA)	0/0 (NA)	NA	8/60 (13.3)
Level 3 (>1.5X ULN)	0/0 (NA)	0/0 (NA)	NA	5/60 (8.3)
PTT, high (sec)				
Level 1 (>1X ULN)	12/144 (8.3)	2/24 (8.3)	0 (-11.9, 11.9)	14/60 (23.3)
Level 2 (>1.21X ULN)	5/144 (3.5)	0/24 (0)	3.5 (0.5, 6.5)[a]	2/60 (3.3)
Level 3 (>1.41X ULN)	3/144 (2.1)	0/24 (0)	2.1 (-0.2, 4.4)	0/60 (0)

Source: adlb.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:

- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; NA, not applicable; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, White blood cells

7.6.2.8. Assessment of Drug-Induced Liver Injury, ION-682884-CS3

Figure 3 shows a screening assessment for potential cases of serious drug-induced liver injury. No Hy's laws cases were noted. Per the 120-Day safety update, abnormal liver function was noted in 7.6% of eplontersen treated subjects versus 6.7% in the external placebo group; in addition, hepatobiliary abnormalities were noted in 11.1% of eplontersen-treated subjects versus 15% in the external placebo group. Tables Table 51, Table 52, Table 53, Table 54, Table 55 below detail AEs related to abnormal liver function and abnormal liver enzyme elevations. Overall, there does not appear to be a significant increased risk of hepatic adverse events with eplontersen. However, it should be noted that in ION-682884-CS1, the Phase 1 study evaluating eplontersen in healthy volunteers, while no subject met the stopping rules for liver chemistry tests, there were 4 healthy subjects with elevated ALT values:

- Subject (b) (6) with a peak ALT of 140 U/L (3.4xULN)
- Subject (b) (6) with a peak ALT of 42 U/L
- Subject (b) (6) with a peak ALT of 91 U/L (2.2xULN)
- Subject (b) (6) with a peak ALT of 145 U/L (3.5xULN)

All resolved without intervention.

It should be noted that these subjects received 90 mg doses of eplontersen every 4 weeks, which is double the dose used in the pivotal efficacy Study ION-682884-CS3 being evaluated in this review (45 mg every 4 weeks).

Notable abnormal laboratory findings related to liver enzyme abnormalities are as follows:

- Subject (b) (6) A 50-year-old male with baseline elevated GGT (74 U/L), had elevated transaminase readings (four occurrences of elevated ALT, ALT highest reading of 431 U/L, AST highest reading at 644 U/L both in Week 51); drug was interrupted for Weeks 53, 57, and 61, and this reading resolved. However, in the 120-day safety update, this subject continued to have fluctuating, elevated AST, ALT, and GGT >3x ULN (with generally normal total bilirubin except for two readings on Study Day 465 (25.1 µmol/L) and study day 491 (24.3 µmol/L) that were both 1.2xULN; both normalized afterwards) to the 120-day safety cutoff date, and the subject was continuing in the study at that point.

This event may possibly be related to the study drug, though the subject's GGT at baseline was elevated.

- Subject (b) (6) A 60-year-old female with a history of hepatitis A and phenytoin (started on study day 281) and imipramine (from study day 141-364) use with baseline normal liver testing parameters, in week 41 (study day 281) began to develop elevated GGT (54 U/L). Her GGT continuously rose throughout the study with a peak of 281 U/L (with ALT 64 U/L and AST 48 U/L) on study day 585, which was her last reading as of the 120-day safety update; this reading occurred more than 80 days after her last dose of study drug (study day 503). There were no changes in bilirubin. No treatment was given for these readings and the subject continued eplontersen with no interruption until her last scheduled dose.

It appears unlikely that this event was caused by the investigational drug given the underlying risk factors for elevated liver testing parameters (such as concomitant medications and hepatitis A history). Phenytoin, in particular, is known to cause elevated GGT levels, and there is a correlation between the subject starting phenytoin and the occurrence of her elevated GGT levels. However, a role for eplontersen cannot be ruled out.

- Subject (b) (6) A 48-year-old male, had a baseline elevated GGT level (85 U/L), and continued to have elevated GGT levels throughout the study. On study day 365, the GGT value reached a peak of 291 U/L, with associated elevated AST (90 U/L) and ALT (76 U/L); the AST and ALT eventually normalized. The GGT value did spontaneously decrease by study day 576 to 53 U/L. The subject's week 57 dose was interrupted due to the AE of transaminases increased with no further increase in transaminases upon rechallenge. There were no changes in bilirubin.

This event may possibly be related to study drug, though the subject's GGT at baseline was elevated.

- Subject (b) (6) A 47-year-old female, had a baseline total bilirubin level of 27.7µMol/L (1.3xULN), and experienced a peak total bilirubin level of 43.6µMol/L on study day 309 with no concurrent changes to AST/ALT. Total bilirubin then normalized with no changes to eplontersen administration.

This event is likely not related to eplontersen given its spontaneous resolution and the abnormal baseline bilirubin level.

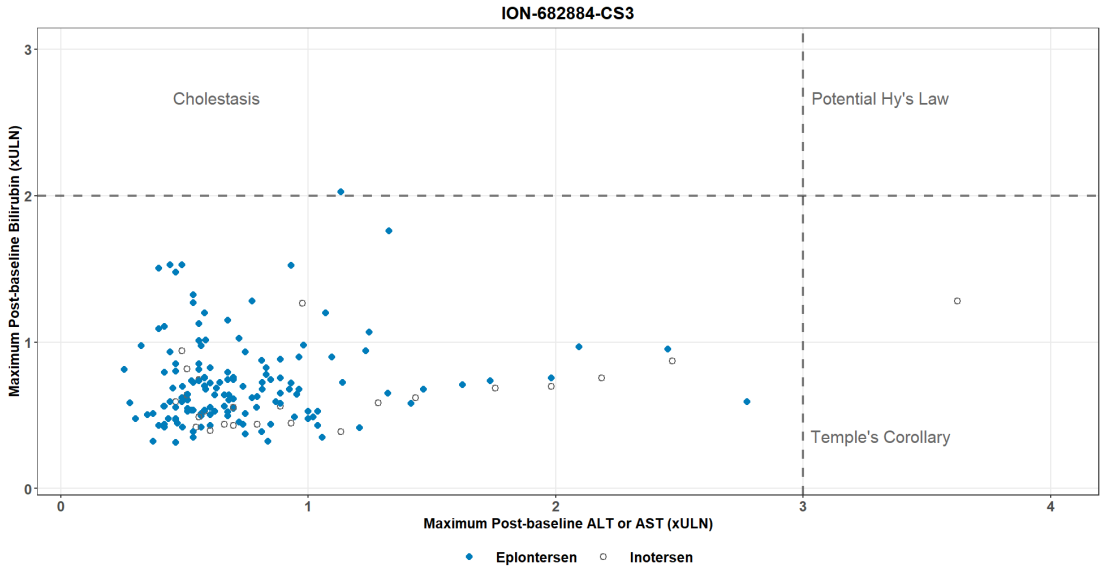
- Subject (b) (6) A 55-year-old male, had three liver function testing elevations while on eplontersen (and normal readings at baseline), with peak values of GGT 449 U/L (8.6xULN), ALT 147 U/L (2.7xULN), AST 118 U/L (2.7xULN), ALP 172 U/L (1.2xULN). Each elevation resolved without treatment and without changes to eplontersen administration. The subject was also concurrently on simvastatin.

This event may possibly be related to the study drug, but the resolution of events without change to the study drug or other treatment make this less likely, and concurrent simvastatin use is a confounding factor.

- Subject (b) (6) A 72-year-old male with a baseline INR of 1.3 (slightly elevated, not on any drugs that are known to elevate INR), had an INR reading of 5.1 on study day 56; this improved on study day 84 to 1.4 (still mildly elevated), and had normalized by study day 168. However, his INR was again elevated to 2.4 (study day 241) and 2.9 (study day 337); the subject continued the study drug with no interruptions and had no other changes to his medications. Per the 120-day safety update, INR coagulation parameters greater than the upper limit of normal postbaseline occurred in a similar proportion in all groups (32.6% of subjects in eplontersen, 30.0% of subjects in external placebo, and 33.3% in concurrent inotersen groups).

Although resolution while still on eplontersen suggests this was unlikely related to study drug, a role for eplontersen cannot be ruled out.

Figure 3. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, ION-682884-CS3

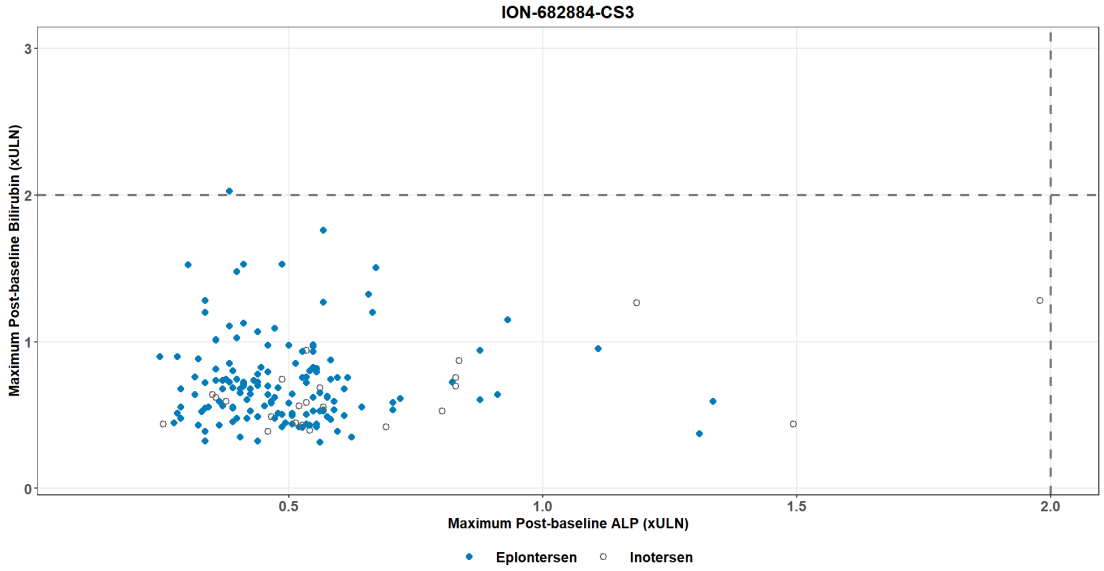


Source: adlb.xpt; Software: R.
Note:

- Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
- A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one postbaseline ALT or AST and bilirubin are plotted.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Figure 4. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Trial ION-682884-CS3



Source: adlb.xpt; Software: R.
Note:

- Each data point represents a subject plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.
- A potential cholestatic DILI case (red circled) was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after postbaseline ALP became equal to or exceeding 2X ULN.

Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 51. Other Adverse Events of Interest Assessment Related to Abnormal Liver Function, Safety Population, Trial ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Abnormal Liver Function OAEI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to OAEI	8 (5.6)	4 (16.7)	-11.1 (-26.5, 4.3)	4 (6.7)
Alanine aminotransferase increased	4 (2.8)	2 (8.3)	-5.6 (-16.9, 5.8)	2 (3.3)
Bilirubin conjugated increased	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Blood alkaline phosphatase increased	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Gamma-glutamyl transferase increased	2 (1.4)	1 (4.2)	-2.8 (-11.0, 5.4)	0
Hepatic enzyme increased	1 (0.7)	1 (4.2)	-3.5 (-11.6, 4.6)	0
Hepatic steatosis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Transaminases increased	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	0	2 (8.3)	-8.3 (-19.4, 2.7)	1 (1.7)
Mild	8 (5.6)	2 (8.3)	-2.8 (-14.5, 8.9)	3 (5.0)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	3 (2.1)	0	2.1 (-0.2, 4.4)	2 (3.3)

Source: adae.xpt; Software: R.

Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OAEI, other adverse events of interest

Table 52. Adverse Events Related to Liver Enzyme Elevations, Safety Population, Pooled Trials ION-682884-CS3 and ISIS-420915-CS2

	ION-682884-CS3			ISIS-420915-CS2
AE Group Related to Liver Enzyme Elevations	**Eplontersen**	**Inotersen**		**Placebo**
AESI	**N=144**	**N=24**	**Risk Difference (%)**	**N=60**
Statistic	**n (%)**	**n (%)**	**(95% CI)**	**n (%)**
AE grouping related to AESI	6 (4.2)	2 (8.3)	-4.2 (-21.9, 3.5)	2 (3.3)
Alanine aminotransferase increased	4 (2.8)	2 (8.3)	-5.6 (-23.3, 1.7)	2 (3.3)
Aspartate aminotransferase increased	2 (1.4)	1 (4.2)	-2.8 (-19.0, 2.0)	2 (3.3)
Bilirubin conjugated increased	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Gamma-glutamyl transferase increased	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	2 (1.4)	1 (4.2)	-2.8 (-19.0, 2.0)	0
Mild	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	2 (3.3)
Serious	0	0	0.0 (-13.9, 2.6)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0.0 (-13.9, 2.6)	0
Relatedness	3 (2.1)	0	2.1 (-11.8, 6.0)	2 (3.3)
Number of subjects with adverse events with end dates on or before treatment end dates	4/6 (66.7)	2/2 (100)	-33.3 (-71.8, 45.2)	½ (50.0)
Duration, days (from AE start date to AE end date)				
Mean (SD)	74.5 (70.9)	18.5 (4.9)	NA	39 (NA)
Median (Q1, Q3)	66.5 (17.5, 123.5)	18.5 (16.8, 20.2)	NA	39 (39, 39)
Min, Max	10, 155	15, 22	NA	39, 39
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	2/6 (33.3)	0/2 (0)	33.3 (-45.2, 71.8)	½ (50.0)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/6 (0)	0/2 (0)	0.0 (-68.7, 42.3)	0/2 (0)

Source: adae.xpt; Software: R.

Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 53. Adverse Events Related to Liver Enzyme Elevations, Safety Population, Trials ION-682884-CS3 and ISIS-420915-CS2, Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Liver Enzyme Elevations	**Eplontersen**	**Inotersen**		**Placebo**
AESI	**N=144**	**N=24**	**Risk Difference (%)**	**N=60**
Statistic	**n (%)**	**n (%)**	**(95% CI)**	**n (%)**
AE grouping related to AESI	4 (2.8)	2 (8.3)	-5.6 (-23.3, 1.7)	2 (3.3)
Alanine aminotransferase increased	4 (2.8)	2 (8.3)	-5.6 (-23.3, 1.7)	2 (3.3)
Aspartate aminotransferase increased	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	2 (3.3)
Bilirubin conjugated increased	1 (0.7)	0	0.7 (-13.2, 3.8)	0
Gamma-glutamyl transferase increased	1 (0.7)	1 (4.2)	-3.5 (-19.6, 0.9)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	0	1 (4.2)	-4.2 (-20.3, -0.7)[a]	0
Mild	4 (2.8)	1 (4.2)	-1.4 (-17.6, 4.1)	2 (3.3)
Serious	0	0	0.0 (-13.9, 2.6)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0.0 (-13.9, 2.6)	0
Relatedness	1 (0.7)	0	0.7 (-13.2, 3.8)	2 (3.3)
Number of subjects with adverse events with end dates on or before treatment end dates	2/4 (50.0)	2/2 (100)	-50.0 (-86.6, 37.1)	1/2 (50.0)
Duration, days (from AE start date to AE end date)				
Mean (SD)	42.5 (46)	18.5 (4.9)	NA	39 (NA)
Median (Q1, Q3)	42.5 (26.2, 58.8)	18.5 (16.8, 20.2)	NA	39 (39, 39)
Min, Max	10, 75	15, 22	NA	39, 39
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/4 (0)	0/2 (0)	0.0 (-69.7, 53.5)	1/2 (50.0)

AE Group Related to Liver Enzyme Elevations AESI Statistic	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	 Inotersen N=24 n (%)	 Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	¼ (25.0)	0/2 (0)	25.0 (-54.6, 72.8)	0/2 (0)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	20 (NA)	NA	NA	NA
Median (Q1, Q3)	20 (20, 20)	NA	NA	NA
Min, Max	20, 20	NA, NA	NA	NA, NA

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 54. Adverse Events Related to Liver Enzyme Elevations, Safety Population, Trials ION-682884-CS3 and ISIS-420915-CS2, Nonrandomized Extension Period

AE Group Related to Liver Enzyme Elevations AESI Statistic	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
AE grouping related to AESI	4 (2.8)	0	4 (2.5)
Alanine aminotransferase increased	2 (1.4)	0	2 (1.2)
Aspartate aminotransferase increased	2 (1.4)	0	2 (1.2)
Gamma-glutamyl transferase increased	3 (2.1)	0	3 (1.9)
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	0	0
Moderate	2 (1.4)	0	2 (1.2)
Mild	2 (1.4)	0	2 (1.2)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	0	0
Relatedness	2 (1.4)	0	2 (1.2)

AE Group Related to Liver Enzyme Elevations AESI Statistic	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Number of subjects with adverse events with end dates on or before treatment end dates	2/4 (50.0)	0/0 (NA)	2/4 (50.0)
Duration, days (from AE start date to AE end date)			
Mean (SD)	89.5 (72.8)	NA	89.5 (72.8)
Median (Q1, Q3)	89.5 (63.8, 115.2)	NA	89.5 (63.8, 115.2)
Min, Max	38, 141	NA, NA	38, 141
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	2/4 (50.0)	0/0 (NA)	2/4 (50.0)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/4 (0)	0/0 (NA)	0/4 (0)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; Rnd., randomized; SD, standard deviation

Table 55. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial ION-682884-CS3

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Laboratory Parameter Level	Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	Placebo N=60 n/N_w (%)
Bilirubin, total, high (mg/dL)				
Level 1 (>1.5X ULN)	6/144 (4.2)	0/24 (0)	4.2 (0.9, 7.4)[a]	2/60 (3.3)
Level 2 (>2X ULN)	1/144 (0.7)	0/24 (0)	0.7 (-0.7, 2.1)	1/60 (1.7)
Level 3 (>3X ULN)	0/144 (0)	0/24 (0)	0 (0, 0)	0/60 (0)

Source: adlb.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note:
- Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022).
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- For specific evaluation of drug-induced liver injury (DILI), see Figure 3 and Figure 4 of this review.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

7.6.2.9. Vital Signs' Analyses, ION-682884-CS3

In the randomized period, 8.3% of subjects receiving eplontersen had postbaseline systolic blood pressure readings <90, and 19.4% had postbaseline diastolic blood pressure readings <60. This is comparable to the external placebo group (16.7% with systolic blood pressure <90, 40% with diastolic blood pressure <60). It is important to note that hATTR patients have a complex, multisystem disease at baseline that can lead to autonomic neuropathy. It is not possible to attribute these blood pressure changes to the investigational drug; however, a role for eplontersen cannot be ruled out.

There were no clinically significant changes in body temperature, respiratory rate or heart rate in subjects receiving eplontersen.

Table 56. Percentage of Subjects With Meeting Specific Hypotension Levels Postbaseline, Safety Population, Trials ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Blood Pressure (mm Hg)	Eplontersen N=144 n/N_w (%)	Inotersen N=24 n/N_w (%)	Risk Difference (%) (95% CI)	Placebo N=60 n/N_w (%)
SBP <90	12/144 (8.3)	0/24 (0)	8.3 (3.8, 12.8)[a]	10/60 (16.7)
DBP <60	28/144 (19.4)	6/24 (25.0)	-5.6 (-24.0, 12.9)	24/60 (40.0)

Source: advs.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SBP, systolic blood pressure

Electrocardiogram

At the pre-NDA stage, the Agency had previously stated the following:

> *"Based on our review of the submitted data, your clinical ECGs and integrated nonclinical assessments can be used as a substitute for a TQT study according to ICH E14 Q&A 5.1 (Feb 2022). The integrated data showed eplontersen does not cause clinically significant QTc interval prolongation."*

ECG findings were balanced between eplontersen and the external placebo groups. QTcF >500ms was noted in 3.6% of eplontersen treated subjects, versus 5% in the external placebo group. There were no significant differences between the cardiomyopathy and noncardiomyopathy subgroups.

Overall, eplontersen does not appear to be associated with a negative effect on ECG parameters.

7.6.2.10. Subgroup Analyses, ION-682884-CS3

The frequency of adverse events and serious adverse events was balanced between male and female subjects. The number of subjects in subgroups of race other than white, age greater than or equal to 65, or location in the United States was too small to draw conclusions about adverse events and serious adverse events in those demographic subgroups.

Table 57. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Trial ION-682884-CS3

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
Characteristic	Eplontersen N=144 n/N_s (%)	Inotersen N=24 n/N_s (%)	Risk Difference (%) (95% CI)	Placebo N=60 n/N_s (%)
Sex, n (%)				
Female	6/44 (13.6)	0/8 (0)	13.6 (3.5, 23.8)[a]	2/19 (10.5)
Male	8/100 (8.0)	3/16 (18.8)	-10.8 (-30.6, 9.1)	11/41 (26.8)
Age group, years, n (%)				
<65	9/100 (9.0)	2/16 (12.5)	-3.5 (-20.6, 13.6)	3/34 (8.8)
65 to 74	2/36 (5.6)	1/7 (14.3)	-8.7 (-35.7, 18.3)	8/17 (47.1)
≥75	3/8 (37.5)	0/1 (0)	37.5 (4.0, 71.0)[a]	2/9 (22.2)
Age group ≥65, years, n (%)				
≥65	5/44 (11.4)	1/8 (12.5)	-1.1 (-25.9, 23.6)	10/26 (38.5)
Race, n (%)				
Asian	0/22 (0)	0/2 (0)	0 (0, 0)	0/3 (0)
Black or African American	0/5 (0)	0/0 (NA)	NA	0/1 (0)
Multiple	1/1 (100)	0/0 (NA)	NA	0/1 (0)
Other	0/3 (0)	0/2 (0)	0 (0, 0)	0/2 (0)
White	13/112 (11.6)	2/19 (10.5)	1.1 (-13.9, 16.1)	13/53 (24.5)
Missing	0/1 (0)	1/1 (100)	NA	0/0 (NA)
Ethnicity, n (%)				
Hispanic or Latino	4/22 (18.2)	0/5 (0)	18.2 (2.1, 34.3)[a]	1/7 (14.3)
Not Hispanic or Latino	10/120 (8.3)	2/18 (11.1)	-2.8 (-18.1, 12.6)	12/53 (22.6)
Missing	0/2 (0)	1/1 (100)	NA	0/0 (NA)

Characteristic	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n/N_s (%)	Inotersen N=24 n/N_s (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n/N_s (%)
Is in United States, n (%)				
United States	2/19 (10.5)	0/4 (0)	10.5 (-3.3, 24.3)	9/26 (34.6)
Non-United States	12/125 (9.6)	3/20 (15.0)	-5.4 (-21.9, 11.1)	4/34 (11.8)

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable

Table 58. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial ION-682884-CS3

Characteristic	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n/N_s (%)	Inotersen N=24 n/N_s (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n/N_s (%)
Sex, n (%)				
Female	41/44 (93.2)	8/8 (100)	-6.8 (-14.3, 0.6)	19/19 (100)
Male	85/100 (85.0)	16/16 (100)	-15.0 (-22.0, -8.0)[a]	41/41 (100)
Age group, years, n (%)				
<65	87/100 (87.0)	16/16 (100)	-13.0 (-19.6, -6.4)[a]	34/34 (100)
65 to 74	32/36 (88.9)	7/7 (100)	-11.1 (-21.4, -0.8)[a]	17/17 (100)
≥75	7/8 (87.5)	1/1 (100)	-12.5 (-35.4, 10.4)	9/9 (100)
Age group ≥65, years, n (%)				
≥65	39/44 (88.6)	8/8 (100)	-11.4 (-20.7, -2.0)[a]	26/26 (100)
Race, n (%)				
Asian	18/22 (81.8)	2/2 (100)	-18.2 (-34.3, -2.1)[a]	3/3 (100)
Black or African American	5/5 (100)	0/0 (NA)	NA	1/1 (100)
Multiple	1/1 (100)	0/0 (NA)	NA	1/1 (100)
Other	3/3 (100)	2/2 (100)	0 (0, 0)	2/2 (100)
White	98/112 (87.5)	19/19 (100)	-12.5 (-18.6, -6.4)[a]	53/53 (100)
Missing	1/1 (100)	1/1 (100)	0 (0, 0)	0/0 (NA)
Ethnicity, n (%)				
Hispanic or Latino	17/22 (77.3)	5/5 (100)	-22.7 (-40.2, -5.2)[a]	7/7 (100)
Not Hispanic or Latino	107/120 (89.2)	18/18 (100)	-10.8 (-16.4, -5.3)[a]	53/53 (100)
Missing	2/2 (100)	1/1 (100)	0 (0, 0)	0/0 (NA)
Is in United States, n (%)				
United States	18/19 (94.7)	4/4 (100)	-5.3 (-15.3, 4.8)	26/26 (100)
Non-United States	108/125 (86.4)	20/20 (100)	-13.6 (-19.6, -7.6)[a]	34/34 (100)

Source: adae.xpt; Software: R.
[a.] Rows where the 95% confidence interval excludes zero.
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable

7.6.3. Safety Results, Trial ION-682884-CS13

ION-682884-CS13 is an ongoing, open-label Phase 3 long-term treatment extension study to assess the long-term safety and efficacy of eplontersen in subjects with hATTR polyneuropathy. It is a multicenter study for dosing of 45 mg of eplontersen subcutaneously once every 4 weeks

for up to 5 years (depending on commercial availability of eplontersen in the subject's country), followed by a 24-week, post-treatment evaluation. The study enrolls subjects from two clinical trials: ION-682884-CS3 (including continuous eplontersen subjects and inotersen-eplontersen switch subjects), and an investigator-sponsored trial 420915-CS101 (subjects in this study had received inotersen for 84 months prior to enrolling in this study). Eplontersen is administered either by vial and syringe, prefilled syringe with safety device, or prefilled syringe with autoinjector. Subjects also receive daily supplemental doses of vitamin A at recommended daily allowances.

The safety discussion in the following sections is inclusive of the 120-day safety update for ION-682884-CS13, with 42 subjects having been enrolled at the time of the data cutoff for the 120-day safety update.

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial ION-682884-CS13

A total of 17 (40.5%) of subjects experienced at least one TEAE. Four subjects experienced at least one serious TEAE. One subject discontinued treatment due to an SAE, which was fatal (TEAE of cardiac arrest, detailed in Section 7.6.3.2). Another subject died after the 120-day safety update data cutoff (detailed in Section 7.6.3.2) and was noted to have significant thrombocytopenia ($16x10^9$/L at the nadir) a few months prior to his death in the setting of a bacterial infection and multiple antibiotics.

7.6.3.2. Deaths, Trial ION-682884-CS13

There was one death within the 120-day safety data cutoff date:

- Subject (b) (6) A 39-year-old female with a history of amyloid cardiomyopathy and syncopal episodes died due to cardiac arrest. While in ION-682884-CS3 she had AEs of atrioventricular block (also present at baseline) and urinary tract infection and was hospitalized. While hospitalized she collapsed and was found to be in asystole without a pulse; she was eventually revived. She later received a pacemaker. She was later hospitalized again for COVID-19 and syncope. Following her transition to ION-682884-CS13, she was hospitalized for hypovolemia and sepsis with a history of worsening chronic diarrhea. She had another episode of syncope, and another episode of dehydration/hypotension in the setting of diarrhea. Soon after this episode of dehydration, she experienced a fatal event of cardiac arrest.

It is not possible to attribute this death to the investigational drug, given her history of cardiomyopathy and ECG changes as well as ongoing sepsis/hypovolemia/diarrhea. It appears unlikely that this death was caused by the investigational drug.

There was one death that occurred after the 120-day safety data cutoff date:

- Subject (b) (6): An 82-year-old male who died of gastrointestinal hemorrhage. His past medical history prior to enrollment in ION-682884-CS3 had included atrial fibrillation (he was on dabigatran for this), left leg thrombophlebitis, and possible chronic myelomonocytic leukemia (CMML). While in ION-682884-CS3 he had the following AEs: unstable angina, cellulitis of the left leg (in the setting of a recent injury to his leg), rectal hemorrhage (platelet

counts of $133x10^9$/L prior to the event and $117x10^9$/L after the event), eye hemorrhage, and ileus. Following enrollment in ION-682884-CS13, he experienced epistaxis (platelet count $116x10^9$/L). He later had another event of cellulitis in his right leg requiring hospital admission and antibiotics (including flucloxacillin, amoxicillin + clavulanic acid, and meropenem), developed a superimposed COVID-19 infection, and then developed severe thrombocytopenia in the setting of all these ongoing issues (platelet nadir $16x10^9$/L). Eplontersen was held and was never restarted. He was discharged from the hospital, and his platelet count eventually recovered a few months later ($162x10^9$/L). He was re-hospitalized later for bacterial arthritis of the left shoulder, and then re-hospitalized again a few months later for a severe gastrointestinal hemorrhage (platelet count of $221x10^9$/L at admission, and ranged between $135x10^9$/L and 204 x 10^9/L during hospitalization). The subject declined further intervention and died.

The complexity of this subject's medical problems are confounding factors (in particular, use of dabigatran is a risk for hemorrhage). Although a role for eplontersen cannot be ruled out, it is unlikely that this death was caused by the investigational drug.

Regarding his profound thrombocytopenia noted during his hospitalization for right leg cellulitis, there were multiple issues ongoing that could lead to reduced platelet count (infection, antibiotics use, COVID-19, and possible history of CMML). Although a role for eplontersen cannot be ruled out, it is unlikely that the severe thrombocytopenia was caused by the investigational drug.

7.6.3.3. Serious Treatment-Emergent Adverse Events, Trial ION-682884-CS13

Of the 58 TEAEs observed in this study, 15 were serious (seen in a total of 4 subjects). These included sepsis, urinary tract infection, and iron deficiency anemia (all three in one subject), cellulitis and thrombocytopenia (both in one subject), transient blindness and cerebral infarction (both in one subject described below), dehydration/hypovolemia, syncope, and cardiac arrest (all in one subject), and ulcerative keratitis (in a subject with a history of dry eye and keratitis).

- Subject (b) (6) A 72-year-old female with a history of elevated blood cholesterol and atrial fibrillation, had an episode of transient vision loss and was found to have strokes in the left occipital lobe and left thalamus. Imaging also revealed a prior stroke in the right basal ganglia. Her vision improved, she was discharged and there was no drug interruption throughout.

The most likely etiology of this subject's transient vision loss was occipital lobe strokes. The most likely etiology of her strokes are her underlying risk factors (atrial fibrillation, elevated blood cholesterol, prior stroke). Although a role for eplontersen cannot be ruled out, it is unlikely that this event was caused by the investigational drug.

7.6.3.4. Adverse Events Leading to Treatment Discontinuation, Trial ION-682884-CS13

There was one discontinuation of eplontersen due to a fatal TEAE of cardiac arrest (detailed in Section 7.6.3.2).

7.6.3.5. Treatment-Emergent Adverse Events, Trial ION-682884-CS13

There has been a total of 58 TEAEs reported. The most frequently reported TEAEs in subjects receiving eplontersen (≥3%, or 2 or more subjects) were COVID-19 (n=3), sepsis (n=2), urinary tract infection (n=2), diarrhea (n=2), headache (n=2), and proteinuria (n=2).

7.6.3.6. Laboratory Findings, Trial ION-682884-CS13

Per the 120-day safety update, there have been no clinically significant changes, trends, or patterns noted in laboratory values for this trial so far, as compared to what has already been noted in ION-682884-CS3, though the data are limited as the study is ongoing.

Subject (b) (6) with a baseline CK (upon entering ION-682884-CS13) of 302 U/L (normal is ≤210 U/L), had a CK of 621 U/L on day 141. As of the last reading prior to the data cutoff point, the subject's CK had reached 448 U/L on day 344.

7.6.3.7. Assessment of Drug-Induced Liver Injury, Trial ION-682884-CS13

There have been two subjects with ALT > ULN, three subjects with AST > ULN, and two subjects with total bilirubin > ULN at any time post-ION-682884-CS13 baseline. In all these subjects, the increases were either single or non-sustained without progressive elevation and no interruption to study drug administration. There were no potential Hy's law cases.

7.6.3.8. Vital Signs' Analyses, Trial ION-682884-CS13

Per the 120-day safety update, there have been no clinically significant changes, trends, or patterns noted in vital signs for this trial so far, as compared to what has already been noted in ION-682884-CS3, though the data are limited as the study is ongoing.

7.7. Key Safety Review Issues

7.7.1. Safety of Autoinjector

Issue

The proposed commercial formulation for eplontersen is a prefilled syringe-autoinjector (PFS-AI). However, this formulation was not used in the pivotal study of ION-682884-CS3 (the vial and syringe formulation was used). The PFS-AI formulation was evaluated in one bioequivalence study (ION-682884-CS21) and has been used in the open-label extension study (ION-682884-CS13). Administration of eplontersen with the PFS-AI showed comparable eplontersen AUC but higher C_{max} compared to the vial with syringe (clinical trial formulation). A potential key safety review issue was to determine whether the Applicant had adequate safety data to support the administration of eplontersen with the PFS-AI.

Background

ION-682884-CS21 was a single dose, randomized, open-label, three-period crossover bioequivalence study comparing three subcutaneous formulations of eplontersen: vial, prefilled syringe (PFS) with safety device, and prefilled syringe-autoinjector (PFS-AI) in healthy adult subjects. Each subject received three doses of eplontersen in each of the three subcutaneous routes with at least a 28-day washout period between study periods. In total, 57 subjects (19 subjects per sequence group) were enrolled, randomized, and dosed in the study, and 44 subjects completed the study. Thirteen subjects discontinued the study early, five of them due to adverse events. There was a total of 18 TEAEs reported, 8 of them in the PFS-AI treatment group. The TEAEs for the PFS-AI include increased ALT, headache, fatigue, injection site pain, nausea, cough, urinary tract infection, and urinary retention (the latter two occurred in one subject with a history of urinary retention, who discontinued study treatment). There were no fatalities.

Please refer to Section 14.2 for an evaluation of C_{max}/AUC of the PFS-AI versus the vial and syringe formulation in ION-682884-CS21; in brief, the PFS-AI C_{max} was higher than that of the vial and syringe.

Assessment

The Agency requested further information regarding the safety of the PFS-AI from the Applicant at the Applicant midcycle meeting on June 5, 2023, specifically a summary of exposure using the PFS-AI based on the 120-day data cut-off date and a more recent data cut. In an information request (IR) dated June 16, 2023, the Applicant provided the following exposure information for the PFS-AI:

Table 59. Exposure Duration of PFS-AI in ION-682884-CS13 (120-Day Safety Update)

Category[a]	Number of Subjects
Any duration	26
≥3 months	12
≥6 months	10
≥9 months	2
≥12 months	0

Source: IR dated June 16, 2023.
[a.] Duration in months is date of last dose minus date of first dose plus 1 day divided by 30.

Table 60, Exposure Duration of PFS-AI in ION-682884-CS13 (April 7, 2023)

Category[a]	Number of Subjects
Any duration	108
≥3 months	58
≥6 months	21
≥9 months	10
≥12 months	9
≥15 months	2
≥18 months	0

Source: IR dated June 16, 2023.
[a.] Duration in months is date of last dose minus date of first dose plus 1 day divided by 30.

Table 61. Number of Injections Using PFS-AI in ION-682884-CS13 (April 7, 2023)

Number of Injections	Number of Subjects
≥1 injection	108
≥3 injections	72
≥6 injections	40
≥9 injections	12
≥12 injections	10
≥15 injections	8
≥18 injections	2
≥21 injections	0

Source: IR dated June 16, 2023.

A single adverse event at injection site was reported in one subject out of 108 subjects using the PFS-AI in ION-682884-CS13, which was "mild injection site hematoma." In contrast, in ION-682884-CS3, where only the vial and syringe formulation was used, there were 25 adverse events at injection sites among 13 subjects (out of 144 subjects in total).

Please refer to Section 8 for the pharmacokinetic/pharmacodynamic assessment of the autoinjector.

Conclusion

The supplemental data provided appear to provide sufficient evidence of the safety of the PFS-AI.

7.7.2. Vitamin A Deficiency

Issue

Given the mechanism of action of eplontersen in targeting reduction of serum TTR, vitamin A deficiency was identified as a potential key safety review issue.

Background

Vitamin A is vital to ocular health. Complications of vitamin A deficiency include night blindness, xerophthalmia (dryness of the conjunctiva and cornea that can progress to corneal xerosis and keratomalacia), retinopathy, and complete blindness in severe cases. Deficiency can also lead to impairment of immune system health, bone development, and other nonspecific dermatologic issues such as hyperkeratosis.

TTR (transthyretin) is a transport protein, and one of its major functions is to transport retinol (vitamin A). The mechanism of action of eplontersen involves reduction in serum TTR levels, and thus potentially reductions in serum vitamin A levels. Serum reduction in vitamin A levels have also been seen in other approved medications targeting TTR.

Given this, all subjects enrolled in ION-682884-CS3 and ION-682884-CS13 received daily vitamin A supplementation of the daily recommended dose. Ophthalmology examination was performed at baseline and at week 35 in ION-682884-CS3.

Assessment

Mean serum vitamin A levels gradually decreased over time in the eplontersen group and remained lower than baseline. In contrast vitamin A levels remained stable in the external placebo group. 90% of subjects on eplontersen had at least one postbaseline vitamin A level that was < lower limit of normal (LLN) despite vitamin A supplementation. A mean serum vitamin A reduction of 71% was seen by week 37 in ION-682884-CS3.

An evaluation of ocular TEAEs potentially related to vitamin A deficiency in ION-682884-CS3 is below. There were no TEAEs of night blindness. There was one TEAE of xerophthalmia. No ocular-related TEAEs led to treatment discontinuation. There were also 8 (5.6%) reports of cataract in the eplontersen group, compared to 1 (1.7%) in the external placebo group and none in the inotersen active comparator group. All subjects had other risk factors for cataracts such as age, prior cataract history, or steroid use. There was one subject with a TEAE of conjunctival hemorrhage that was noted as mild with a baseline ophthalmology exam revealing mild conjunctival congestion. Since the 120-day safety update, there were no further cases of vision blurred.

Table 62. Adverse Events Related to Vision Change, Safety Population, Trials ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Vision Change AESI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to Vision Change	12 (8.3)	3 (12.5)	-4.2 (-18.1, 9.8)	4 (6.7)
Dry eye	2 (1.4)	1 (4.2)	-2.8 (-11.0, 5.4)	2 (3.3)
Glaucoma	0	0	0 (0, 0)	0
Retinal ischemia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Vision blurred	6 (4.2)	2 (8.3)	-4.2 (-15.7, 7.4)	1 (1.7)
Visual acuity reduced	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Visual impairment	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0
Moderate	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Mild	10 (6.9)	3 (12.5)	-5.6 (-19.4, 8.3)	4 (6.7)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	1 (0.7)	0	0.7 (-0.7, 2.1)	1 (1.7)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 63. Adverse Events of Special Interest Assessment Related to Vitamin A Deficiency, Safety Population, Trials ION-682884-CS3 Randomized Period

	ION-682884-CS3 Randomized Period (Weeks 1 to 37)			ISIS-420915-CS2
AE Group Related to Vitamin A Deficiency Ocular AESI	Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	Placebo N=60 n (%)
AE grouping related to AESI	17 (11.8)	4 (16.7)	-4.9 (-20.7, 11.0)	12 (20.0)
Age-related macular degeneration	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Corneal disorder	0	0	0 (0, 0)	1 (1.7)
Deposit eye	0	0	0 (0, 0)	1 (1.7)
Detachment of retinal pigment epithelium	0	0	0 (0, 0)	1 (1.7)
Dry eye	2 (1.4)	1 (4.2)	-2.8 (-11.0, 5.4)	2 (3.3)
Dyschromatopsia	0	0	0 (0, 0)	1 (1.7)
Eye disorder	0	0	0 (0, 0)	0
Eye irritation	0	0	0 (0, 0)	0
Foreign body in eye	0	0	0 (0, 0)	1 (1.7)
Foreign body sensation in eyes	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Keratitis	0	0	0 (0, 0)	2 (3.3)
Macular edema	0	0	0 (0, 0)	0
Ophthalmological examination abnormal	0	0	0 (0, 0)	0
Photophobia	0	0	0 (0, 0)	1 (1.7)
Photopsia	0	1 (4.2)	-4.2 (-12.2, 3.8)	0
Punctate keratitis	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Retinal detachment	0	0	0 (0, 0)	0
Retinal ischemia	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Retinal vein occlusion	0	0	0 (0, 0)	0
Ulcerative keratitis	0	0	0 (0, 0)	0
Vision blurred	6 (4.2)	2 (8.3)	-4.2 (-15.7, 7.4)	1 (1.7)
Visual acuity reduced	2 (1.4)	0	1.4 (-0.5, 3.3)	1 (1.7)
Visual field defect	0	0	0 (0, 0)	0
Visual impairment	1 (0.7)	0	0.7 (-0.7, 2.1)	0
Vitamin A deficiency	3 (2.1)	1 (4.2)	-2.1 (-10.4, 6.2)	0
Vitamin D deficiency	0	0	0 (0, 0)	0
Vitreous disorder	0	0	0 (0, 0)	1 (1.7)
Vitreous floaters	0	0	0 (0, 0)	0
Maximum severity				
Death	0	0	0 (0, 0)	0
Life-threatening	0	0	0 (0, 0)	0
Severe	0	0	0 (0, 0)	0

AE Group Related to Vitamin A Deficiency Ocular AESI	ION-682884-CS3 Randomized Period (Weeks 1 to 37) Eplontersen N=144 n (%)	Inotersen N=24 n (%)	Risk Difference (%) (95% CI)	ISIS-420915-CS2 Placebo N=60 n (%)
Moderate	2 (1.4)	0	1.4 (-0.5, 3.3)	0
Mild	15 (10.4)	4 (16.7)	-6.2 (-22.0, 9.5)	12 (20.0)
Serious	0	0	0 (0, 0)	0
Deaths	0	0	0 (0, 0)	0
Resulting in discontinuation	0	0	0 (0, 0)	0
Relatedness	4 (2.8)	1 (4.2)	-1.4 (-9.8, 7.0)	1 (1.7)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks for Trial ION-682884-CS3 and 65 weeks for Trial ISIS-420915-CS2.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 64. Adverse Events of Special Interest Assessment Related to Vitamin A Deficiency, Safety Population, Trial ION-682884-CS3 Extension Period

AE Group Related to Vitamin A Deficiency Ocular AESI	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
AE grouping related to AESI	21 (14.9)	3 (15.0)	24 (14.9)
Age-related macular degeneration	1 (0.7)	0	1 (0.6)
Corneal abrasion	1 (0.7)	0	1 (0.6)
Dry eye	2 (1.4)	0	2 (1.2)
Eye hemorrhage	1 (0.7)	0	1 (0.6)
Eye irritation	1 (0.7)	0	1 (0.6)
Photophobia	0	1 (5.0)	1 (0.6)
Retinal hemorrhage	1 (0.7)	0	1 (0.6)
Vision blurred	4 (2.8)	0	4 (2.5)
Visual impairment	1 (0.7)	0	1 (0.6)
Vitamin A decreased	1 (0.7)	0	1 (0.6)
Vitamin A deficiency	11 (7.8)	2 (10.0)	13 (8.1)
Xerophthalmia	1 (0.7)	0	1 (0.6)

AE Group Related to Vitamin A Deficiency Ocular AESI	Eplontersen (Rnd.) to Eplontersen (Ext.) N=141 n (%)	Inotersen (Rnd.) to Eplontersen (Ext.) N=20 n (%)	Combined Eplontersen N=161 n (%)
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	0	0
Moderate	3 (2.1)	1 (5.0)	4 (2.5)
Mild	18 (12.8)	2 (10.0)	20 (12.4)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	0	0
Relatedness	13 (9.2)	2 (10.0)	15 (9.3)

Source: adae.xpt; Software: R.
Note:

- Treatment-emergent adverse events defined as AEs that first occurred or worsened after the first dose of study drug.
- Duration is 84 weeks.
- Relatedness is determined by investigator

Abbreviations: AE, adverse event; AESI, adverse events of special interest; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; Rnd., randomized

In ION-682884-CS13, there has been one subject who experienced ulcerative keratitis; however, this subject had a history of keratitis prior to enrollment.

Conclusion

Serum vitamin A levels are reduced in subjects taking eplontersen, though with daily supplementation, there did not appear to be a significant risk of symptomatic vitamin A deficiency in relation to serum vitamin A reduction (and no serious symptoms such as night blindness have been noted). However, 95.8% of subjects in ION-682884-CS3 had at least one vitamin A reading < LLN despite daily supplementation. As such, the below will be noted as a warning in the label:

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking eplontersen. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with eplontersen, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

7.7.3. Thrombocytopenia and Glomerulonephritis

Issue

Given the clinical experience with inotersen, thrombocytopenia and glomerulonephritis were identified as potential key safety review issues.

Background

The Applicant considered thrombocytopenia and glomerulonephritis adverse events of special interest for eplontersen because these events were observed during inotersen clinical trials, are included in boxed warnings for inotersen and are the reason for a REMS. The Applicant noted that inotersen is an antisense oligonucleotide (ASO) with the same sequence as eplontersen.

Inotersen labeling includes the following boxed warnings for thrombocytopenia and glomerulonephritis:

Thrombocytopenia

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial subject died from intracranial hemorrhage. TEGSEDI is contraindicated in patients with a platelet count below 100 x 109/L [see Contraindications (4) and Warnings and Precautions (5.2)]. Prior to starting TEGSEDI, obtain a platelet count [see Dosage and Administration (2.3)]. During treatment, monitor platelet counts weekly if values are 75 x 109/L or greater, and more frequently if values are less than 75 x 109/L [see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]. If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional [see Warnings and Precautions (5.1)]. Following discontinuation of treatment for any reason, continue to monitor platelet count for 8

weeks, or longer if platelet counts are less than 100 x 109/L, to verify that platelet counts remain above 75 x 109/L [see Dosage and Administration (2.4)].

Glomerulonephritis

TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial subject who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection [see Warnings and Precautions (5.2)]. TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher [see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]. Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis [see Dosage and Administration (2.3)]. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every two weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause. If a dose is held, once eGFR increases to ≥45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued [see Dosage and Administration (2.4) and Warnings and Precautions (5.2)].

The boxed warning also states that because of thrombocytopenia and glomerulonephritis, inotersen is available only through restricted distribution under a REMS program.

In the safety review of Tegsedi dated October 4, 2018, that was the basis for the above boxed warning, two types of thrombocytopenia with inotersen were identified. The first type of thrombocytopenia was rare, had rapid onset, and was associated with severe decline in platelets. Also identified was a type of thrombocytopenia that presented with a gradual, slow decline in platelets that was mild.

For the first type of thrombocytopenia, three inotersen-exposed subjects (2.7%, 3/112) were identified from Study CS-2 who developed severe "…thrombocytopenia that was precipitous and unpredictable, with normal platelet counts immediately prior to the nadir platelet counts."[1] These subjects had platelet counts <$25x10^9$/L, all tested positive for a treatment-emergent antiplatelet IgG antibodies and 1 of these subjects died from a cerebral hemorrhage while the other two improved after stopping inotersen and administration of corticosteroids.

For the second type of thrombocytopenia, Table 24 in the inotersen review included on-treatment low platelet low outlier results from Study CS-2. Twenty-five percent (28/112) of inotersen-treated subjects had a platelet count <$100x10^9$/L compared to 1.7% (1/60) of placebo-treated subjects. In addition, 14.3% (16/112) of inotersen treated subjects had a platelet count <$75x10^9$/L compared to no (0/60) placebo-treated subjects.

[1] Inotersen Clinical Safety Review

In the inotersen safety review dated October 4, 2018, it was noted that "Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, sometimes leading to increased tubular proteinuria, has been described in preclinical studies. Glomerulonephritis, considered a proinflammatory effect, has also been described in preclinical and clinical studies of antisense oligonucleotides." In Study CS-2 3% (3/112) of inotersen subjects were identified with biopsy-confirmed glomerulonephritis, compared to 0 of 60 placebo subjects. It was noted that glomerulonephritis was accompanied by nephrotic syndrome in these three subjects. In addition to stopping inotersen, one of these subjects was treated with hemodialysis and the other two required immunosuppressive treatment.

Assessment

Eplontersen Phase 1 Data Related to Thrombocytopenia and Glomerulonephritis

The Phase 1 studies did not suggest a relationship between eplontersen and thrombocytopenia or glomerulonephritis, although these studies included a small number of subjects administered few study drug doses. The Applicant did not identify any subjects with TEAEs of thrombocytopenia or glomerulonephritis in these Phase 1 studies. Occasional abnormal lab results were reported but the significance of these events is not clear.

Study CS-1

There were no reported renal or thrombocytopenia TEAEs in this study. One subject in the single-dose cohort had a platelet count between 100,000 and <140,000/mm^3. No other subject in any cohort had a platelet count <140,000/mm^3. No subjects met the stopping rules for platelet counts or renal function tests.

Study CS-20

There were no reported renal TEAEs and no TEAEs of thrombocytopenia. No subjects met prespecified study criteria for additional platelet or renal function monitoring.

Study CS-21

There were no reported TEAEs of glomerulonephritis or thrombocytopenia. Two subjects experienced nonserious TEAEs of GFR decreased. A total of 6 subjects had eGFR values below 60 mL/min/1.73 m^2. In 2 subjects, the decreased eGFR occurred only once during study participation (Subject (b) (6) 56 mL/min/1.73 m^2 at period 2 run-in and Subject (b) (6) 58 mL/min/1.73 m^2 at end of study only [eGFR at all other visits were normal]). In one subject (Subject (b) (6)), eGFR was <60 mL/min/1.73 m^2 at Screening (55 mL/min/1.73 m^2) and throughout the study (range: 44 to 59 mL/min/1.73 m^2) except on period 1 day 15 (92 mL/min/1.73 m^2). In one subject (Subject (b) (6)), eGFR was <60 mL/min/1.73 m^2 on 4 visits (range: 57 to 59 mL/min/1.73 m^2) and was normal at the end of study. None of the decreases in eGFR in these four subjects were considered clinically significant. In the remaining two subjects, the decreased eGFR values were reported as TEAEs (noted above), both of which had PTs of glomerular filtration rate decreased, were mild and nonserious, and resolved. Summaries for those events are provided below.

- Subject (b) (6) A 62-year-old female, experienced a mild TEAE of glomerular filtration rate decreased. The subject was not taking any relevant concomitant medications at the time of

the event. eGFR was normal at screening and at the period 1 run-in (both 77 mL/min/1.73 m^2) and remained normal at Period 1 Day 15 (94 mL/min/1.73 m^2). At the period 2 run-in, the subject's eGFR was 56 mL/min/1.73 m^2 (normal value: >60 mL/min/1.73 m^2), and the investigator reported a TEAE of glomerular filtration rate decreased. No concomitant medication was administered for the event, and study drug was discontinued. Six days after the Period 2 Run-in, eGFR was 56 mL/min/1.73 m^2. Thirty-five days after the period 2 run-in, eGFR was 78 mL/min/1.73 m^2 and the TEAE was considered resolved. The subject was subsequently withdrawn from the study.

- Subject (b) (6) A 63-year-old female, experienced a TEAE of glomerular filtration rate decreased. At screening and at the period 1 run-in, eGFR (both 95 mL/min/1.73 m^2) and creatinine (both 56μmol/L) were normal. At period 1 day 15, eGFR decreased to 37 mL/min/1.73 m^2, and a repeat measurement was not performed. On the same day, creatinine was elevated at 131μmol/L (normal range: 50 to 100 μmol/L), which was assessed by the investigator as not clinically significant. Eleven days after period 1 day 15, eGFR (94 mL/min/1.73 m^2) and creatinine (58μmol/L) were normal, and the TEAE of glomerular filtration rate decreased was considered resolved. She completed the study and eGFR and creatinine remained normal. The Applicant suggested that a laboratory error was a possible explanation for this event as all subsequent eGFR measurements until the end of study were normal.

Eplontersen Phase 3 Pivotal Study, ION-682884-CS3 and Extension CS-13

Protocol CS-3 and CS-13 required that platelets, serum creatinine, estimated glomerular filtration rate (eGFR creat-cys, calculated using the CKD-EPI creatinine-cystatin C equation), urinalysis, and UPCR were collected every 4 weeks in all subjects randomized to eplontersen. More frequent monitoring of platelets and renal function were required during treatment for those subjects randomized to inotersen.

Study CS-3 Data Related to Thrombocytopenia

CS-3 Thrombocytopenia AEs

A total of 3 eplontersen subjects (2.1%, 3/144) experienced 4 TEAEs coded as either thrombocytopenia or platelet decreased[2] compared to 1.7% (1/60) in the external placebo group, 25% (6/24) in the concurrent inotersen group, and 24.1% (27/112) in the historic inotersen group.

Two events were coded as "thrombocytopenia" in one eplontersen-treated subject and two events as "platelet count decreased" in two eplontersen-treated subjects. The nadir platelet counts of these subjects were 102 × 10^9/L (Subject (b) (6) [thrombocytopenia]) on study day 1, prior to the first dose of eplontersen), 136 × 10^9/L (Subject (b) (6) [platelet count decreased] on study day 57), and 115 × 10^9/L (Subject (b) (6) [platelet count decreased] on study day 55). None of the thrombocytopenia AEs were serious or led to study drug discontinuation.

[2] One additional patient had an event of thrombocytosis that was incorrectly coded as thrombocytopenia.

CS-3 Platelet Lab Data

The Applicant provided platelet mean change, outlier, and shift table analyses that did not suggest a risk for decline in platelets in patients exposed to eplontersen.

The Applicant provided a plot of mean platelet counts over time that demonstrated similar results for eplontersen and the external placebo cohort.

Platelet outlier results suggested that eplontersen subjects had similar risks to placebo subjects for low platelet results and lower risks when compared to historical or concurrent inotersen subjects. Platelet counts below the LLN (<140 × 10^9/L) at any time postbaseline occurred in 34% (49/144) of subjects in the eplontersen group compared with 18.3% (11/60) of subjects in the historical placebo group, 54.2% (13/24) in the concurrent inotersen group and 55.4% of subjects (n=62) in the historical inotersen group. Platelet counts <100 × 10^9/L were observed for 4.2% (6/144) of subjects in the eplontersen group compared to 3.3% (2/60) for the historical placebo group, 37.5% (9/24) in the concurrent inotersen group, and 25% (28/112) for the historical inotersen group. One eplontersen subject had a platelet count <50× 10^9/L (0.7%, 1/144) compared to no placebo subjects, 1 concurrent inotersen subject (4.2%, 1/24), and 3.6% (4/112) of historical inotersen subjects. No eplontersen, historical placebo or concurrent inotersen subjects had a platelet count <25 × 10^9/L compared to 4 subjects (3.6%, 4/112) in the historic inotersen group.

There were 8 eplontersen treated subjects (5.6%, 8/144) who experienced ≥50% platelet reduction from baseline, compared to 1 external placebo subject (1.7%, 1/60), 6 (25%, 6/24) concurrent inotersen subjects and 23 (20.5%, 23/112) historical inotersen subjects. For the 8 eplontersen-treated subjects with ≥50% platelet reduction from baseline, 6 subjects had nadir Grade 1 platelet reductions (≥75× 10^9/L-<140× 10^9/L), one subject had Grade 2 (≥50 × 10^9/L to <75 × 10^9/L) and one had Grade 3 (≥25 × 10^9/L to <50 × 10^9/L)) platelet reductions.

A total of 29 (20.1%, 29/144) eplontersen subjects had decreased platelet count lab results (<140 × 10^9/L) that also represented a 30% decrease from baseline. 13 of these subjects had a single low platelet count. Of the 16 subjects who had >1 low platelet count, 14 subjects had their platelet counts returning to within normal range during the study while remaining on eplontersen and 2 returned to >100,000 x10^9/L while continuing eplontersen.

Study CS-13 Data Related to Thrombocytopenia

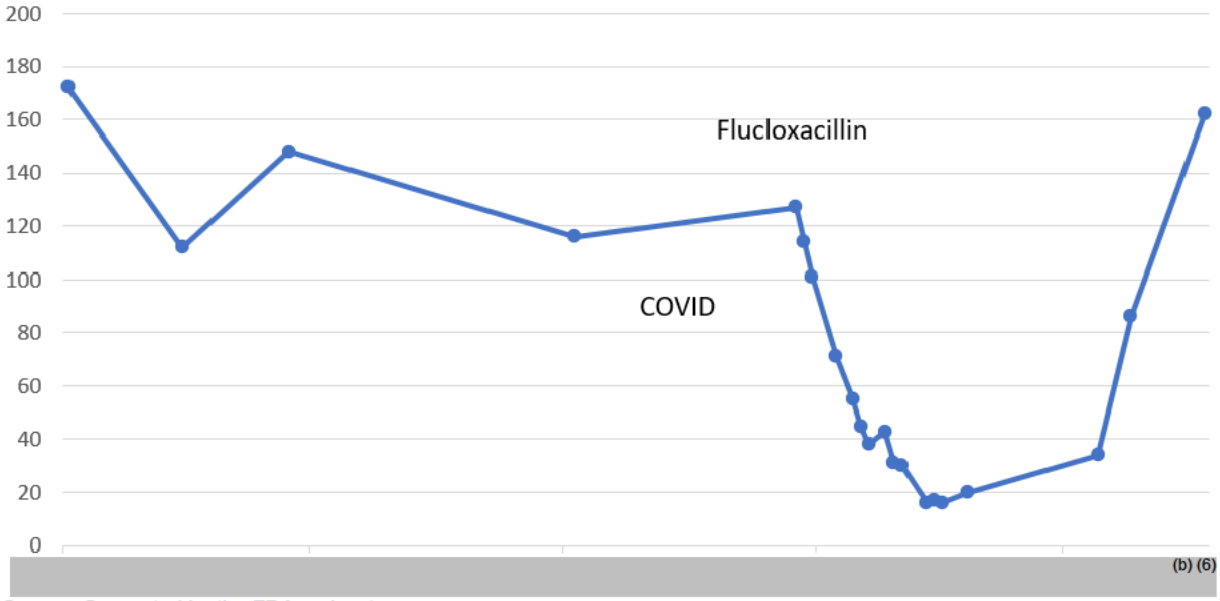
CS-13 Thrombocytopenia AEs

The 120-Day safety update identified an eplontersen treated subject with thrombocytopenia, and that case is summarized below.

- Subject (b) (6) An 82-year-old white male with hATTR-PN developed thrombocytopenia during Study CS13. This subject's medical history included myocardial ischemia, cardiac amyloidosis, cardiomyopathy, atrial fibrillation, left leg thrombophlebitis, renal insufficiency, and possible CMML not further described. Prior to the first dose of eplontersen in Study CS-3, his platelet count was 145 × 10^9/L (NR 140-400). He completed the CS-3 study treatment and received a total of 20 doses of eplontersen. During Study CS-3, his platelet counts fluctuated with the lowest recorded platelet count of 70 × 10^9/L on study day 437 (preceded by a platelet count of 103× 10^9/L on study day 428 and followed by a platelet count of 134× 10^9/L on study day 450). He had an SAE of rectal hemorrhage during the study that was not

associated with thrombocytopenia and did not result in changes to his study treatment. His last dose of eplontersen was on (b) (6) (Study Day 611). On (b) (6) (study day 618) he experienced cellulitis of the right leg that was initially treated with topical agents and pain medications. The next day he was admitted to a hospital and his treatment included various antibiotics over the course of his stay including IV flucloxacillin, Augmentin, and meropenem. On (b) (6) he was diagnosed with COVID-19 (mild) and was treated with remdesivir. Figure 5 depicts platelet counts around this time.

Figure 5. Subject (b) (6) Platelet Counts



Source: Generated by the FDA review team.

- On (b) (6) (study day 642) his platelet count was 71 × 10^9/L and on (b) (6) (b) (6) study day 653) his platelet count declined to 16× 10^9/L. The thrombocytopenia event was attributed to flucloxacillin use, progression of underlying CMML and possible effect of study drug. After recovering from the cellulitis his platelet count on (b) (6) (b) (6) (study day 688) was 162× 10^9/L and it remained above 100× 10^9/L for the remainder of his observation in the study (study day 771). He was hospitalized for a gastrointestinal bleed on study day 760 that was not associated with thrombocytopenia (platelet count 221× 10^9/L) and concomitant dabigatran was stopped. He discontinued from the study at this time due to his decision to forgo additional treatment. He was transfused, discharged with palliative care, and died.

Although it is not possible to completely rule out a contributory role of eplontersen in the event above, the thrombocytopenia appears more likely related to the subject's treatment during a hospitalization for cellulitis. The subject tolerated 20 eplontersen doses in the controlled trial prior to the profound drop in platelet count. The decline in platelet count was more closely temporally related to the subject's hospitalization and treatment with antibiotics that are known to cause thrombocytopenia (flucloxacillin, meropenem) and the subject's platelet counts began rebounding after completion of the antibiotic treatment for cellulitis.

CS-13 Platelet Lab Data

In the 120-day safety update, the Applicant identified 5 additional subjects in the eplontersen-treated set with decreased platelets <140 × 10^9/L and at least 30% decrease from baseline. In addition, one subject with a previous report of decreased platelets and at least 30% decrease from baseline with two new occurrences of decreased platelets and at least 30% decrease from baseline since the NDA data cutoff date. Of the 5 additional subjects, 3 had a single occurrence of decreased platelets <140 × 10^9/L. For the 2 subjects who had >1 occurrence of decreased platelets, platelet counts returned to within normal range during the study while continuing eplontersen treatment.

Glomerulonephritis

Through the 120-day safety update, no eplontersen treated subjects had AEs of glomerulonephritis or nephrotic syndrome. The Applicant reported that from the historical comparator data two placebo subjects and three inotersen-treated subjects[3] had TEAEs of glomerulonephritis.

Other Renal AEs

Three study subjects had serious renal AEs and the relationship of these events to eplontersen is not clear due to confounding by underlying disease and concomitant medications. Summaries of those cases are provided below.

- Subject (b) (6) A 76-year-old female, experienced an SAE of renal impairment that was characterized by decline in eGFR from screening 47 mL/min/1.73 m^2 (LLN >60 mL/min/1.73 m^2) to a nadir of 27 mL/min/1.73 m^2. This was accompanied by peripheral edema. She was discontinued from the study and the event was ongoing. The case was confounded by abnormal renal function at screening, presence of congestive heart failure, and concomitant medications (ACE inhibitors). A consulting nephrologist felt that the event was due to amyloidosis.
- Subject (b) (6) A 33-year-old white male experienced an SAE of glomerular filtration rate decreased. Baseline eGFR (average pretreatment value) was 86.5 mL/min/1.73 m^2 (normal range: >60 mL/min/1.73 m^2). eGFR remained above 80 mL/min/1.73 m^2 through study day 365. On study day 379, TEAEs of glomerular filtration decreased (78 mL/min/1.73 m^2) and proteinuria (UPCR of 302 mg/g; normal range: <200 mg/g) and urine protein (31 mg/dL; normal range: <29 mg/dL) were reported. No treatment was given for these events and eplontersen was continued without interruption. On study day 435, the TEAEs of glomerular filtration rate decreased and proteinuria were considered resolved with an eGFR of 94 mL/min/1.73 m^2; however, UPCR and urine protein were elevated at 534 mg/g and 70 mg/dL, respectively. On study day 493, the subject experienced an SAE of glomerular filtration rate decreased of moderate intensity with an eGFR of 56 mL/min/1.73 m^2, which was a 35% change from baseline. On the same day, the subject's UPCR, urine protein, and serum creatinine reached peak values at 759 mg/g, 134 mg/dL, and 139 μmol/L, respectively. On study day 519, eGFR returned to normal range at 74 mL/min/1.73 m^2; the subject's UPCR remained elevated throughout the remainder of the study participation. Study drug

[3] One of these patients had an AE coded as acute kidney injury and subsequent renal biopsy demonstrated glomerulonephritis.

was interrupted as a result of the event. On study day 533, urine protein returned to normal range at 22 mg/dL. On study day 535, the SAE of glomerular filtration rate decreased was considered resolved.

- Subject (b) (6) A 71-year-old white male experienced SAEs of hematuria and urinary retention that resolved without study drug interruption. Creatinine remained normal throughout study participation, while eGFR was normal (LLN >60 mL/min/1.73 m^2) throughout study participation except on study days 170, 313, and 327 (54, 58, and 56 mL/min/1.73 m^2, respectively).

No other renal TEAEs led to study drug discontinuation.

The Applicant summarized and compared to historical controls the TEAEs that were included in the Standardized MedDRA Query for Acute Renal Failure. These TEAE risks appeared similar for the eplontersen and historical placebo groups, and lower in the eplontersen group than in the historical inotersen group.

In Study CS-3, renal impairment other adverse events of interest were reported in 16.7% of subjects (n=24) in the Eplontersen Treated subjects compared with 10.0% of subjects (n=6) in the external placebo group and 20.5% of subjects (n=23) in the historical inotersen group. Renal impairment TEAEs that occurred in at least one eplontersen-treated subject are summarized in Table 65.

Table 65. Renal Impairment Treatment-Emergent Adverse Events

	ISIS-420915-CS2 Historical Controls		ION-682884-CS3
Acute Renal Failure SMQ Preferred Term	Placebo (N=60) % (n)	Inotersen (N=112) % (n)	Eplontersen (N=144) % (n)
Proteinuria	3.3% (2)	6.3% (7)	8.3% (12)
Renal impairment	0	3.6% (4)	3.5% (5)
Glomerular filtration rate decreased	3.3% (2)	5.4% (6)	2.1% (3)
Acute kidney injury	0	2.7% (3)	1.4% (2)
Albuminuria	1.7% (1)	1.8% (2)	1.4% (2)
Blood creatinine increased	1.7% (1)	1.8% (2)	0.7% (1)
Blood Urea increased	0	2.7% (3)	0.7% (1)
Protein urine present	0	0.9% (1)	0.7% (1)
Renal failure	0	2.7% (3)	0.7% (1)

Source: Applicant Table 40, p.190, 120-day safety update.
Abbreviations: N, total number of subjects in treatment arm; n, number of subjects with renal AE; SU, safety update

One of the events coded as renal impairment was serious (renal dysfunction, Subject (b) (6) summarized above). All 5 eplontersen-treated subjects with TEAEs of renal impairment had risk factors including history of congestive heart failure, hypertension, renal impairment, neurogenic bladder, and proteinuria.

The event coded as renal Failure (CS-3/Subject (b) (6)) was reported using the verbatim term “renal failure” and was not an SAE.

Proteinuria was the most commonly reported TEAE among eplontersen patients in Table 65. None of these events were SAEs. A total of 8 events were considered resolved, and 5 events were considered not resolved at the time of database lock. No dose changes were made for 10 subjects, drug was withdrawn for 1 subject, and dosing was interrupted for 1 subject. Subjects

with proteinuria TEAEs had abnormal renal function laboratory results (i.e., proteinuria, microalbuminuria, and increased UPCR) at Baseline/Screening.

Renal Function-Related Lab Data

The Applicant summarized creatinine, eGFR, UPCR, and urine albumin to creatinine ratio (UACR) data from Study CS-3. Although there were occasional abnormal results, there did not appear to be evidence of an effect of eplontersen on renal function based on the lack of meaningful differences when compared to historical placebo data. This assessment was limited by the small size of the database and confounding by factors such as effects of the underlying disease and concomitant medications.

Creatinine

The mean creatinine analyses did not suggest differences over time between the eplontersen and external placebo group.

The percentages of subjects with creatinine > ULN was similar for the eplontersen (9.6%; n=16), and external placebo (10%, n=6) group and lower than the historical inotersen group (17.1%; n=19).

A total of 3% (n=5) of eplontersen-treated subjects had an increase in creatinine of at least 0.5 mg/dL from baseline compared to 1.7% (n=1) of subjects in the historical placebo group and 10.7% (n=12) of subjects in the historical inotersen group.

No eplontersen-treated subject experienced a shift from baseline normal and Grade 1 to postbaseline Grade 3, compared to 2 subjects from the historical inotersen group.

Estimated Glomerular Filtration Rate

The mean eGFR analyses did not suggest differences between the eplontersen and historical placebo groups. The Applicant noted that there was a small decline in mean eGFR in the historical inotersen group that was first observed at week 10 and persisted through the treatment period.

Approximately 24% (n=35) of eplontersen-treated subjects experienced ≥25% eGFR decreases from baseline compared to 11.7% (n=7) in the external placebo group and 27.7% (n=31) in the historical inotersen group. The Applicant noted that eGFR assessments were performed more frequently in eplontersen subjects compared to the external placebo subjects which could impact this comparison. Of the 35 eplontersen-treated subjects with ≥25% eGFR decline, 14 had single occurrences that the Applicant felt represented “natural variation in eGFR.” Of the 21 remaining subjects with more than a single eGFR decline ≥25%, 12 had confounding risk factors (i.e., heart failure, concomitant medications including NSAIDs, loop diuretics, ACE inhibitors, and ARBs). Eleven of the 21 subjects had eGFR return to baseline or near baseline levels with continued treatment. Two subjects (Subject (b) (6) and Subject (b) (6)) had no identified confounding risk factors and no renal TEAEs were reported for these two subjects, both continued dosing with eplontersen with no further declines in eGFR. An additional 5 subjects had eGFR return to baseline levels with continued treatment. For the remaining subjects, 10 had confounding risk factors that complicated the assessment of a causal relationship between eplontersen and the event. Two remaining subjects without identified confounding factors continued dosing with eplontersen with no further declines in eGFR and no renal TEAEs.

Approximately 45% of eplontersen-treated subjects (n=65) had a shift to a lower eGFR category compared with 30.0% (n=18) in the external placebo group and 42.8% (n=48) in the historical inotersen category.

Urine Protein to Creatinine Ratio

The mean UPCR analyses did not suggest differences over time between the eplontersen and the external placebo group.

A total of 3.5% (n=5) of eplontersen-treated subjects had a UPCR>=2000 mg/g compared to 3.3% (n=2) of subjects in the external placebo group and 9.8% (n=11) in the historical inotersen group.

A total of 7.6% (n=11) of eplontersen-treated subjects had increases in UPCR to >5 × ULN compared with 8.3% (n=5) of subjects in the external placebo group and 15.2% (n=17) of subjects in the historical inotersen group.

Urine Albumin to Creatinine Ratio

The mean UACR analyses did not suggest differences over time between the eplontersen and external placebo groups.

A total of 17.4% (n=25) of eplontersen-treated subjects had increases in UACR to >5 × ULN compared to 23.3% (n=14) of subjects in the external placebo group and in 28.6% (n=32) of subjects in the historical inotersen group.

Conclusion

Despite the experience with inotersen, the available safety data did not suggest a causal relationship between eplontersen and thrombocytopenia or glomerulonephritis. Although a strength of the studies in the eplontersen development program was close monitoring for platelet and kidney toxicity, an important limitation was the relatively small number of exposed subjects. One eplontersen-treated subject did experience a profound drop in platelet count, but that event was more closely temporally related to hospitalization and treatment with antibiotics that have established causal relationships to thrombocytopenia and the event resolved following completion of this treatment. Both historical and contemporaneous lab data suggested an increased risk for platelet declines with inotersen while the data for eplontersen did not appear meaningfully different from the historical placebo data. The Applicant identified no cases of glomerulonephritis in the development program and neither lab nor adverse event data suggested an increased risk for kidney-related toxicity with eplontersen.

Based on these findings, the Agency concurs with the Applicant that, if approved, eplontersen would not require a REMS program for thrombocytopenia or glomerulonephritis, and the Applicant's proposal to not include a Boxed Warning or Warnings and Precautions statements for these events in labeling given the absence of empirical evidence suggesting increased risk.

It would be reasonable to monitor postmarketing reports for unconfounded cases of thrombocytopenia or glomerulonephritis in patients treated with eplontersen. In addition, as noted above, the Applicant has an ongoing study of eplontersen, ION-682884-CS2 in ATTR-CM. The Applicant expects the enrollment of 1,400 subjects to be completed by June/July 2023 and the last subject to complete the week 140 visit by March 2026. The results from this study

should provide valuable comparative data that would allow for more robust assessment of risk of thrombocytopenia and glomerulonephritis with eplontersen.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

Effect of hepatic impairment on the pharmacokinetics of eplontersen was not evaluated in dedicated clinical pharmacology studies. Eplontersen is not metabolized by CYP450 enzymes but expected to be metabolized by endo- and exonucleases in the tissues. Therefore, the change of CYP enzyme activity due to hepatic impairment is not expected to influence the metabolism and plasma PK of eplontersen. According to the popPK analysis, 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) did not significantly affect the PK of eplontersen. The effect of moderate and severe hepatic impairment on PK, PD, efficacy, and safety of eplontersen cannot be ruled out because of the potential change in asialoglycoprotein receptor (ASGPR) expression and asialoglycoprotein receptor-mediated uptake of GalNAc-ASO conjugates into the livers of hepatically-impaired patients. No dosage adjustment is recommended for patients with mild hepatic impairment. Eplontersen has not been studied in patients with moderate or severe hepatic impairment or in patients with prior liver transplant. Please refer to Section 14.5 for details.

Renal Impairment

Effect of renal impairment on the pharmacokinetics of eplontersen was not evaluated in dedicated clinical pharmacology studies. Eplontersen is highly bound to plasma proteins (>98%) and less than 1% of the administered dose excreted as total full-length ASOs in urine within the first 24 hours. Therefore, renal impairment is not expected to influence the plasma PK of eplontersen. According to population PK analysis, mild (eGFR ≥60 and <90 mL/min/1.73m^2, N=53) or moderate (eGFR ≥45 to <60 mL/min/1.73m^2, N=3) renal impairment did not significantly affect the PK of eplontersen. Although the sample size for moderate renal impairment subjects (N=3) is too small to draw a conclusion, it is reasonable to expect that moderate renal impairment does not affect the PK of eplontersen due to minimal excretion of eplontersen in urine. Therefore, no dosage adjustment is recommended for patients with mild or moderate renal impairment. Eplontersen has not been studies in patients with severe renal impairment or end stage renal disease. Please refer to Section 14.5 for details.

Other Intrinsic Factors

Based on the population PK analysis results, eplontersen plasma PK exposure is unlikely affected by body weight, sex, age, race, and Val30Met mutation status. Therefore, no dosage adjustment is required for patients with these intrinsic factors. Please refer to Section 14.5 for details.

8.2. Extrinsic Factors

Eplontersen Presentation

The proposed to-be-marketed formulation, eplontersen solution for injection (56 mg/mL) in prefilled syringe with auto-injector (PFS-AI), delivers 45 mg eplontersen in 0.8 mL. The clinical formulation used in the Phase 3 study, ION-682884-C3, is eplontersen 150 mg/mL solution for injection in stoppered glass vial and used with syringe (vial and syringe).

To bridge the proposed PFS-AI with vial and syringe, the Applicant evaluated plasma PK profiles of eplontersen following administration of eplontersen with the presentation from vial and syringe, PFS-AI, and prefilled syringe with safety device (PFS) in a Phase 1 bioequivalence (BE) study, ION-682884-CS21.

The results of the BE study (ION-682884-CS21) demonstrated similar eplontersen AUC but 13% higher C_{max} for PFS-AI compared to vial with syringe for the delivery of 45 mg eplontersen SC (refer to Section 14.2 for details). These results support the bridging of eplontersen efficacy between the presentation of vial with syringe and PFS-AI. Considering the acceptable clinical safety data to support the use of PFS-AI in hATTR-PN subjects and no apparent difference across C_{max} quartiles for the incidence of adverse events (Refer to Section 14.5 and Section 17 for details), the 13% increase in C_{max} with PFS-AI is not expected to have clinically significant effect on safety.

Injection Site

The Applicant evaluated the impact of SC injection site (arm, abdomen/thigh) on PK, PD, efficacy, and safety using data from the following clinical studies: ION-682884-CS1, ION-682884-CS20, ION-682884-CS21, and ION-682884-CS3. Based on population PK analysis, geometric mean C_{max} (%CV) for injection into the arm and abdomen/thigh are 0.142 (56.7) µg/mL (N=33) and 0.221 (51.3) µg/mL (N=204), respectively. There was a 22% reduction in C_{max} but no change on AUC_{tau},ss or C_{trough} with injection into the arm comparing to the injection into abdomen/thigh (refer to Section 14.5 for details). In addition, the differences in %TTR reduction between injections into arm [-85.7 (1.28)] and abdomen [-81.8 (0.692)] were minimal. Refer to Section 14.5 for details. Considering no trends or substantial differences in clinical response (mNIS+7 and Norfolk QoL-DN) and safety endpoints (moderate or severe treatment-emergent adverse events) across the exposure quartiles (refer to Section 14.5), the review team concluded that eplontersen can be administered into the arm or abdomen/thigh without affecting PD, safety, and efficacy.

Drug-Drug Interactions

Based on in vitro data, eplontersen is not expected to have plasma protein-binding displacement interaction with highly plasma protein-bound drugs, warfarin or ibuprofen. Based on in vitro data, eplontersen is not a substrate or inhibitor of major transporters, and not a substrate or inhibitor/inducer of CYP enzymes (refer to Section 14.1 for details). Therefore, clinical drug-drug interaction studies were not conducted, and no dosing adjustments are proposed for use of eplontersen with concomitant medications.

8.3. Plans for Pediatric Drug Development

No data are available for pediatric subjects (<18 years of age). Symptom onset for hATTR amyloidosis usually occurs between 20 and 70 years of age.

Because this product has an orphan indication, there are no requirements under the Pediatric Research Equity Act (PREA) to study pediatric patients.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

No formal studies of eplontersen in pregnant or lactating women have been performed. Pregnant or lactating women were excluded from participation in the eplontersen clinical studies, and women of childbearing potential were required to use acceptable methods of birth control throughout the study.

As of the July 19, 2022, data cutoff date, there have been no reported pregnancies in the eplontersen clinical development program.

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 217388 for Wainua (eplontersen injection). Based on the evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling is adequate to meet the regulatory requirements.

9.1. Device or Combination Product Considerations

CDRH/OPEQ reviewed device aspects of the product (autoinjector and syringe). The review, dated August 22, 2023, recommends approval of the application.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

See the OSI report for a full discussion of site inspections and specific findings.

Sites 1817, 1863, 1823, and the Applicant, were inspected in support of this NDA covering protocol ION-682884-CS3. Based on these inspection results, the study appears to have been conducted adequately, and the data generated by these sites and submitted by the Applicant appear acceptable in support of the respective indication. Primary and secondary efficacy data were reviewed at the clinical investigator sites and no discrepancies were identified. Additionally, there was no evidence of under-reporting of adverse events.

11. Advisory Committee Summary

This application was not referred to an FDA advisory committee because the application did not raise significant efficacy or safety issues in the intended population.

III. Additional Analyses and Information

12. Summary of Regulatory History

Eplontersen was developed under investigational new drug (IND) 139521 by Ionis Pharmaceuticals, Inc. (Applicant), in collaboration with Akcea Therapeutics, Inc., for the treatment of the polyneuropathy of hereditary transthyretin (TTR)-mediated amyloidosis (hATTR) in adults. Eplontersen is an antisense oligonucleotide that specifically binds to and leads to degradation of TTR messenger ribonucleic acid, reducing the TTR protein synthesis process. The Applicant initially had a Type B PIND meeting request to receive feedback on their development plans for eplontersen. The meeting occurred on February 21, 2019, and the Applicant's proposals were discussed. The FDA did not agree with the proposal to use TTR reduction as a primary endpoint for the Phase 3 study but instead, proposed the use of the Norfolk-QOL-DN and mNIS+7 as co-primary endpoints as TTR reduction would be most appropriate as a secondary endpoint, with adjustment for multiplicity. The FDA received IND 139521 for eplontersen (investigational product ION-682844) injection on August 8, 2019. The study was allowed to proceed after the Applicant agreed to amend Study ION-682884-CS3 by changing the safety monitoring plan to follow the paradigm in the Tegsedi USPI. The amended protocol was submitted on October 2, 2019.

On March 5, 2021, the Applicant requested a Type C meeting to discuss the suitability of their proposed Phase 1 study (ION-682884-CS21) for demonstrating bioequivalence between a vial, prefilled syringe with safety device, and autoinjector configurations. The Agency provided written responses to the Applicant on May 19, 2021, stating that the proposed clinical study design for ION-682884-CS21 was not adequately designed to demonstrate bioequivalence between the vial, prefilled syringe with safety device, and autoinjector configurations and provided recommendations for the Applicant's consideration. In addition, the Applicant was advised to conduct a comprehensive use-related risk analysis, which would determine the need to submit a human factors validation study.

On April 6, 2021, the Applicant requested a Type C chemistry, manufacturing, and controls meeting to obtain advice from FDA regarding the proposed classification (b) (4) (b) (4) Written responses were provided on June 11, 2021, stating that the final designation (b) (4) will be determined during the new drug application (NDA) review with the completion of the commercial manufacturing process of the drug substance.

Eplontersen received orphan drug designation for the treatment of the polyneuropathy of hereditary transthyretin (TTR)-mediated amyloidosis (hATTR) in adults on January 6, 2022.

In response to the Applicant's March 31, 2022, thorough QT (TQT) study waiver request, the QT-IRT team determined that nonclinical assessments could be used as a substitute for a TQT study because the integrated data showed that eplontersen does not cause clinically significant QTc interval prolongation. The Applicant was notified of this determination on August 4, 2022.

A pre-NDA meeting was requested on June 24, 2022, to obtain the Agency's feedback on the adequacy of the high-level results of the ION-682884-CS3 interim analysis for an NDA

submission and the content and format of the planned NDA submission. The Agency provided comments on August 15, 2022.

The NDA was submitted on December 22, 2022, and contained the following clinical studies: two completed Phase 1 ascending-dose studies (Study ION-682884-CS1 and Study ION-682884-CS20), one completed Phase 1 bioequivalence study (Study ION-682884-CS21), one ongoing Phase 3 study (ION-682884-CS3 in hATTR-PN) and one ongoing Phase 3 treatment extension study (ION-682884-CS13 in hATTR-PN) corresponding to the Phase 3 study. ION-682884-CS3 is an ongoing, Phase 3, multicenter, open-label study with external controls and an active reference arm (inotersen) with Stage 1 and Stage 2 hATTR polyneuropathy. The Applicant submitted the NDA based on the endpoints from the week 35 analysis: change from baseline in serum TTR concentration, the mNIS+7, and Norfolk QOL-DN. Despite the Agency's advice, the Applicant maintained TTR reduction as a co-primary endpoint with the mNIS+7.

The proprietary name, Wainua, was found conditionally acceptable on September 6, 2023.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

Eplontersen (ION-682884) is a 20-mer chimeric 2′-MOE mixed (PS/PO) backbone ASO conjugated to GalNAc3 that targets the 3′-UTR of human TTR mRNA to suppress both wild type and mutant TTR transcription. In vitro studies in human hepatocytes indicated an IC_{50} of 0.059 µM for the suppression of human TTR mRNA by eplontersen. Eplontersen is complimentary to human and monkey, but not rodent, TTR mRNA; therefore, transgenic mice carrying the Ile84Ser human TTR mutant were used to test the pharmacologic effects of eplontersen. Subcutaneous (SC) administration of 0.6-6 mg/kg eplontersen for 3 weeks QW in male human TTR transgenic mice resulted in dose-dependent reductions in hepatic hTTR mRNA levels, with an ED_{50} of 0.5 mg/kg/week, which corresponded to reductions in plasma hTTR protein, with an ED_{50} of 1.5 mg/kg/week.

13.1.2. Safety Pharmacology

Safety pharmacology studies did not indicate any adverse effects on CNS, cardiovascular, or respiratory endpoints in male cynomolgus monkeys administered a single ascending dose of eplontersen of up to 24 mg/kg by SC injection.

13.1.3. PK/ADME

PK parameters were evaluated following SC dosing in cynomolgus monkeys and Sprague Dawley (SD) rats administered [^{3}H]ASO-eplontersen or [^{3}H]THA-eplontersen. In monkey, eplontersen peaked in plasma at 1-2 h postdose, then distributed extensively to liver and kidney

as the unconjugated form and was excreted in urine primarily as the fully conjugated form. Low levels of linker-related metabolites (M5, M7, M8, and M12) and shortmer metabolites of eplontersen were observed in monkey plasma and tissues (liver and kidney), respectively. Additionally, both oligonucleotide metabolites (i.e., shortmer metabolites of eplontersen) and linker metabolites (i.e., M5 and M8) were observed in monkey urine.

In SD rats administered [^{3}H]ASO-eplontersen, radioactivity levels peaked in plasma at 0.5 h postdose, then distributed into tissues, primarily liver and kidney, with the highest levels observed in the liver at 8 h and kidney at 2 days; radioactivity was undetectable in brain and spinal cord. Excretion of radioactivity in rat was slow and occurred primarily via urine, with an overall recovery of radioactivity of 89% of the administered dose throughout the 56-day observation period, with 59.4% accounted for by urine. Fully conjugated and unconjugated eplontersen were the major components in blood and plasma at 2 h postdose. Unconjugated eplontersen was the major component in tissues (liver and kidney) at 24 h postdose, along with several shorter metabolites of unconjugated eplontersen, which were present as major components in urine and consistent with nuclease-mediated metabolism of the nucleotide moiety of eplontersen.

In SD rats administered [^{3}H]THA-eplontersen, radioactivity levels peaked in plasma at 1 h postdose, then distributed rapidly into tissues, primarily liver, kidney, and GI tract, reaching peak concentrations at 2 h; radioactivity was undetectable in brain and spinal cord. Excretion of radioactivity in rat was rapid and occurred primarily via feces, with an overall recovery of radioactivity of 90% of the administered dose at 24 h postdose, with 80.2% accounted for by feces. Low levels of linker-related metabolites were observed in monkey plasma (only M5 and M8 at 2 h), liver (main observed metabolite M8 at 2 h), and kidney (main observed metabolites were M5 and M8 at 2 h and 24 h). The most abundant linker-related metabolites in feces were M12, M11, M10, M9, M6, M5, and M8, and M8 was the most abundant linker-related metabolite in urine. The linker-associated metabolites were generated via hydrolysis, dephosphorylation, desaturation, dealkylation, acetylation, deamination, dehydration, oxidation, and conjugation.

In vitro studies demonstrated that plasma protein binding of eplontersen was high (>96%) in mouse, monkey, and human, and that eplontersen did not act as a substrate or inhibitor of any of the transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP) or as an inducer of CYPs 1A2, 2B6, and 3A4 or inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

13.1.4. General Toxicology

13.1.4.1. Study 682884-AS01, 13-Week Repeat Dose Toxicity Study of ION-682884 in Mice With a 13-Week Recovery Period (GLP)

In a 13-week study in CD-1 mice, eplontersen (0, 5, 25, or 75 mg/kg SC QW) resulted in cytoplasmic alteration in the liver at the MD and HD, basophilic granules in liver Kupffer cells in MDF, HDM, and HDF, and kidney tubular cells at the MD and HD, and vacuolated/granular macrophages at the skin/injection sites at all doses. All effects were at least partially reversed during the 13-week recovery period.

13.1.4.2. Study 682884-AS04, 26-Week Subcutaneous Toxicity Study of ION-682884 and ION-1184986 in Mice With a 13-Week Recovery Period (GLP)

In a 26-week study in CD-1 mice, eplontersen (0, 10, 50, or 150 mg/kg SC Q2W) resulted in decreases in IgG at the high dose (HD), basophilic granules in kidney tubular cells at all doses, and vacuolated/granular macrophages in the liver at the HD, injection sites at all doses except the LD in M, skin at the mid dose (MD) and HD, testes in MDM and HDM, epididymides in HDM, and lymph nodes in HDM. No drug-related histopathological findings were observed following a 13-week recovery period. The NOAEL in the 26-week study in mouse was 150 mg/kg. A parallel group administered 10 mg/kg SC ION-1184986, the mouse-specific ASO, showed reduction of ~82% in hepatic TTR mRNA, compared to controls; no adverse effects were observed.

13.1.4.3. Study 682884-AS02, 13-Week Repeat Dose Toxicity Study of ION-682884 in Cynomolgus Monkeys With a 13-Week Recovery Phase (GLP)

In a 13-week study in cynomolgus monkeys, eplontersen (0, 2, 6, or 24 mg/kg SC QW) resulted in thrombocytopenia and secondary hemorrhage in 1 HDF, increases in complement Bb in control F and HDF, basophilic granules in liver Kupffer cells at the MD and HD, and granular macrophages in the lymph nodes at all doses. All changes showed at least partial reversibility during the 13-week recovery period. Dose-dependent reductions in hepatic TTR mRNA expression and plasma TTR and RBP4 protein levels (up to 62, 68, and 60%, respectively) were observed following 13 weeks of treatment.

13.1.4.4. Study 682884-AS05, 9-Month Repeat Dose Toxicity Study of ION-682884 in Cynomolgus Monkeys With a 3-Month Recovery Phase (GLP)

In a 39-week study in cynomolgus monkeys, eplontersen (0, 5, 10, or 25 mg/kg SC Q4W) resulted in an increase in complement Bb in HDM, basophilic granules in liver Kupffer cells and kidney tubular cells at the HD, and granular macrophages in the lymph nodes at all doses. No adverse effects were observed following a 39-week recovery period. The NOAEL in the 39-week study in monkey was 25 mg/kg. Dose-dependent reductions in hepatic TTR mRNA expression and plasma TTR and RBP4 protein levels (up to 62, 52, 29%, respectively) were observed following 39 weeks of treatment. Genetic Toxicology

13.1.5. Genetic Toxicology

Eplontersen was negative in adequately conducted in vitro (Ames, chromosomal aberration) and in vivo (mouse bone marrow micronucleus) assays.

13.1.6. Carcinogenicity

13.1.6.1. Study 682884-AS10P, 14-Week Repeat Dose Toxicity Study of Eplontersen in CByB6F1-Tg(HRAS)2Jic Hemizygous Transgenic Mice (Non-GLP)

To support dose selection for a 26-week study in Tg.rasH2 mice, the sponsor conducted a 14-week study in CByB6F1-Tg(HRAS)2Jic mice administered 0 (saline), 300, 600, or 1000 mg/kg eplontersen by SC injection weekly for 3 doses, then Q2W for 12 weeks. One HDM was found dead on Day 98 of uncertain cause. Increases in MCP-1 levels (up to 1.8-fold relative to controls) were observed at all doses. Drug-related histopathological findings were observed in the liver (basophilic granules in the cytoplasm of Kupffer cells at all doses except the low dose (LD) in females; karyomegaly and multinucleation of hepatocytes at all doses except the MD in females) and kidney (basophilic granules in the cytoplasm of tubular epithelial cells in HDF).

13.1.7. Reproductive and Developmental Toxicology

13.1.7.1. Study 682884-AS07, Combined Fertility and Embryofetal Development Study of ION-682884 and ION-1184986 in Mice Via Subcutaneous Administration (GLP)

In a combined fertility and developmental toxicity study in CD-1 mice, eplontersen (0, 5, 25, or 75 mg/kg SC QW for 28 days prior to mating and continuing for 10 weeks in males and QW for 14 days prior to mating and continuing Q2D through gestation day (GD) 16 in females) resulted in kidney cysts in HDF that correlated with increased kidney weight, and an increase in fetal weight in the MD group relative to controls. The NOAEL for effects on fertility, maternal toxicity, and fetal development in mouse was 75 mg/kg/week. A parallel group administered 25 mg/kg/week SC ION-1184986, the mouse-specific ASO, showed reductions of 93 and 97% in hepatic TTR mRNA in males and females, respectively, compared to controls; no adverse effects were observed.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. General Toxicology

13.2.1.1. Study 682884-RS02, 18-Week Repeat Dose Maximum Tolerated Dose Toxicity Study of ION-682884 in Mice (Non-GLP)

Male and female CD1 mice (6-12/sex/group) were administered doses of 0 (saline), 300, 600, or 1000 mg/kg eplontersen by SC injection on Days 0, 7, and 14 then every other week starting on Day 28 and continuing to Day 126. Increases in MCP-1 (up to 2-fold) and TNF-α (up to 1.9-fold)

levels were observed at all doses, relative to controls. Hypertrophy of hepatocytes, hypertrophy/ hyperplasia of granular/vacuolated Kupffer cells, and increased splenic cellularity of germinal centers were observed at MD and/or HD. Increases in tissue concentrators of unconjugated eplontersen in the kidney and liver were less than dose proportional.

Toxicokinetics

Table 66. Study 682884-RS02 Toxicokinetic Data

Dose Level (mg/kg)	Kidney		Liver	
	Male	Female	Male	Female
300	252 ± 66.9	536 ± 192.6	269 ± 74.9	277 ± 80.5
600	365 ± 191.9	1071 ± 419.4	481 ± 127.8	295 ± 92.1
1000	504 ± 220.4	964 ± 328.2	410 ± 76.1	320 ± 38.5

Source: Applicant's table.

13.2.2. Impurities

13.2.2.1. Study 682884-AS09, 13-Week Repeat Dose Subcutaneous Toxicity and Impurity Qualification Study of ION-682884 and Associated TAMs in ICR Mice

Table 67. Study 682884-AS09 Information

Study Feature	Details
Study no.:	682884-AS09
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 08, 2021
GLP compliance:	Yes
QA statement:	Yes
Lot Numbers	**ION-682884** (eplontersen) Lot # RP682884-024, 99.8% **ION-682884 TAM1** Lot # RP682884-025, 98.2% **ION-682884 TAM2** Lot # RP682884-026, 100.8% **ION-682884 TAM3** Lot # RP682884-027, 101.0%

Source: Generated by the FDA review team from Applicant's submission.
Abbreviations: EDR, electronic document room; GLP, good laboratory practice; TAM, test article mixture; QA, quality assurance

Table 68. Study 682884-AS09 Methods

Parameter	Method Details
Doses:	0, 200 mg/kg
Frequency of dosing:	Weekly
Route of administration:	SC injection
Dose volume:	10 mL/kg
Formulation/Vehicle:	Saline
Species/Strain:	CrljOri:CD1 (ICR) mice
Number/Sex/Group:	10/S/G
Age:	7-8 weeks
Weight:	28.8 to 34.5 g M; 24.7 to 29.7 g F
Comment on Study Design and Conduct:	None
Deviation from study protocol:	No significant deviations

Source: Generated by the FDA review team from Applicant's submission.
Abbreviations: F, female; G, group; ICR, Institute of Cancer Research; M, male; S, sex; SC, subcutaneous(ly)

Table 69. Impurities in Study 682884-AS09

Impurity	Composition (%)[a]		
	Test Article 1	Test Article 2	Test Article 3
			(b) (4)

Source: Applicant's table.

Results

Mortality, Clinical Signs, Body Weight, Food Consumption, Ophthalmoscopic Examinations

No drug-related effects on survival, clinical findings, body weights, food consumption, or ophthalmoscopic exams were observed.

Clinical Pathology

There were no drug-related effects on hematology parameters. Drug effects on clinical chemistry included increases in ALP levels in ION-682884 and TAM#3 treated groups.

Table 70. Clinical Chemistry Results

Group	G1		G2		G3		G4		G5	
Test articles	Saline		ION-682884		TAM#1		TAM#2		TAM#3	
Dose (mg/kg)	0 mg/kg		200 mg/kg		200 mg/kg		200 mg/kg		200 mg/kg	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No. examined	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)	(n=5)
Parameters (control mean or fold-increase over control or % decrease from control)										
Treatment										
ALP(IU/L)	155.3	192.7	-	1.6x*R	-	-	-	-	1.3x*D	1.6x*D

Source: Applicant's table.
Note:
- *R = Dunn Rank Sum Test significant at the 0.05 level
- +D = Dunnett LSD Test significant at the 0.01 level
- *D = Dunnett LSD Test significant at the 0.05 level

Abbreviations: ALP, alkaline phosphatase ;G, group; n, number of subjects

Gross Pathology and Organ Weights

There were no drug-related gross pathology findings. While increases in absolute and relative liver weights were observed in ION-682884 and TAM#2 treated males, increases in absolute and relative spleen weights were only observed in TAM#2 treated males.

Table 71. Organ Weight Results

Group	G1		G2		G3		G4		G5	
Test articles	Saline		ION-682884		TAM#1		TAM#2		TAM#3	
Dose (mg/kg)	0 mg/kg		200 mg/kg		200 mg/kg		200 mg/kg		200 mg/kg	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No. examined	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)
Parameters (control mean or fold-increase over control or % decrease from control)										
Treatment										
Mean body wt. (g)	40.5	33.8	1.0x	1.1x*R	1.0x	1.1x+R	1.0x	1.1x	1.0x	1.1x*R
Spleen (control mean or fold-increase over control or % decrease from control)										
Absolute wt. (g)	0.0958	0.1454	-	-	-	-	1.3x*D	-	-	-
To body wt. (%)	0.2363	0.4283	-	-	-	-	1.2x*D	-	-	-
To brain wt. (%)	20.1135	29.3670	-	-	-	-	1.3x+D	-	-	-
Liver with gall bladder (control mean or fold-increase over control or % decrease from control)										
Absolute wt. (g)	2.1084	1.7578	1.2x+D	-	-	-	1.2x+D	-	-	-
To body wt. (%)	5.2059	5.1874	1.1x +D	-	-	-	1.1x+D	-	-	-
To brain wt. (%)	441.8983	355.5472	1.2x +D	-	-	-	1.2x+D	-	-	-

Source: Applicant's table.
Note:
- *R = Dunn Rank Sum Test significant at the 0.05 level
- +D = Dunnett LSD Test significant at the 0.01 level
- *D = Dunnett LSD Test significant at the 0.05 level

Abbreviations: G, group, n, number of subjects; No., number; wt, weight

Histopathology

The battery of tissues examined was adequate. No Peer Review was conducted. A signed pathology report was provided.

Histological Findings

Drug-related histopathology findings in ION-682884, TAM#1, 2, and 3 treated groups included vacuolated histiocytes in lymph nodes, testes, and epididymides, as well as mononuclear cell infiltration in injection site.

Table 72. Terminal Sacrifice Histological Findings

Sex	Males					Females				
Group	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
Test articles	Saline	ION	TAM#1	TAM#2	TAM#3	Saline	ION	TAM#1	TAM#2	TAM#3
Dose (mg/kg)	0	200	200	200	200	0	200	200	200	200
No. examined	10	10	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR										
Vacuolated histiocyte	-	(5)	(4)	(5)	(5)	-	(3)	(7)	(4)	(5)
minimal	-	5	4	5	5	-	3	7	4	5
LYMPH NODE, INGUINAL										
Vacuolated histiocyte	-	(4)	(7)	(8)	(8)	-	(5)	(7)	(2)	(8)
minimal	-	4	7	8	8	-	5	7	2	8
LYMPH NODE, MESENTERIC										
Vacuolated histiocyte	-	(4)	(6)	(10)	(5)	-	(4)	(4)	(5)	(4)
minimal	-	4	6	10	5	-	4	4	5	4
TESTES										
Vacuolated histiocytes/interstitial	-	(10)	(10)	(10)	(10)					
minimal	-	9	5	6	6					
slight	-	1	5	4	4					
EPIDIDYMIS										
Vacuolated histiocytes/interstitial	-	(6)	(8)	(7)	(7)					
minimal	-	6	8	7	7					
INJECTION SITE(S)										
Infiltration, mononuclear cell	-	(2)	(4)	(6)	(5)	(1)	(6)	(5)	(7)	(6)
minimal	-	2	4	6	5	1	4	4	6	5
slight	-	-	-	-	-	-	2	1	1	1

Source: Applicant's table.
Abbreviations: G, group; No, number

Toxicokinetics

Levels of unconjugated ION-682884 in liver were comparable among the four formulations (ION-682884, TAM#1, 2, and 3) tested.

Table 73. Study 682884-AS09 Toxicokinetic Data

Group	Treatment	Dose Level	Tissue	Necropsy Day	N	Gender	Mean ± SD (µg/g)
G2	ION-682884	200 mg/kg	Liver	87	6	F	305.3 ± 7.9
						M	295.7 ± 72.5
G3	TAM #1	200 mg/kg	Liver	87	6	F	270.5 ± 35.6
						M	273.0 ± 34.6
G4	TAM #2	200 mg/kg	Liver	87	6	F	203.0 ± 18.4
						M	230.3 ± 26.7
G5	TAM #3	200 mg/kg	Liver	87	6	F	286.0 ± 53.4
						M	310.2 ± 35.3

Source: Applicant's table.
Abbreviations: F, female; G, group; M, male; N, number of subjects; SD, standard deviation

14. Clinical Pharmacology

14.1. In Vitro Studies

In vitro studies of eplontersen yielded the following findings:

- >98% of eplontersen binds to human plasma proteins and it was found to be concentration independent over a range of 0.1 to 5 µg/mL.
- Eplontersen plasma protein binding was not found to be altered by the presence of warfarin (1 and 30 µg/mL) or ibuprofen (30 and 300 µ/mL)
- Eplontersen (0.5 and 5 µg/mL) was not found to alter plasma protein binding of either warfarin or ibuprofen.
- Blood to plasma ratio of eplontersen was found to be 0.632 to 0.739 over a concertation range of 0.01 to 1 µg/mL.
- Eplontersen up to 50µM did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.
- Eplontersen up to 50µM did not induce CYP1A2, CYP2B6, or CYP3A4 enzyme as measured by mRNA levels.
- 100µM eplontersen did not significantly inhibit the activity of following transporters: OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BSEP, BCRP, or P-gp.
- Eplontersen at a concentration of 10µM was not found to be a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and BSEP.

14.2. In Vivo Studies

Eplontersen was evaluated in three completed clinical studies (ION-682884-CS1, ION-682884-CS20, and ION-682884-CS21) and two on-going clinical studies (ION-682884-CS3 and ION-

682884-CS13). A summary of clinical studies for eplontersen clinical pharmacology assessment is presented in Table 74.

Table 74. Summary of Clinical Studies for Eplontersen Clinical Pharmacology Assessment

Study Number (Status)	Study Design	Study Population	Objectives	Dosing Regimen, Route and Duration of Administration [a]	Number of Subjects Evaluable for PK
ION-682884-CS1 (completed)	Phase 1, double-blind, randomized, placebo-controlled, single- and multiple-dose study	Healthy adult subjects [b]	To evaluate the safety, tolerability, PK and PD of single and multiple doses of eplontersen administered SC	Multiple dose 45, 60, and 90 mg eplontersen or placebo Q4W (total of 4 doses) for 13 weeks Single dose 120 mg eplontersen or placebo	N = 39
ION-682884-CS20 (completed)	Phase 1, randomized, double-blinded, placebo-controlled, single-dose [c] escalation of eplontersen	Healthy adult subjects of Japanese descent	To evaluate the safety, tolerability, PK and PD of single doses of eplontersen	Single dose 45, 60, and 90 mg eplontersen or placebo	N = 18
ION-682884-CS21 (completed)	Phase 1, single-dose, randomized, open-label, 3-period, crossover study	Healthy adult subjects	To assess the bioequivalence of 45 mg eplontersen from 3 different SC drug product presentations (vial and syringe, PFS with safety device, and PFS with AI)	Periods 1, 2, and 3 eplontersen 45 mg SC with a 4-week (28 days) washout between study periods	N = 57

Continued

Table 74, continued

Study Number (Status)	Study Design	Study Population	Objectives	Dosing Regimen, Route and Duration of Administration [a]	Number of Subjects Evaluable for PK
ION-682884-CS3 (ongoing)[d]	Phase 3, global, open-label, randomized study	Adult subjects with ATTRv-PN	To evaluate the efficacy and safety of eplontersen in subjects with ATTRv-PN (i.e., primary objective) and to evaluate the trough and post-treatment concentrations of eplontersen or inotersen in all subjects and plasma PK parameters in a subset of subjects (i.e., PK objective)	Eplontersen treatment arm Eplontersen: 45 mg Q4W SC Inotersen/eplontersen reference arm Inotersen sodium (for first 34 weeks): 300 mg Q1W SC Eplontersen (from Week 37): 45 mg Q4W SC	N=168 [all subjects] (N=144 for eplontersen treatment arm and N=24 for inotersen/ eplontersen reference arm) PK subset N=35 (N=28 for eplontersen treatment arm and N=7 for inotersen/ eplontersen reference arm)

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 3.
[a] The doses of eplontersen administered in these studies are defined with respect to the eplontersen free acid. The dose of inotersen administered in the inotersen/eplontersen reference arm of Study ION 682884-CS3 is defined with respect to inotersen sodium, with inotersen sodium 300 mg equivalent to 284 mg inotersen free acid.
[b] The Study ION-682884-CS1 protocol included an open-label, multi-center cohort in which eplontersen was to be administered to patients with ATTRv-PN. However, due to a shortage of suitable subjects, this cohort was not initiated.
[c] The multiple-dose cohort proposed in the Study ION-682884-CS20 protocol was not initiated because the single-dose results were sufficiently similar to those in Study ION-682884-CS1 in healthy subjects of non-Japanese descent.
[d] The interim analysis data cutoff dates for Study ION-682884-CS3 were 18 April 2022 for the PK, PD, and efficacy data and 19 July 2022 for the post hoc safety and immunogenicity data.
AI, autoinjector; ATTR, transthyretin-mediated amyloidosis; ATTRv, hereditary ATTR; ATTRv-PN, polyneuropathy of ATTRv; PD, pharmacodynamics; PFS, prefilled syringe; PD; pharmacodynamics; PK, pharmacokinetics; Q4W, once every 4 weeks; Q1W, once a week; SAD, single ascending dose; SC, subcutaneous.

14.2.1. ION-682884-CS1

ION-682884-CS1 was a first-in-human Phase 1, double-blind, randomized, placebo-controlled, dose-escalation study conducted in healthy volunteers. The objectives of the study were to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple doses of eplontersen following subcutaneous administration. The study included three multiple-dose cohorts (Cohorts A, B, and E) and a single-dose cohort (Cohort C).

Multiple-Dose Cohorts

A total of 36 subjects completed the multiple-dose portion of the study. In each cohort, 12 subjects were randomized to treatment and placebo in a ratio of 10:2.

- Cohort A: 10 subjects received 45 mg of eplontersen and 2 subjects received placebo once every 4 weeks for 12 weeks (4 doses).
- Cohort B: 10 subjects received 90 mg of eplontersen and 2 subjects received placebo once every 4 weeks for 12 weeks (4 doses).
- Cohort E: 10 subjects received 60 mg of eplontersen and 2 subjects received placebo once every 4 weeks for 12 weeks (4 doses).

Single-Dose Cohort

A total of 11 subjects were randomized to eplontersen or placebo at a ratio of 9:2 and received a single dose of 120 mg eplontersen or a matching placebo. For this study active treatment or placebo were presented in vial and syringe format. The dose range (45 mg to 120 mg) of eplontersen has a safety margin 14 to 37-fold compared to no observed adverse effect level 6 mg/kg/wk. Intensive plasma PK samples were collected from all subjects in the single-dose cohort and following the first and last dose in the multiple-dose cohorts to assess plasma PK. Urine samples for the determination of eplontersen concentrations were collected over a 24-hour interval following dose administration on day 1 in the single-dose and multiple-dose cohorts and following the last dose in the multiple-dose cohorts.

Results

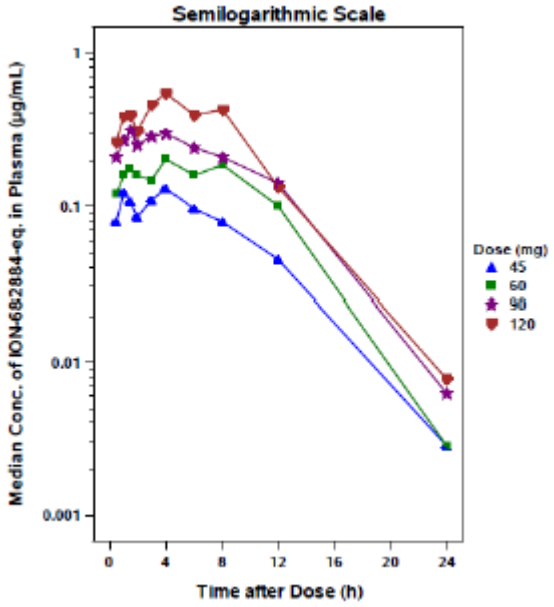
Pharmacokinetics

Intact fully conjugated eplontersen was the most abundant circulating species in human plasma and accounted for >99% of total detected full-length oligonucleotides. No shorter oligonucleotide metabolites (oligonucleotide missing one or more nucleotides) were detected in plasma. Figure 6 shows the median eplontersen-equivalent concentrations in plasma over 24 hours (A) and full profile following the first or single dose and following the last dose of eplontersen in the multiple-dose cohorts (B).

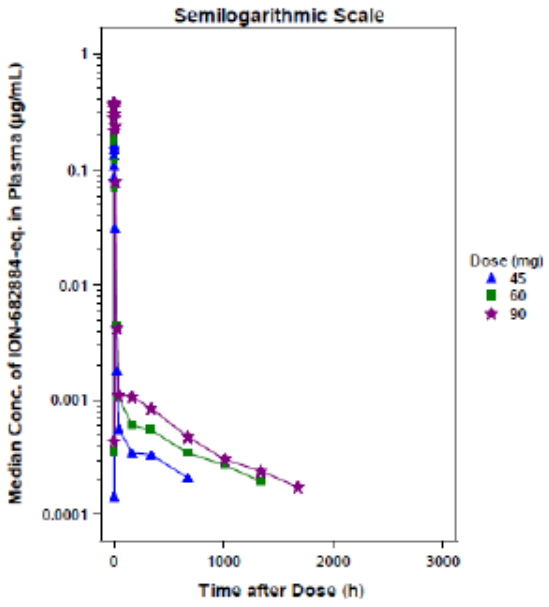
A summary of plasma PK parameters on eplontersen is presented in Table 75. Eplontersen was absorbed with a time to maximum concentration of 1-6 hours. The mean maximum plasma concentration (C_{max}) and AUC increased proportionally to slightly greater than dose proportionally over 45 mg to 120 mg. The elimination half-life of eplontersen in plasma was approximately 3 to 4 weeks after multiple doses.

Figure 6. (A) Median Plasma Concentrations of Eplontersen-Equivalent vs. Time by Dose Following the Single/First SC Administration (B) Median Plasma Concentrations of Eplontersen-Equivalent vs. Time by Dose Following the Last SC Administration in the Multiple-Dose Cohorts

A



B



Source: Clinical Study Report ION-682884-CS1, Figures 3 and 4.
Abbreviations: Conc., concentration; SC, subcutaneous(ly)

Table 75. Summary of Plasma Pharmacokinetic Parameters of Eplontersen-Equivalent in Healthy Subjects

Cohort	Dose[a] (mg)	Study Day	N	C_{max} (ug/mL)	T_{max} (h)	AUC_{0-24h} (ug*h/mL)	AUC_{τ}[b] (ug*h/mL)	%AUC_{extr} (%)	CL_{0-24h}/F[c] (L/h)	CL_{ss}/F[d] (L/h)	V_z/F (L)	$t_{½\lambda z}$[e] (day)
A	45	1	10	0.143 (39.3)	2.01 (1.00, 4.00)	1.21 (24.1)	NC	NC	37.3 (24.1)	NC	NC	NC
A	45	85	10	0.215 (66.1)	3.00 (1.00, 3.00)	1.40 (35.4)	1.81 (36.3)	NC	32.1 (35.4)	24.8 (36.3)	18662 (64.0)	22.0 (72.1)
E	60	1	10	0.239 (62.6)	6.00 (3.00, 12.0)	2.42 (43.2)	NC	NC	24.8 (43.2)	NC	NC	NC
E	60	85	10	0.282 (74.5)	1.00 (1.00, 3.00)	2.26 (47.5)	2.73 (43.2)	NC	26.6 (47.5)	22.0 (43.2)	22115 (55.3)	30.6 (33.9)
B	90	1	10	0.332 (43.6)	2.25 (1.00, 6.00)	3.26 (33.5)	NC	NC	27.6 (33.5)	NC	NC	NC
B	90	85	10	0.471 (69.5)	3.00 (1.00, 8.00)	3.64 (49.8)	4.35 (43.2)	NC	24.7 (49.8)	20.7 (43.2)	15664 (24.7)	24.3 (30.8)
C	120	1	9	0.542 (65.0)	4.00 (1.00, 8.00)	4.93 (42.7)	6.78 (20.3)	2.29 (54.5)	24.3 (42.7)	17.7 (20.3)	11137 (40.8)	18.2 (40.0)

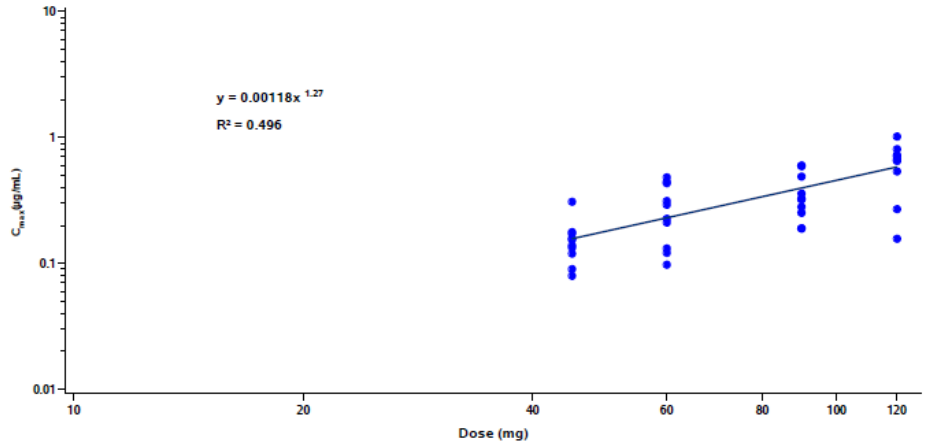
Source: Clinical Study Report ION-682884-CS1, Table 11.
[a] Cohort C received a single dose, Cohorts A, B, and E were dosed once monthly
[b] τ is 672 h for Cohorts A, B, and E, while AUC $_{0-\infty}$ was presented for Cohort C
[c] CL_{0-24h}/F = Actual Dose/AUC_{0-24h}
[d] CL_{ss}/F = Actual Dose/AUC_{τ} for Cohorts A, B, and E, while CL/F was presented for Cohort C
[e] Subject's $t_{½\lambda z}$ was not included in descriptive statistics if the r-square adjusted < 0.8 or less than 3 data points in the elimination phase because λz cannot be accurately defined.
Note: Data presented are geometric mean (geometric %CV) except T_{max}, which is presented as median (minimum, maximum).
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; %CV, percent coefficient of variation; N, number of subjects; NC, not calculated; $t_{1/2\lambda z}$, terminal half-life; T_{max}, time to maximum concentration; V_z/F, apparent volume of distribution

Dose Proportionality

Per the Applicant's analysis, eplontersen exposure (C_{max} and AUC) increased slightly greater than proportionally with dose at doses ranging from 45 to 120 mg (slope of 1.27 for C_{max} and 1.26 for AUC using linear regression analyses of the log-transformed data) Figure 7 and Figure 8. The reviewer independently analyzed the dose proportionality between C_{max} or AUC_{τ} after the first

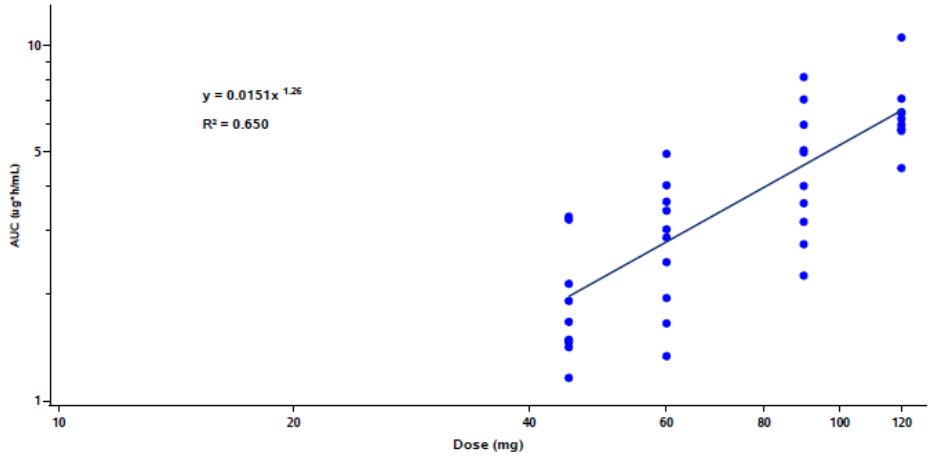
dose versus natural logarithm of dose using power model. Results confirmed a more than dose proportional increase in C_{max} and AUC_{τ}.

Figure 7. Analysis of Dose Proportionality Between C_{max} and Dose



Source: Clinical Study Report ION-682884-CS1, Figure 14.2.2.3-1.
Note: Day 1 C_{max} values were plotted against dose.
Abbreviations: C_{max}, maximum plasma concentration

Figure 8. Analysis of Dose Proportionality and Dose



Source: Clinical Study Report ION-682884-CS1, Figure 14.2.2.3-2.
Note: AUC_{T} was used for the 45, 60, and 90 mg multiple dose cohorts while $AUC_{0-\infty}$ was used for the 120 mg single dose cohort.
Abbreviations: AUC, area under the concentration-time curve

Urinary Excretion

Urinary excretion of total full-length antisense oligonucleotide (ASO) within the first 24 hours represented a small fraction of the administered dose (<1% of administered dose) and was dose-independent as showed in Table 76.

Table 76. Summary of Urine Pharmacokinetic Parameters of Eplontersen-Equivalent in Healthy Subjects

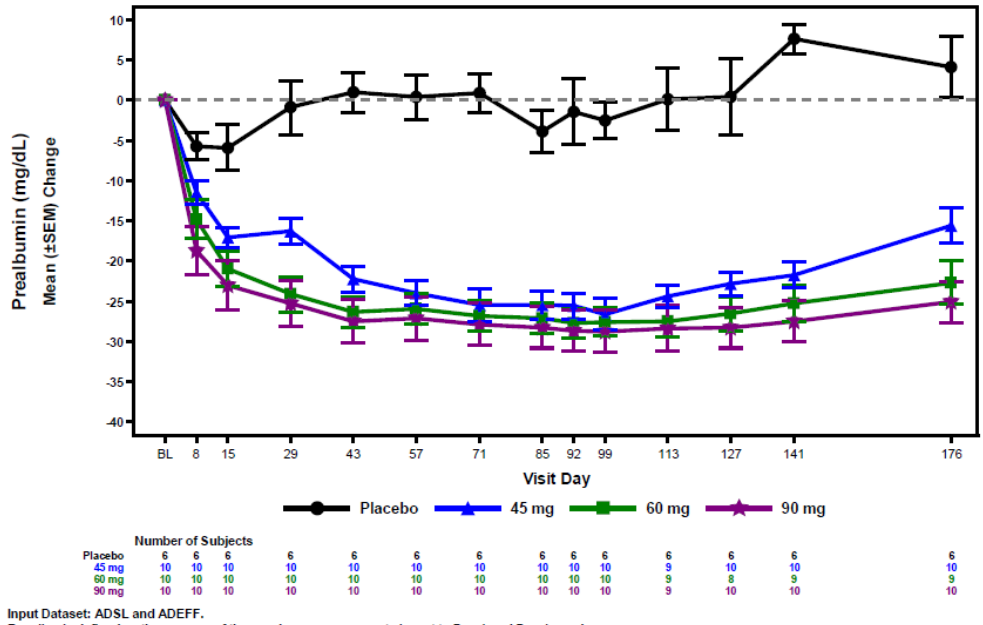
Cohort	Dose[a] (mg)	Study Day	N	Ae_{0-24h}[b] (ug)	% Dose Excreted (%)	CLr[c] (mL/h)
A	45	1	10	17.0 (54.1)	0.0377 (54.1)	14.1 (57.1)
		85	10	40.6 (38.0)	0.0903 (38.0)	29.0 (61.4)
E	60	1	10	23.5 (62.3)	0.0392 (62.3)	9.72 (56.2)
		85	10	68.3 (57.2)	0.114 (57.2)	30.3 (36.4)
B	90	1	10	29.9 (146)	0.0332 (146)	9.16 (157)
		85	9	133 (33.8)	0.147 (33.8)	37.4 (37.7)
C	120	1	9	87.4 (87.9)	0.0728 (87.9)	17.7 (90.9)

Source: Clinical Study Report ION-682884-CS1, Table 12.
[a] Cohorts C received a single dose, Cohorts A, B and E were dosed once monthly
[b] Ae_{0-24h} = amount excreted in the urine over a 24-hour period (i.e., 0 to 24 hours)
[c] CLr = renal clearance over a 24-hour period (i.e., 0 to 24 hours)
Note: Data presented are geometric mean (geometric %CV).
Abbreviations: %CV, percent coefficient of variation; N, number of subjects

Pharmacodynamics

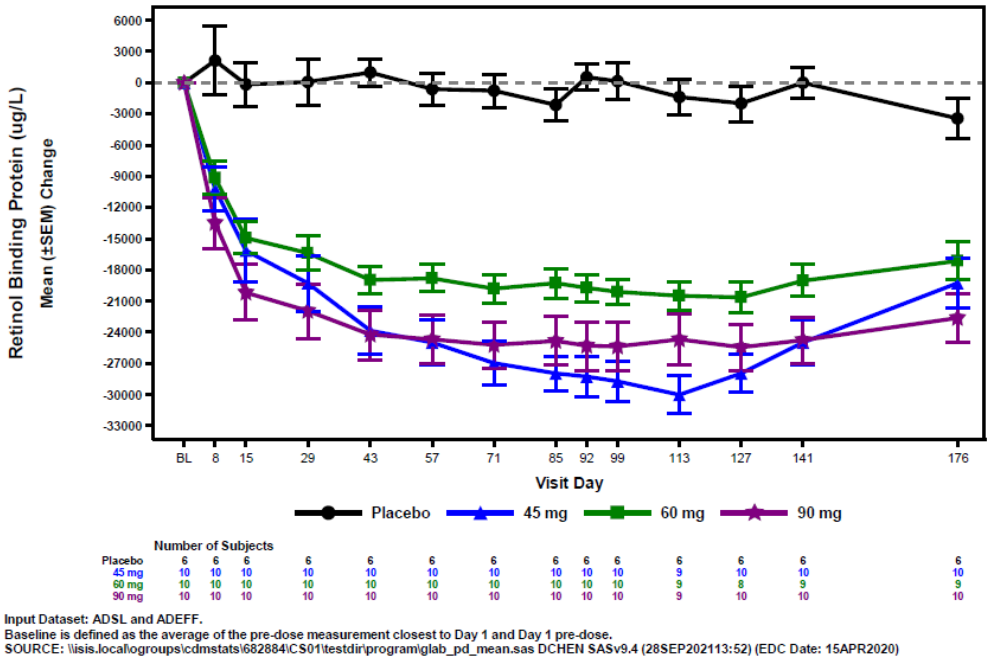
The mean percent change in TTR from baseline in the 45, 60 and 90 mg treatment cohorts was -86%, -91% and -94%, respectively, 2 weeks after the last dose [day 99] (Figure 9). The mean percent change in RBP4 from baseline in the 45, 60 and 90 mg treatment cohorts was -77%, -79% and -84%, respectively, 2 weeks after the last dose [day 99] (Figure 10).

Figure 9. Mean (± SEM) Percent Change From Baseline in Transthyretin (Prealbumin) Over Time for Multiple-Dose Cohorts (Full Analysis Set)



Source: Clinical Study Report ION-682884-CS1, Figure 14.2.1.1.1-1b.

Figure 10. Mean (± SEM) Percent Change From Baseline in RBP4 (Retinol Binding Protein) Over Time for Multiple-Dose Cohorts (Full Analysis Set)



Source: Clinical Study Report ION-682884-CS1, Figure 14.2.1.1.1-1b.
Abbreviations: SEM, standard error of the mean

14.2.2. ION-682884-CS21

This was a single dose, randomized, open-label, three-period crossover, bioequivalence study comparing three subcutaneous formulations: vial and syringe, prefilled syringe with safety device (PFS) and prefilled syringe with autoinjector (PFS-AI) with eplontersen (ION-682884) in healthy adult participants. The objective of the study was to assess the bioequivalence of eplontersen PK resulted from 3 different SC drug product presentations (vial and syringe (reference), PFS (treatment A), and PFS-AI (treatment B) with a single dose of 45 mg.

The products were studied using a crossover design in healthy male and female subjects who were not of childbearing potential. Subjects were randomized to the three treatments, which were administered with a 28-day washout period. Intensive plasma PK samples were collected from all available subjects up to 168 hours post-dose in each period, and during the post-treatment period up to day 148. Serum PD samples for TTR protein were collected for all subjects from screening through day 148.

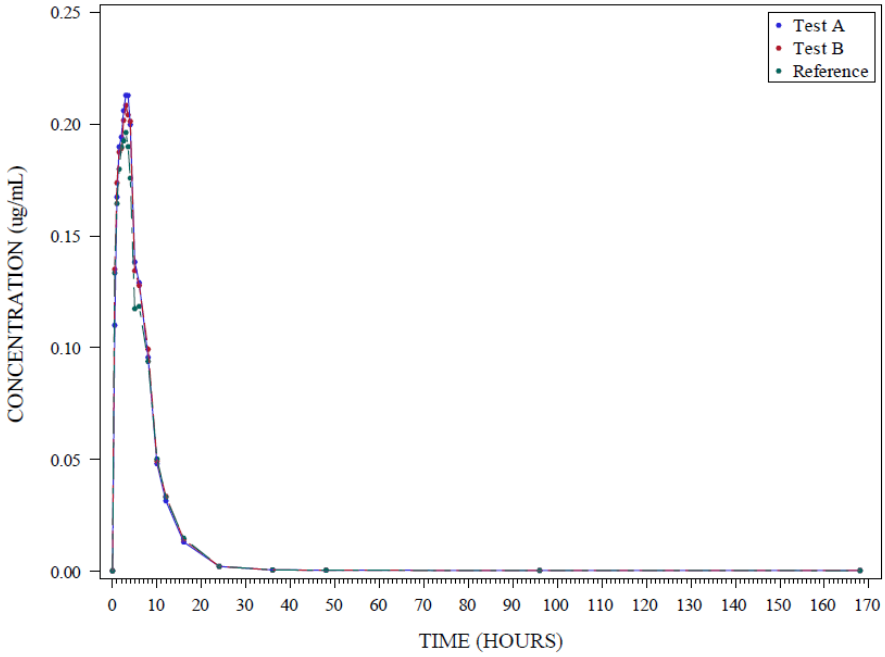
Results

A total of 57 subjects were enrolled in the study and received at least one dose of study drug (PK population). A total of 56 subjects were included in the pharmacodynamic population. Subjects received at least one test treatment and the reference treatment were included in the PK statistical population for BE evaluation (45 subjects for the PFS presentation and 47 subjects for the PFS-AI presentation and vial and syringe presentation).

Pharmacokinetics

Figure 11 shows geometric mean plasma concentration-time profiles of eplontersen by treatment and Table 77 shows descriptive statistics of pharmacokinetic parameters for plasma eplontersen by period and treatment. The geometric LSMs and ratios for eplontersen $AUC_{0\text{-}168h}$ comparing PFS (Treatment A) to vial and syringe (Treatment C, reference) and comparing Treatment B (PFS with AI) to vial and syringe (Treatment C, reference) are presented in Table 78 and Table 79, respectively.

Figure 11. Geometric Mean Plasma Eplontersen – Time Profile in Linear Scale by Treatment



Source: ION-682884-CS20 Clinical Study Report, page 44, Figure 2
Note:

- Test A: Treatment A or prefilled syringe with safety device (PFS)
- Test B: Treatment B or prefilled syringe with autoinjector (PFS-AI)
- Reference: Treatment C or vial and syringe

Table 77. Descriptive Statistics of Pharmacokinetic Parameters for Plasma Eplontersen by Period and Treatment (PK Statistical Population)

Treatment	A PFS with safety device				B PFS with AI				C Vial and syringe			
PK Parameter	N	$AUC_{0\text{-}168h}$ (µg•h/mL) Geometric mean (%CV)	C_{max} (µg/mL) Geometric mean (%CV)	T_{max} (h) Median (min, max)	N	$AUC_{0\text{-}168h}$ (µg•h/mL) Geometric mean (%CV)	C_{max} (µg/mL) Geometric mean (%CV)	T_{max} (h) Median (min, max)	N	$AUC_{0\text{-}168h}$ (µg•h/mL) Geometric mean (%CV)	C_{max} (µg/mL) Geometric mean (%CV)	T_{max} (h) Median (min, max)
Period 1	16	1.851 (33.92)	0.243 (69.75)	3.50 (2.000, 8.017)	15	1.964 (25.49)	0.287 (54.33)	3.00 (1.500, 8.000)	16	1.561 (26.74)	0.195 (64.23)	2.50 (1.000, 8.000)
Period 2	16	1.588 (23.60)	0.218 (41.51)	3.00 (1.000, 4.000)	16	1.751 (25.36)	0.242 (41.20)	2.75 (1.500, 4.000)	15	1.787 (18.56)	0.248 (40.19)	3.00 (1.000, 8.000)

Treatment	A PFS with safety device				B PFS with AI				C Vial and syringe			
Period 3	13	1.973 (20.14)	0.295 (41.37)	3.00 (1.500, 8.000)	16	1.714 (22.54)	0.228 (40.75)	3.00 (0.500, 8.000)	16	1.705 (28.48)	0.211 (51.14)	2.50 (1.000, 3.500)
All periods combined	45	1.786 (27.88)	0.247 (52.97)	3.00 (1.000, 8.017)	47	1.803 (24.71)	0.250 (45.68)	3.00 (0.500, 8.000)	47	1.68 (25.17)	0.216 (52.58)	2.50 (1.000, 8.000)

Source: ION-682884-CS21 Clinical Study Report, page 48, Table 7.
Note on treatments administered:

- Treatment A 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen

Abbreviations: AI, autoinjector; $AUC_{0\text{-}168h}$, area under the concentration-time curve from time 0 to 168 hours postdose; C_{max}, maximum plasma concentration; %CV, percent coefficient of variation; N, number of subjects; PFS, prefilled syringe; PK, pharmacokinetic(s); T_{max}, time to maximum concentration

Table 78. Analysis Results for Plasma Eplontersen, Treatment A (Prefilled Syringe With Safety Device) vs. Treatment C (Vial and Syringe) (PK Statistical Population)

	Geometric LSM		Percentage Geometric Mean Ratio (%)	90% CI	Intrasubject CV (%)
	Treatment A PFS with safety device N = 45	Treatment C Vial and syringe N = 47			
$AUC_{0\text{-}168h}$ (µg•h/mL)	1.844	1.743	105.79	100.63, 111.22	11.04
C_{max} (µg/mL)	0.264	0.232	113.96	99.95, 129.94	29.48

$AUC_{0\text{-}168h}$ = area under the curve from time 0 to 168 hours post-dose; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; LSM = least squares mean; PFS = prefilled syringe; PK = pharmacokinetic(s).
Treatments administered: Treatment A, 0.8 mL × 56 mg/mL ION-682884; Treatment B, 0.8 mL × 56 mg/mL ION-682884; and Treatment C, 0.3 mL × 150 mg/mL ION-682884.
Source: ION-682884-CS21 Clinical Study Report, page 49, Table 8.
Note on treatments administered:

- Treatment A 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen

Abbreviations: AI, autoinjector; $AUC_{0\text{-}168h}$, area under the concentration-time curve from time 0 to 168 hours postdose; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; LSM, least squares mean; N, number of subjects in treatment group; PFS, prefilled syringe; PK, pharmacokinetic(s)

Table 79. Analysis Results for Plasma Eplontersen, Treatment B (Prefilled Syringe With Autoinjector) vs. Treatment C (Vial and Syringe) (PK Statistical Population)

	Geometric LSM		Percentage Geometric Mean Ratio (%)	90% CI	Intrasubject CV (%)
	Treatment B PFS with AI N = 47	Treatment C Vial and syringe N = 47			
$AUC_{0\text{-}168h}$ (µg•h/mL)	1.858	1.743	106.64	101.47, 112.07	11.04
C_{max} (µg/mL)	0.261	0.232	112.51	98.76, 128.17	29.48

Source: ION-682884-CS21 Clinical Study Report, page 50, Table 9.
Note on treatments administered:

- Treatment A 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen

Abbreviations: AI, autoinjector; $AUC_{0\text{-}168h}$, area under the concentration-time curve from 0 to 168 hours postdose; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; LSM, least squares mean; N, number of subjects in treatment group; PFS, prefilled syringe; PK, pharmacokinetic(s)

Pharmacodynamics

As presented in Table 80, following single dose treatment of eplontersen irrespective of method of drug presentation, serum TTR reduction (pharmacodynamic endpoint) was observed starting from day 8 and maximum reduction in TTR was observed at day 29 with a mean percent change in TTR reduction from baseline of 69% for treatment A, 57.6% for treatment B, and 58.7% for treatment C. However, there is no significant difference in the TTR reduction between the drug presentation from treatment C versus treatment A (Table 81) and treatment B versus treatment C (Table 82).

Table 80. Percent Change From Baseline (%) in Serum Transthyretin Protein by Treatment (PD Population)

Treatment	A PFS with Safety Device	B PFS with AI	C Vial and Syringe
Baseline Level (mg/dL)	n = 19	n = 18	n = 19
Mean (SD)	22. 98 (5.42)	22.57 (4.62)	24.32 (5.35)
Median (min, max)	22.30 (15.45, 39.40)	22.68 (13.85, 32.80)	25.50 (13.85, 33.95)
Day 8 (%)	n = 19	n = 18	n = 18
Mean (SD)	-42.85 (14.45)	-35.21 (16.81)	-36.11 (11.17)
Median (min, max)	-43.18 (-65.93, -18.58)	-37.87 (-58.99, -11.79)	-35.02 (-59.29, -16.63)
Day 15 (%)	n = 18	n = 18	n = 19
Mean (SD)	-62.18 (15.81)	-54.08 (18.91)	-54.53 (15.32)
Median (min, max)	-62.44 (-88.09, -35.40)	-55.23 (-80.45, -12.74)	-59.23 (-78.59, -29.81)

Treatment	A PFS with Safety Device	B PFS with AI	C Vial and Syringe
Day 29 (%)	n = 16	n = 15	n = 16
Mean (SD)	-69.00 (15.85)	-57.60 (17.93)	-58.72 (16.94)
Median (min, max)	-69.36 (-94.26, -39.13)	-54.73 (-85.98, -29.31)	-59.29 (-83.80, -31.08)

Source: ION-682884-CS21 Clinical Study Report, page 51, Table 11
Note on treatments administered:
- Treatment A 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen

Abbreviations: AI, autoinjector; max, maximum; min, minimum; SD, standard deviation; n, number of subjects in treatment group at specified study timepoint; PD, pharmacodynamic(s); PFS, prefilled syringe

Table 81. Analysis of Covariance for Serum Transthyretin Percent Reduction From Baseline, Treatment A (Prefilled Syringe With Safety Device) vs. Treatment C (Vial and Syringe) (PD Population)

Day	N	Least Square Mean		Least Square Mean Difference	Standard Error	95% CI	p-Value
		Treatment A PFS with safety device	Treatment C Vial and syringe				
8	18	-42.83	-36.17	-6.6665	4.80116	-16.3053, 2.9722	0.1710
15	19	-62.08	-54.78	-7.2995	5.57864	-18.4991, 3.9000	0.1966
29	16	-68.96	-58.88	-10.0821	6.03279	-22.2483, 2.0842	0.1019

Source: ION-682884-CS21 Clinical Study Report, page 52, Table 12
Note on treatments administered:
- Treatment A, 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen.

Abbreviations: CI, confidence interval; PD, pharmacodynamic(s); N, number of subjects; PFS, prefilled syringe

Table 82. Analysis of Covariance for Serum Transthyretin Percent Reduction From Baseline, Treatment B (Prefilled Syringe With Autoinjector) vs. Treatment C (Vial and Syringe) (PD Population)

Day	N	Least Square Mean		Least Square Mean Difference	Standard Error	95% CI	p-Value
		Treatment B PFS with AI	Treatment C Vial and syringe				
8	18	-35.17	-36.17	0.9981	4.88780	-8.8146, 10.8108	0.8390
15	19	-53.90	-54.78	0.8815	5.59613	-10.3532, 12.1162	0.8755

Day	N	Least Square Mean		Least Square Mean Difference	Standard Error	95% CI	p-Value
		Treatment B PFS with AI	Treatment C Vial and syringe				
29	16	-57.47	-58.88	1.4086	6.14348	-10.9809, 13.7981	0.8197

Source: ION-682884-CS21 Clinical Study Report, page 53, Table 13
Note on treatments administered:

- Treatment A, 0.8 mL x 56 mg/mL eplontersen
- Treatment B, 0.8 mL x 56 mg/mL eplontersen
- Treatment C, 0.3 mL x 150 mg/mL eplontersen

Abbreviations: AI, autoinjector; CI, confidence interval; PD, pharmacodynamics; PFS, prefilled syringe

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspection for Study ION-682884-CS21. The OSIS conducted a remote regulatory assessment of the analytical portion of Study ION-682884-CS21 and noted that no objectionable conditions observed during remote regulatory assessment, therefore clinical and PK data from the study are reliable (refer to the OSIS review, dated September 25, 2023).

14.2.3. ION-682884-CS3

ION-682884-CS3 was a Phase 3 global, open-label, randomized study with external control and an active reference arm (inotersen, followed by eplontersen) in subjects with Stage 1 and Stage 2 hATTR-PN. The primary objectives of the study were to evaluate the efficacy and safety of eplontersen in patients with hATTR-PN. One of the additional/exploratory objectives of the study are to evaluate the trough and post-treatment concentrations of eplontersen or inotersen in all subjects and plasma PK parameters in a subset of subjects (refer to Section 6.2.1.1 for the study design).

As showed in Figure 1, subjects were randomized 6:1 to receive SC injections of either 45 mg eplontersen once every four weeks (Q4W) through the end-of-treatment (EOT) period or 300 mg inotersen (equivalent to 284 mg inotersen free acid) Q1W up to and including week 34, followed by dosing with eplontersen 45 mg Q4W from week 37 through the EOT period.

A total of 168 subjects were enrolled in the study, 144 subjects were randomized in the eplontersen arm, and 24 subjects were randomized in the inotersen arm. A total of 35 (out of the 168) subjects were enrolled in the PK subgroup, 28 in the eplontersen arm and 7 in the inotersen arm. An interim analysis for efficacy was conducted when the last ongoing subject progressed past Week 35, i.e., April 18, 2022, when the first data cut was made. All PK and PD data cutoff date was the same as that for efficacy. The post hoc safety and immunogenicity data cutoff date was on July 19, 2022.

Results

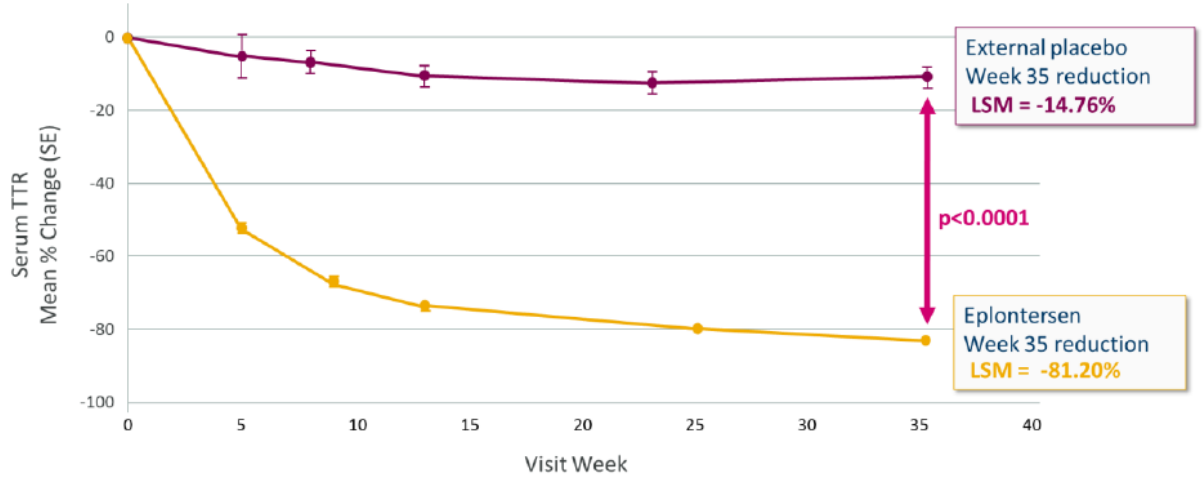
Pharmacokinetics

Blood samples for sparse PK are being collected in the ongoing Phase 3 study. Population PK and PD data are analyzed and summarized in the Pharmacometrics section. See Section 14.5 for details.

Pharmacodynamics

Pharmacodynamic analyses included comparison of change from baseline in TTR between eplontersen and ISIS 420915-CS2 placebo groups. With once every 4 week dosing of 45 mg eplontersen, mean serum TTR protein was decreased at Week 5, which was the first post-dose assessment, with continued decrease up to the interim analysis time point of Week 35, where the LSM (standard error [SE]) for percent change from baseline in TTR was -81.20 (1.70) in the eplontersen group and -14.76 (1.98) in the external placebo group (Figure 12). The LSM difference for percent change from baseline at Week 35 between eplontersen and external placebo was statistically significant: 66.43 (95 % confidence interval [CI] -71.39, -61.47; p <0.0001).

Figure 12. Mean (±SE) Percent Change of Serum TTR (g/L) Over Time up to Week 35



Source: Eplontersen Investigator's Brochure, Revision 4, Page 72, Figure 11.
Abbreviations: LSM, least squares mean; SE, standard error; TTR, transthyretin

14.3. Bioanalytical Method Validation and Performance

Quantification of Eplontersen Concentrations in Human Plasma

Full-length ASO concentrations in plasma samples obtained from the clinical pharmacology studies (ION-682884-CS1, ION-682884-CS3, ION-682884-CS20, and ION-28-2884-CS21) were measured using a validated hybridization electrochemiluminescence (ECL) method (Validation Report ICD 735). The method is designed to assess the total concentration of full-length ASOs, including fully conjugated, partially conjugated (i.e., eplontersen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated eplontersen. Samples were pretreated with proteinase K to eliminate potential interference from ADAs. Eplontersen in samples was hybridized to a complementary capture probe, which is biotinylated on the 3′-end. The hybridized solution was then immobilized on a streptavidin-coated Meso Scale Discovery (MSD) plate. A detection probe, which was ruthenium-labeled on the 5′-end (MSD-Tag), was added to the plate to hybridize with the unhybridized portion of the analyte.

After addition of read buffer, the plate was read on an MSD SECTOR S 600 or 6000 plate reader. The hybridization ECL is capable of quantifying both eplontersen and unconjugated eplontersen (ION-700994) equally. Eplontersen concentrations were reported as eplontersen-equivalent, i.e., eplontersen-eq (ION-682884-eq), which included fully, partially (eplontersen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated eplontersen. In ION-682884-CS1, incurred sample reanalysis was performed in 128 out of 1,264 samples, and 128 (100%) of the samples met the prespecified criteria. In ION-682884-CS3, incurred sample reanalysis was performed in 86 out of 1487 samples, and 61 (70.6%) of the samples met the prespecified criteria. In ION-682884-CS20, incurred sample reanalysis was performed in 35 samples, and 35 (100%) of the samples met the prespecified criteria.

A summary of bioanalytical method validation (682884-MV04) is presented in Table 83. Additional validation work established analyte stability in a frozen matrix for up to 132 days at -25°C and for up to 494 days at -80°C (ICD 735 Validation Report Addendum 1). There was no effect on the quantitation of eplontersen in human plasma containing dipotassium EDTA fortified to 10 µg/mL and 30 µg/mL tafamidis, which corresponds to C_{max} and three times C_{max}, respectively, of the clinical dose. (ICD 735 Validation Report Addendum 2).

Table 83. Summary of Bioanalytical Method Validation for the Quantification of Eplontersen Concentrations in Human Plasma (682884-MV04)

Analyte	ION-682884				
Matrix	Human plasma				
Anticoagulant	Dipotassium EDTA				
Minimum Required Dilution	N/A				
Method Description	Hybridization ECL				
Sample Volume (µL)	30.0-µL aliquot				
Sample Storage Temperature	-80 °C ± 10 °C				
Lower Limit of Quantitation (LLOQ)	0.0150 nM (0.129 ng/ml)				
Upper Limit of Quantitation (ULOQ)	10.0 nM (86.1 ng/mL)				
Regression, Weighting	Four-parameter logistic, 1/response²				
Standard Curve Concentrations	0.00750 to 10.0 nM (0.0645, 0.129, 0.258, 0.387, 4.30, 64.5, and 86.1 ng/mL respectively)				
QC Concentrations	0.0150, 0.0300, 0.0450, 0.500, 7.50, and 10.0 nM (0.129, 0.258, 0.387, 4.30, 64.5, and 86.1 ng/mL, respectively)				
Core Accuracy and Precision (A&P) – Intra-Assay (%)	**Level**	**Conc. (nM)**	**Conc. (ng/mL)**	**Precision**	**Accuracy**
	LLOQ	0.0150	0.129	17.0	-2.03
	Back-up LLOQ	0.0300	0.258	3.84	6.69
	Low	0.0450	0.387	4.17	4.48
	Mid	0.500	4.30	3.17	-1.33
	High	7.50	64.5	1.93	4.97
	ULOQ	10.0	86.1	2.82	8.54
Core Accuracy and Precision (A&P) – Inter-Assay (%)	**Level**	**Conc. (nM)**	**Conc. (ng/mL)**	**Precision**	**Accuracy**	**Total Error**
	LLOQ	0.0150	0.129	18.9	-2.03	21.0
	Back-up LLOQ	0.0300	0.258	5.25	6.69	11.9
	Low	0.0450	0.387	6.16	4.48	10.6
	Mid	0.500	4.30	3.17	-1.33	4.50
	High	7.50	64.5	2.16	4.97	7.12
	ULOQ	10.0	86.1	3.00	8.54	11.5
Dilutional Linearity	2000 nM diluted 400-, 4000-, and 40,000-fold				
Prozone or "Hook Effect"	No prozone or hook-effect was observed at concentrations up to 2000 nM.				
Freeze/Thaw Stability (Cycles)	Six cycles thawed at room temperature				
Analyte Stability in Thawed Matrix (Hours)	24 hours at room temperature				
Analyte Stability in Frozen Matrix (Days)	35 days at -80 °C ± 10 °C and 35 days at -25 °C ± 5 °C				
Selectivity (Matrix Interference)	Acceptable with ten out of ten unfortified individual donors meeting the acceptance criteria. Acceptable with ten out of ten individual donors fortified at the LLOQ level, and ten out of ten fortified at the high QC level, meeting the acceptance criteria.				

Source: ICD 735 Method Validation Report (682884-MV04), Page 7.
Abbreviations: Conc, concentration; ECL, electrochemiluminescence; EDTA, ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; QC, quality control; %TE, percent total error; ULOQ, upper limit of quantitation

The bioanalytical method for the measurement of plasma eplontersen concentrations (measured as full length ASO) is acceptable to support quantitation of plasma eplontersen from clinical studies.

Quantification of Eplontersen Concentrations in Human Urine

Full-length ASO concentrations in urine samples obtained from the clinical pharmacology study, ION-682884-CS1, were measured using a partially validated enzyme-linked immunosorbent assay (ELISA) method, ICD 735.2. The bioanalytical methodology is described in and detailed in the validation report (682884-MV05). Eplontersen in the samples was hybridized to a biotinylated probe that included digoxigenin. The hybridized eplontersen was then immobilized on a NeutrAvidin-coated ELISA plate and S1 nuclease was added to digest any unhybridized probes. An anti-digoxigenin antibody conjugated to alkaline phosphatase was used to detect the hybridized analyte with AttoPhos as a substrate for fluorometric readout. Fluorescence intensity was determined using a fluorescent plate reader. The method is applicable to the quantification of total full-length ASOs of eplontersen, which included fully, partially (eplontersen with 1, 2, or 3 GalNAc sugar deletions), and unconjugated eplontersen; concentrations were reported as eplontersen-equivalent, i.e., eplontersen-eq (ION-682884-eq). The validated method was employed to measure plasma concentrations of eplontersen and full length ASO with a passing rate 100% in ION-682884-CS1. Incurred sample reanalysis was performed in 9 out of 69 samples, and 8 (88.9%) of the samples met the prespecified criteria.

A summary of bioanalytical method validation (682884-MV04) is presented in Table 84.

Table 84. Bioanalytical Method Partial Validation Summary Eplontersen in Human Urine

Analyte	ION-682884					
Matrix	Human urine					
Minimum Required Dilution	N/A					
Method Description	Hybridization ELISA					
Sample Volume (µL)	25.0-µL aliquot					
Sample Storage Temperature	-80 °C					
Lower Limit of Quantitation (LLOQ)	0.150 nM (1.29 ng/mL)					
Upper Limit of Quantitation (ULOQ)	20.0 nM (172 ng/mL)					
Regression, Weighting	Four-parameter logistic, 1/response²					
Standard Curve Concentrations	0.0750 (anchor), 0.150, 0.300, 0.500, 1.00, 2.50, 5.00, 10.0, and 20.0 nM (0.645 [anchor], 1.29, 2.58, 4.30, 8.61, 21.5, 43.0, 86.1, and 172 ng/mL, respectively)					
QC Concentrations	0.150, 0.300, 0.450, 3.00, 15.0, and 20.0 nM (1.29, 2.58, 3.87, 25.8, 129, and 172 ng/mL, respectively)					
Intra-Assay Accuracy and Precision (%)	Level	Conc. (nM)	Conc. (ng/mL)	Precision	Accuracy	%TE
	LLOQ	0.150	1.29	12.3	-2.67	15.0
	Back-up LLOQ	0.300	2.58	11.6	6.75	18.4
	Low	0.450	3.87	10.2	3.25	13.5
	Mid	3.00	25.8	9.82	-6.12	15.9
	High	15.0	129	4.66	-11.3	15.9
	ULOQ	20.0	172	13.6	0.249	13.8

Inter-Assay Accuracy and Precision (%)	Level	Conc. (nM)	Conc. (ng/mL)	Precision	Accuracy
	Low	0.450	3.87	22.5	1.70
	Mid	3.00	25.8	11.9	-7.50
	High	15.0	129	11.0	-6.01
Dilutional Linearity	2000 nM diluted 150-, 600-, and 4500-fold				
Prozone or "Hook Effect"	No prozone or hook-effect was observed at concentrations up to 2000 nM.				
Freeze/Thaw Stability (Cycles)	This experiment was not evaluated during partial validation of the method for human urine.				
Analyte Stability in Thawed Matrix (Hours)	This experiment was not evaluated during partial validation of the method for human urine.				
Analyte Stability in Frozen Matrix (Days)	27 days at -80 °C				
Selectivity (Matrix Interference)	This experiment was not evaluated during partial validation of the method for human urine.				

Source: ICD 735.2 Partial validation Report (682884-MV05), Page 7.
Abbreviations: Conc, concentration; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantitation; QC, quality control; %TE, percent total error; ULOQ, upper limit of quantitation

Duration of the sample collection to analysis is not provided in the method performance report. In response to an information request received on September 15, 2023 (Sequence No. 0023), the Applicant noted that urine samples were stored at -80°C for 230 days before analysis and Incurred Sample Reanalysis was conducted after 257 days of the primary analysis.

Considering the small fraction (<1%) of the administered dose excreted in urine, the review team concluded the lack of stability support for measuring eplontersen in urine should have minimal impact to this qualitative conclusion.

Quantification of Transthyretin in Human Serum by Electrochemiluminescence

TTR concentrations in serum samples obtained from the clinical pharmacology studies (ION-682884-CS1, ION-682884-CS3, ION-682884-CS20, and ION-28-2884-CS21) were measured using a validated ligand binding with ECL endpoint method, TM-JPO-0006. The bioanalytical methodology is summarized in and detailed in the validation report, JPO-20-193-VR01. TTR concentrations were determined in human serum using ligand binding with an ECL endpoint. Samples were added to an ECL plate that has been coated with a monoclonal anti-TTR antibody capture antibody (clone EPR20073-79). The plate was then blocked, with diluted MSD Blocker B, and a ruthenium-labeled monoclonal antibody detection antibody (clone EPR20073-155) added. After addition of read buffer, the plate was read on an MSD plate reader. Summary of the method validation report is presented in Table 85.

Table 85. Summary of Method Performance for Quantification of Transthyretin in Human Serum by Electrochemiluminescence (TM-JPO-0006)

Method	Validation Information
Materials used for standard calibration curve and concentration	• TTR (Calibration Standard): Lot GR3283284 • MRD of 1:4000: 0.0244, 0.0672, 0.185, 0.508, 1.40, 3.85, 10.6, 29.1, 80.0, and 240 mg/dL • MRD of 1:8000: 0.0489, 0.134, 0.370, 1.02, 2.80, 7.70, 21.2, 58.2, and 160 mg/dL

Method	Validation Information	
Validated assay range	• MRD of 1:4000: 0.0672 to 80.0 mg/dL (0.0244 and 240 mg/dL were anchor points) • MRD of 1:8000: 0.134 to 160 mg/dL (0.0489 mg/dL was an anchor point)	
Material used for QCs and concentration	TTR (Calibration Standard): Lot GR3283284 0.247, 1.59, 12.3, and 38.7 mg/dL	
Minimum required dilutions	1:4000 or 1:8000	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	• All data: -10.9% to 11.5% • Data without Runs 23 and 24: -10.9% to 11.1%
	Cumulative precision (%CV) from LLOQ to ULOQ	• All data: 3.1% to 20.8% • Data without Runs 23 and 24: 2.5% to 20.8%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	• All data: 7.1% to 8.6% • Data without Runs 23 and 24 and outliers: 6.2% to 8.9%
	Inter batch %CV	• All data: ≤14.5% • Data without Runs 23 and 24 and outliers: ≤11.2%
	Total error (TE)	• All data: 19.3% to 23.1% • Data without Runs 23 and 24 and outliers: NR
Interference and specificity	No interference was seen from eplontersen up to 100× C_{trough} (1 µg/mL [%difference: -17.0% to -4.9%]). No interference was seen from RBP4 and retinol (%difference: -30.3% to 18.8%).	
Hemolysis effect	No effect from hemolysis on the quantification of TTR was observed in 3 lots of matrix containing 100% hemolysate of washed red blood cells (%difference: -11.1% to 5.5%).	
Bench-top/process stability	Up to 21 hours at room temperature Up to 21 hours at refrigerated temperature (2° C to 8° C) Up to 29 days at -70° C	
Freeze-thaw stability	5 cycles at -70° C	
Parallelism	The range of back-calculated concentrations of TTR was 8174 to 123262 mg/dL. Parallelism was demonstrated up to the 1:16000 dilution, where the % recovery was within ±3 times the average %CV of the validation controls (100±28.8%).	

Source: Method Validation Report JPO-20-193-VR01.
Abbreviations: C_{trough}, lowest plasma concentration at steady-state; %CV, percent coefficient of variation; LLOQ, lower limit of quantitation; MRD, minimal residual disease; NR, no runs; QC, quality control; RBP4, retinol binding protein 4; TE, total error; TTR, transthyretin; ULOQ, upper limit of quantitation

It should be noted that the maximum time of serum sample storage was 832 days in Study CS-3, exceeding the established long term stability duration of 729 days at -70°C. Reviewer's independent analysis of the biomarker sample storage duration and response to information request received on November 2, 2023 (Sequence No. 0028) revealed that less than 1% of TTR samples exceeded the established long-term stability of 729 days at -70°C. The Applicant plans to evaluate TTR stability for four years.

The TTR level from the external placebo arm was converted using the following formula to match data generated by the current assay y=0.0057x^2+0.5843x-0.3819. The converted value was then used in the primary analysis. While full cross validation to confirm the equation was not reviewed, these differences in the assay are not expected to impact the interpretation regarding the significance of reduction and the clinical meaningfulness of the reduction. Longitudinal data from the eplontersen treatment arm was collected with the same assay.

Overall, the lack of stability coverage for all TTR samples is not expected to have significant impact on the TTR results considering the human serum samples out of established stability are a small fraction of all analyzed TTR samples (<1%).

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Immunogenicity of eplontersen was evaluated in the Phase 1 Study ION-682884-CS1 in healthy subjects and the ongoing Phase 3, open-label Study ION-682884-CS3 in subjects with hATTR-PN. In Study ION-682884-CS3, anti-inotersen antibodies were assessed prior to the switch to eplontersen treatment, and both anti-inotersen and anti-eplontersen antibodies were assessed after the switch (week 37 and after) in the inotersen/eplontersen reference arm. Refer to the immunogenicity assay review by the Office of Biotechnology Products for details regarding the immunogenicity assay validation (NDA 217388, dated September 21, 2023)).

A summary of subjects' immunogenicity incidence and incidence rate by ADA type is presented in Table 86. Treatment-emergent ADA, defined as the proportion of the subjects found to have seroconverted or boosted their preexisting ADA during the study period, were detected in 36.8% of subjects (53/144) in the eplontersen treatment group. As a reference, 6.9% of subjects (10/144) were ADA-positive at baseline. In the inotersen-eplontersen treatment arm, treatment-emergent anti-inotersen antibodies were detected in 12 (50.0%) subjects.

Table 86. Overview of Treatment, Time Points for Immunogenicity Assessment, and Immunogenicity Results in Individual Studies

Study Number	Study Title	Time Points for Immunogenicity Assessment	Treatment	ADA Results
ION-682884-CS1	A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis [a]	Multiple-dose cohorts (Q4W for 12 weeks): Days 1 (at pre-dose), 15, 29 (at pre-dose), 92/99 (or ET), and 176 (or ET-FU)	Eplontersen: treatments overall	Anti-eplontersen ADA Prevalence:28.2% (11 of 39); Incidence: 12.8% (5 of 39)
			Eplontersen: 45 mg Q4W, SC	Anti-eplontersen ADA Prevalence: 30.0% (3 of 10); Incidence: 10.0% (1 of 10)
			Eplontersen: 60 mg Q4W, SC	Anti-eplontersen ADA Prevalence: 30.0% (3 of 10); Incidence: 10.0% (1 of 10)
			Eplontersen: 90 mg Q4W, SC	Anti-eplontersen ADA Prevalence: 20.0% (2 of 10); Incidence: 10.0% (1 of 10)
		Single-dose cohort: Days 1 (at pre-dose), 15, 29, and 92	Eplontersen: single-dose 120 mg, SC	Anti-eplontersen ADA Prevalence: 33.3% (3 of 9); Incidence: 22.2% (2 of 9)
		Multiple- and single-dose cohorts (timepoints are the same as above, respectively)	Placebo: Q4W or single dose	Anti-eplontersen ADA Prevalence: 0% (0 of 8); Incidence: 0% (0 of 8)
ION-682884-CS3	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	Pre-dose on Days 1, 29, 85, 225, 337, 449, 589, and 729 (or ET)	Eplontersen: 45 mg Q4W, SC	Anti-eplontersen ADA Prevalence: 42.4% (61 of 144); Incidence: 36.8% (53 of 144)
			Inotersen sodium (for first 34 weeks): 300 mg Q1W, SC Eplontersen (from Week 37): 45 mg Q4W, SC	Anti-inotersen ADA Prevalence: 50.0% (12 of 24); Incidence: 50.0% (12 of 24) Anti-eplontersen ADA Prevalence: 54.2% (13 of 24); Incidence: 37.5% (9 of 24) Anti-eplontersen ADA or anti-inotersen ADA Prevalence: 62.5% (15 of 24); Incidence: 50.0% (12 of 24)

Source: ION-682884-CS3 Clinical Study Report, Table 21.
ADA, antidrug antibody; ATTRv-PN, polyneuropathy of hereditary transthyretin-mediated amyloidosis; ET, early termination; ET-FU, follow-up of early termination; Q4W, once every 4 weeks; Q1W, once a week; SC, subcutaneous.
[a] The Study ION-682884-CS1 protocol included an open-label, multi-center cohort in which eplontersen was to be administered to patients with ATTRv-PN. However, due to a shortage of suitable subjects, this cohort was not initiated.

Impact of Immunogenicity on Pharmacokinetics

In Study ION-682884-CS1 and Study ION-682884-CS3, the descriptive plasma PK parameters (including C_{max}, AUC, elimination half-life, and clearance) stratified by eplontersen ADA status were similar between ADA-negative and ADA-positive subjects, suggesting no immunogenicity impact on these PK parameters (Table 87). Higher plasma eplontersen C_{trough} levels were observed in both healthy subjects and subjects with hATTR-PN who tested ADA-positive. In Study ION-682884-CS3, higher trough levels were observed in ADA-positive subjects compared to ADA-negative subjects as presented in Figure 13. Population PK analysis support the conclusions based on pooled data from individual studies. Refer to Section 14.5 for details.

Table 87. Summary of Eplontersen Plasma Pharmacokinetic Parameters Following Subcutaneous Administration of Eplontersen 45 mg Once Every 4 Weeks With Stratification by Subject Immunogenicity Status (Studies ION-682884-CS1 and ION-682884-CS3)

Study	Dosing Day	IM Status	n	PK Parameter [a]				
				C_{max} (µg/mL)	AUC_{0-6h} or AUC_{0-24h} [b] (µg•h/mL)	$t_{½λz}$ (day)	CL_{0-24h}/F (L/h)	C_{trough} (µg/mL)
ION-682884-CS1	Day 1	Positive	3	0.143 (15.2)	1.30 (10.8)	NA	34.7 (10.8)	NA
		Negative	7	0.143 (48.1)	1.17 (28.3)	NA	38.5 (28.3)	NA
	Day 85	Positive	3	0.176 (11.0)	1.31 (14.4)	NA [c]	34.2 (14.4)	0.000830 (NA) [e, f]
		Negative	7	0.234 (81.7)	1.44 (42.7)	23.2 (70.9) [c]	31.2 (42.7)	0.000260 (NA) [f]
ION-682884-CS3	Day 1	Positive	14	0.204 (133)	0.888 (120)	NC	NC	NA
		Negative	9	0.203 (80.7)	0.845 (73.1)	NC	NC	NA
	Day 225	Positive	15	0.203 (87.7)	0.778 (75.4) [d]	NC	NC	0.000782 (239) [g]
		Negative	4	0.264 (71.4)	1.08 (60.6)	NC	NC	0.000210 (83.0) [g]

Source: Clinical Pharmacology Summary, page 97, Table 8.

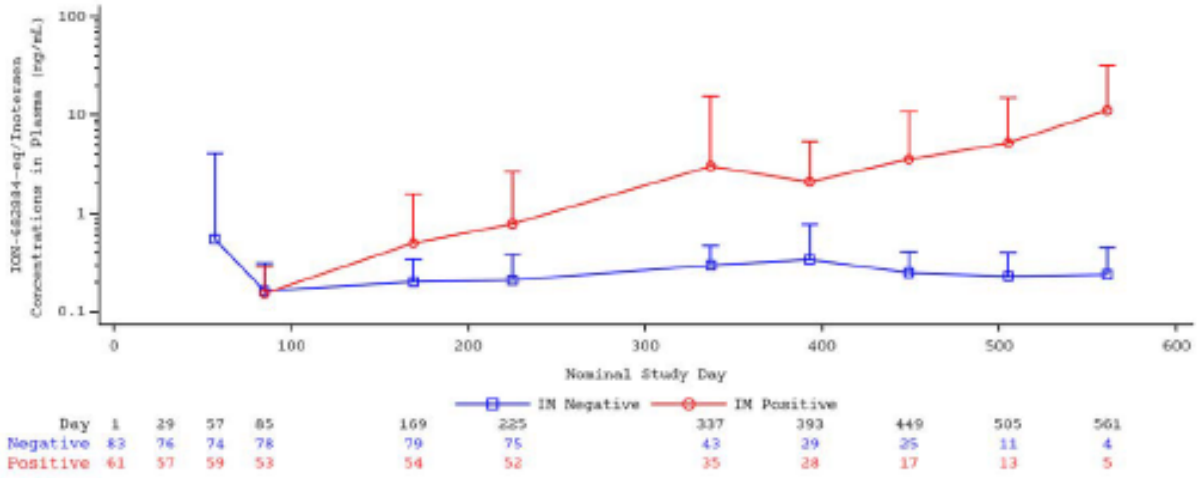
[a] The PK parameters are presented as geometric mean (%geometric CV) except C_{trough}, which is presented as arithmetic mean (%CV).

[b] AUC_{0-6h} was calculated in Study ION-682884-CS3 and AUC_{0-24h} was calculated in Study ION-682884-CS1.

[c] n = 2 for positive status and 4 for negative status. Although geometric mean ((%geometric CV) for the positive status could not be calculated as n = 2, the mean values (23.9 µg•h/mL for the positive status vs. 27.1 µg•h/mL for the negative status) were comparable.

Note: NA means that the number of data was not sufficient for a calculation of geometric mean.
%CV, percent coefficient of variation; AUC, area under the concentration-time curve; AUC_{0-6h}, AUC from time 0 to 6 hours post-dose; AUC_{0-24h}, AUC from time 0 to 24 hours post-dose; C_{trough}, trough concentration; IM, immunogenicity; NA, not applicable; NC, not calculated; PK, pharmacokinetic; $t_{½λz}$, elimination half-life.

Figure 13. Mean + Standard Deviation of Eplontersen Plasma Trough Concentrations Over Time Stratified by Subject Immunogenicity Status (Semi-Log Scale) (Study ION-682884-CS3)



Source: ION-682884-CS3 CSR, Figure 3.04.
Abbreviations: CSR, clinical study report; IM, immunity

Impact of Immunogenicity on Pharmacodynamics

In healthy subjects and subjects with hATTR-PN, ADA status did not appear to have an effect on mean percent change from baseline in serum TTR levels in the eplontersen treatment groups at Week 35.

In subjects with hATTR-PN at Week 35 following the administration of eplontersen Q4W, the mean TTR percent change from baseline in ADA-positive subjects (-80.1%) was similar to that in ADA-negative subjects (-83.4%). ADA titer did not appear to impact TTR reduction because similar TTR reductions were observed among different peak ADA titer level quartiles (Table 88 and Figure 14)

Impact of Immunogenicity on the Efficacy of Eplontersen

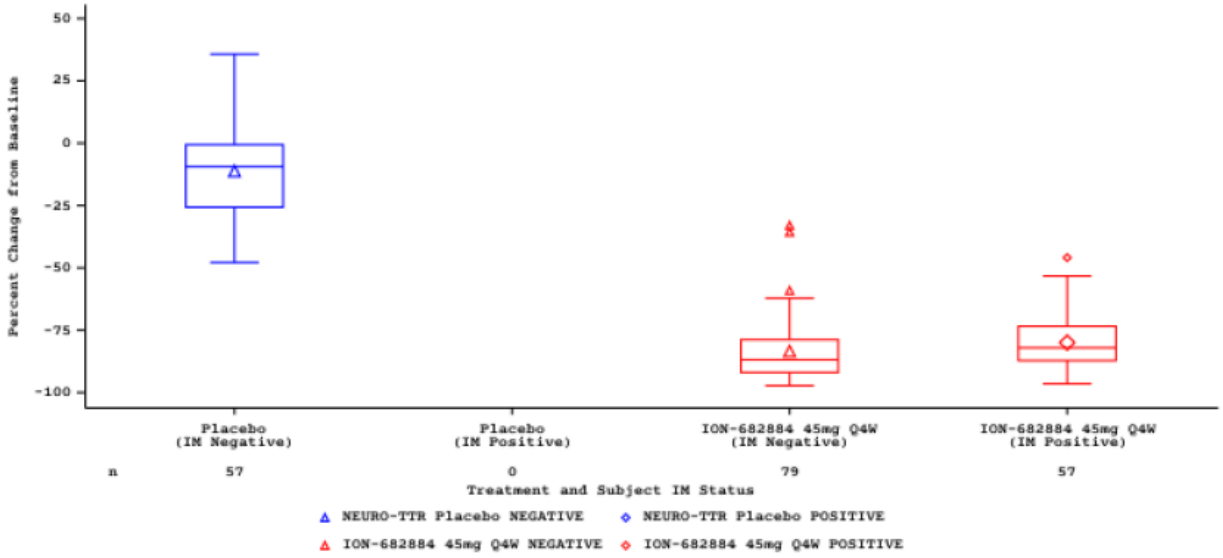
In patients with hATTR-PN, ADA positivity and peak titer quartiles do not appear to have an impact on change from baseline in clinical efficacy endpoints mNIS+7 and Norfolk QOL-DN scores. Please refer to the Section 7.6.1.1 for further details.

Table 88. Summary of On-Treatment Transthyretin Reduction at Week 35 From Baseline Following Subcutaneous Administration of Eplontersen 45 mg Once Every 4 Weeks With Stratification by Treatment-Emergent and Treatment-Unaffected ADA or by Peak Titer Quartile (Study ION-682884-CS3)

Stratification Factor	ADA	N	Mean (SD) TTR Percent Change at Week 35 From Baseline
ADA status	Positive	56	-80.1% (11.2%)
	Negative	79	-83.4% (12.0%)
ADA peak titer quartile	Q1 [50, 50]	14	-80.4% (9.3%)
	Q2 (50, 200]	21	-80.5% (12.9%)
	Q3 (200, 400]	7	-82.8% (5.1%)
	Q4 (400, 12800]	14	-78.0% (12.8%)

Source: ION-682884-CS3 CSR, Table 23 and Table 24.
Abbreviations: ADA, antidrug antibody; CSR, clinical study report; Q, quartile, SD, standard deviation; TTR, transthyretin

Figure 14. Box Plot of Percent Change From Baseline in Serum Transthyretin (On-Treatment) at Week 35 by Treatment and Subject Immunogenicity Status (Study ION-682884-CS3)



Source: ION-682884-CS3 CSR, Figure 23.
Abbreviations: CSR, clinical study report; IM, immunity; Neuro, neuropathy; Q4W, once every four weeks; TTR, transthyretin

About 37% of the subjects who received eplontersen have developed ADAs. At the 35-week interim analysis ADA status did not affect steady state C_{max} and AUC, but C_{trough} was significantly higher, and it appears to increase with the treatment duration. Based on the population PK analysis, steady state C_{trough} (mean and %CV) at week 35 is 0.210 (83) ng/mL in ADA negative subjects and 0.782 (239) ng/mL in ADA positive subjects. There was no impact of ADA on TTR reduction. Refer to Section 7.6.1.1 for details on the effect of ADA on safety and efficacy.

14.5. Pharmacometrics Assessment

Population Pharmacokinetic-Pharmacodynamic Analysis

The objectives of this analysis were to:

1. Develop a population pharmacokinetic (PK) model of eplontersen using data from studies ION-682884-CS1, ION-682884-CS20, ION-682884-CS21, and ION-682884-CS3.
2. Develop a population pharmacokinetic-pharmacodynamic (PKPD) model of eplontersen using data from studies ION-682884-CS1, ION-682884-CS20, ION-682884-CS21, and ION-682884-CS3. See details in Table 89.
3. Perform simulations using the final population PKPD model to support dose selection.

Table 89. Studies Included in PK, PKPD Analysis

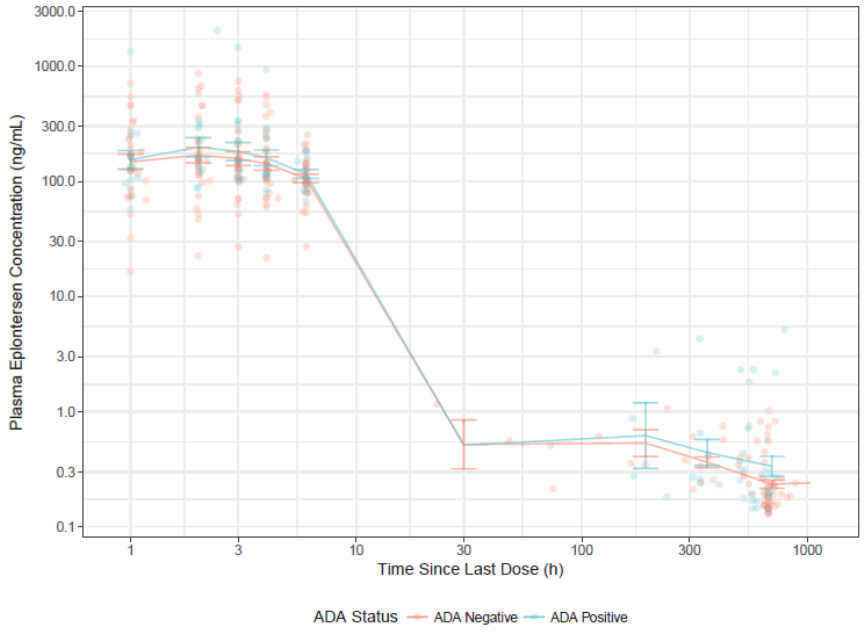
Study	Study Description	Dose (mg)	N*	PK Sampling	PD (TTR) Sampling
ION-682884-CS1	Phase 1 open-label, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of eplontersen in healthy volunteers. 12 weeks active treatment (for multiple dose) followed by 12 weeks of post-treatment evaluations.	45, 60, 90 mg SC Q4W for 12 weeks [D1 and D29 injection on arm; D57 and D85 injection in the abdomen]	30	**Multiple-dose (Cohorts A, B, E)** D1 & D85: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 h post-dose. D8, D15, D43, D71, D92, D99, D113, D127, D141, D155, D176: anytime. D29, D57: pre-dose.	**Multiple-dose (Cohorts A, B, E)** Screening (-4 weeks), Baseline, D8, D15, D29, D43, D57, D71, D85, D92, D99, D113, D127, D141, D176
		120 mg SC single-dose [arm]	9	**Single-dose (Cohort C)** D1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post-dose. D8, D15, D29, D50, D71, D92: anytime.	**Single-dose (Cohort C)** Screening (-4 weeks), Baseline, D2, D4, D8, D15, D29, D43, D50, D71, D92
ION-682884-CS20	Phase 1 randomized, double-blinded, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of eplontersen in healthy Japanese participants.	45, 60, 90 mg SC single-dose [abdomen]	18	D1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post-dose. D8, D15, D29, D50, D71, D92: anytime.	Screening (-4 weeks), Baseline, D2, D4, D8, D15, D29, D50, D71, D92
ION-682884-CS21	Phase 1 open-label, three-period crossover, bioequivalence study comparing three SC formulations: vial, pre-filled syringe with safety device and auto-injector with eplontersen in healthy adults.	45 mg SC [abdomen] (three-period crossover with 4-week washout)	57	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 96, 168 h post-dose for each study period. Follow-up period at D85, D113, D148.	Screening (-4 weeks), Baseline (D1 pre-dose), D8, D15, D29 (Period 2 pre-dose), D57 (Period 3 pre-dose), and follow-up period at D85, D113, D148.
ION-682884-CS3	Phase 3 multi-center, open-label, randomized study to evaluate the efficacy and safety of eplontersen in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy (ATTRv-PN).	45 mg Q4W SC for 84 weeks [arm, abdomen, or thigh]	116	**All patients except PK subgroup:** W1, W5, W9, W13, W25, W33, W49, W57, W65, W73, W81: pre-dose. W35, W66, W85, W93, W105: anytime.	Screening (up to 10 weeks before first dose), Baseline, W5, W9, W13, W25, W35, W49, W57, W65, W73, W81, W85 (or end of treatment), W93, W105
			28	**PK subgroup only:** D1, D225 (W33), D449 (W65): pre-dose, 1, 2, 3, 4, 6 h post-dose. W5, W9, W13, W25, W49, W57, W73, W81: pre-dose. W35, W66, W85, W93, W105: anytime.	

Source: Page 5 of ppk01-final-report.pdf.
* Subjects with active treatment of eplontersen (i.e., non-placebo)
Note: Subjects in ION-682884-CS3 administered inotersen were not included in the analysis population.
Abbreviations: hATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; D, days; N, number of subjects; PD, pharmacodynamic; PK, pharmacokinetic; PKPD, pharmacokinetic-pharmacodynamic; Q4W, once every four weeks; SC, subcutaneous(ly); TTR, transthyretin; W, weeks

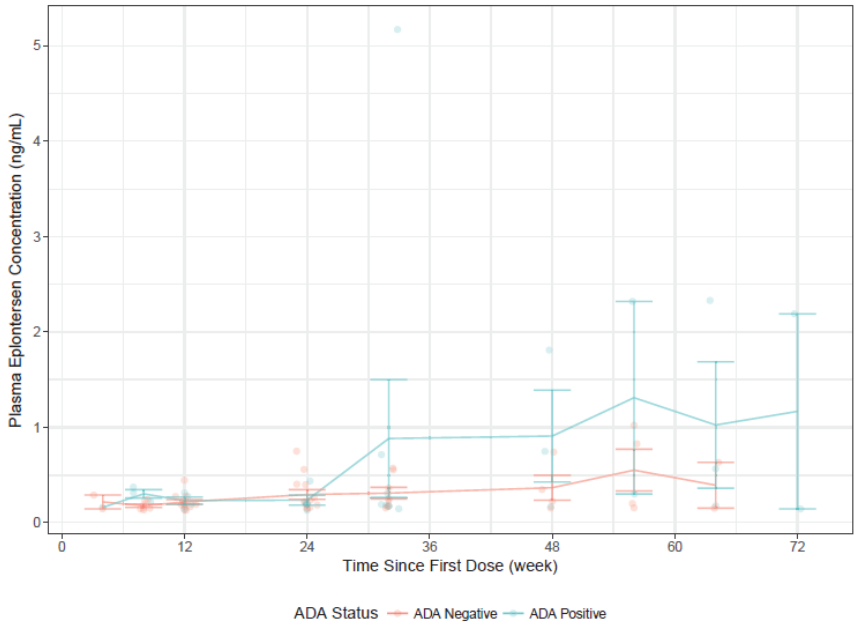
On visual inspection of the data, it was evident that eplontersen trough concentrations taken at and beyond the onset of ADA were substantially higher than eplontersen trough concentrations prior to onset of ADA, while no substantial difference in TTR concentrations were observed (Figure 15 and Figure 16).

Figure 15. (A) Mean (±SEM) Concentration-Time Profiles by ADA Status (Study CS-3, PK Subgroup); (B) Mean (±SEM) Trough Concentrations by ADA Status (Study CS-3, PK Subgroup)

(A)



(B)

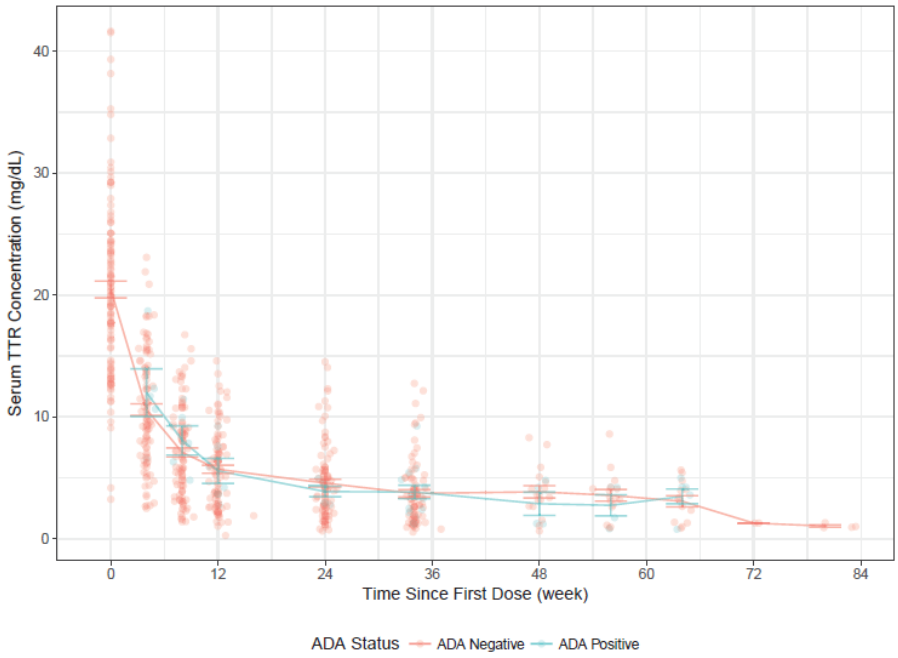


Source: Figure 17 and Figure 18 on Page 85, 86 of ppk01-final-report.pdf.
Note:

- Lines = mean
- Error bar = standard error of mean
- Circles = individual observations
- Values below the lower limit of quantification were excluded from the plot. Eplontersen plasma concentrations at and beyond onset of ADA were included.

Abbreviations: ADA, antidrug antibody; h, hour; PK, pharmacokinetic; SEM, standard error of the mean

Figure 16. Mean (±SEM) TTR Concentration-Time Profiles for hATTR-PN Subjects Receiving Eplontersen by ADA Status (Study CS-3)

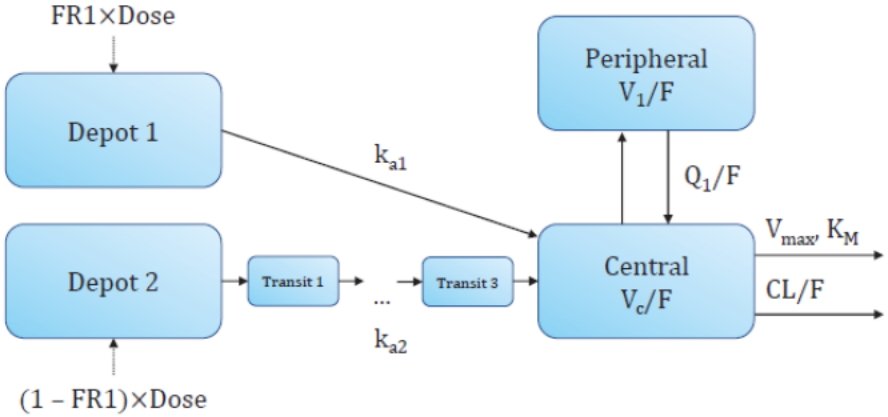


Source: Figure 22 on Page 91 of ppk01-final-report.pdf.
Abbreviations: ADA, antidrug antibody; hATTR-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; SEM, standard error of the mean; TTR, transthyretin

PK samples at and beyond onset of ADA were omitted from the population PK analysis, while TTR concentrations at and beyond onset of ADA were retained in the population PKPD analysis. The overall percentage of PK concentrations below the lower limit of quantification was 9.35%. Therefore, PK concentrations below the lower limit of quantification were omitted during model development.

The final population PKPD model was a two-compartment disposition model with parallel first-order/3-transit absorption (Figure 17). Based on the observed slightly greater than dose-proportional increase in PK exposure, parallel linear/nonlinear elimination was implemented in the model.

Figure 17. Schematic of the Final Population PK Model

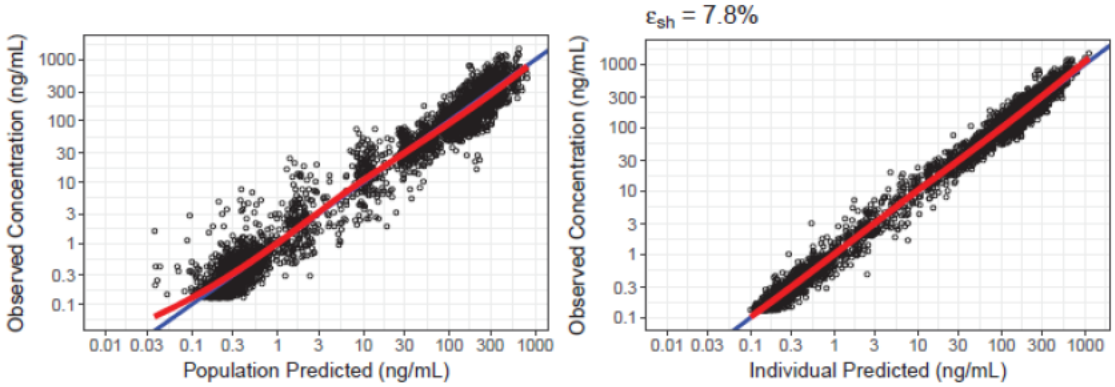


Source: Figure 25 on Page 95 of ppk01-final-report.pdf.

FR1 = fraction of the dose absorbed via the first pathway, k_{a1} = first-order absorption rate constant for the slow pathway, k_{a2} = first-order absorption rate constant for the fast pathway, CL/F = apparent clearance, V_{max} = maximum metabolic rate, K_M = Michaelis-Menten constant, Q/F = apparent inter-compartmental clearance, V_c/F = apparent volume of distribution for the central compartment, V_p/F = apparent volume of distribution for the peripheral compartment.

Plots of the observed versus the population predicted concentration demonstrated minimum bias, with the majority of data evenly scattered around the line of unity (Figure 18). The estimates from the final population PK model are provided in Table 90.

Figure 18. Observed vs. Predicted Concentrations From the Final Population PK Model



Source: Figure 26 on Page 97 of ppk01-final-report.pdf.

Note:

- The solid blue lines represent the line of unity.
- The solid red lines represent the trend in the data (Loess smooth).
- ε_{sh} shows shrinkage for the residual variability.

Abbreviations: PK, pharmacokinetic

Table 90. Parameter Estimates From the Final Population PK Model

Parameter Name	Estimated Value (%RSE)
Apparent Clearance (CL/F, L/h)†	6.19 (7.0)
Exponent for WT on CL/F	1.92 (14.7)
Exponent for eGFR on CL/F	1 (31.1)
Maximum Metabolic Rate (V_{max}, mg/h)	0.395 (6.6)
Michaelis-Menten Constant (K_m, ng/mL)	3.63 (7.2)
Apparent Inter-compartmental Clearance (Q/F, L/h)††	14.8 FIX
Exponent for WT on Q/F	0.748 FIX
Apparent Central Volume of Distribution (V_c/F, L)#	12.2 (5.3)
Exponent for WT on V_c/F	1.38 (21.5)
Apparent Peripheral Volume of Distribution (V_p/F, L)##	11100 FIX
Exponent for WT on V_p/F	0.969 FIX
Percent of the Dose Absorbed via the Slow Pathway (FR1)	0.814 FIX
First-order Absorption Rate Constant for the Slow Pathway (k_{a1}, 1/h)*	0.176 (2.6)
Exponent for WT on k_{a1}	-0.656 (21.6)
Covariate Effect of Arm as Site of Injection on k_{a1} and k_{a2} (Fold)	0.768 (1.9)
First-order Absorption Rate Constant for the Fast Pathway (k_{a2}, 1/h)**	0.639 (4.8)
Exponent for WT on k_{a2}	-1.61 (16.4)
Covariate Effect of Device (AI, PFS) on k_{a2} (Fold)	1.52 (3.9)
Between Subject Variability for CL/F (% CV)	42.1 (20.8)
Between Subject Variability for V_{max} (% CV)	27.3 (9.0)
Between Subject Variability for K_m (% CV)	15.8 FIX
Between Subject Variability for Q/F (% CV)	15.8 FIX
Between Subject Variability for V_c/F (% CV)	30 (18.7)
Between Subject Variability for V_p/F (% CV)	34 FIX
Between Subject Variability for FR1 (Additive)§	101 FIX
Between Subject Variability for k_{a1} (% CV)	23.4 (8.6)
Between Subject Variability for k_{a2} (% CV)	38.6 (10.2)
Residual Unexplained Variability (Proportional) (%)	28.2 (1.2)

Source: Table 8 on Page 96 of ppk01-final-report.pdf.

†$CL/F = 6.19 \cdot (WT/70)^{1.92} \cdot (eGFR/100)^{1}$

††$Q/F = 14.8 \cdot (WT/70)^{0.748}$

#$V_c/F = 12.2 \cdot (WT/70)^{1.38}$

##$V_p/F = 11100 \cdot (WT/70)^{0.969}$

*$k_{a1} = 0.176 \cdot (WT/70)^{-0.656} \cdot 0.768$ (if arm as site of injection)

**$k_{a2} = 0.639 \cdot (WT/70)^{-1.61} \cdot 0.768$ (if arm as site of injection) · 1.52 (if drug presentation auto-injector or pre-filled syringe)

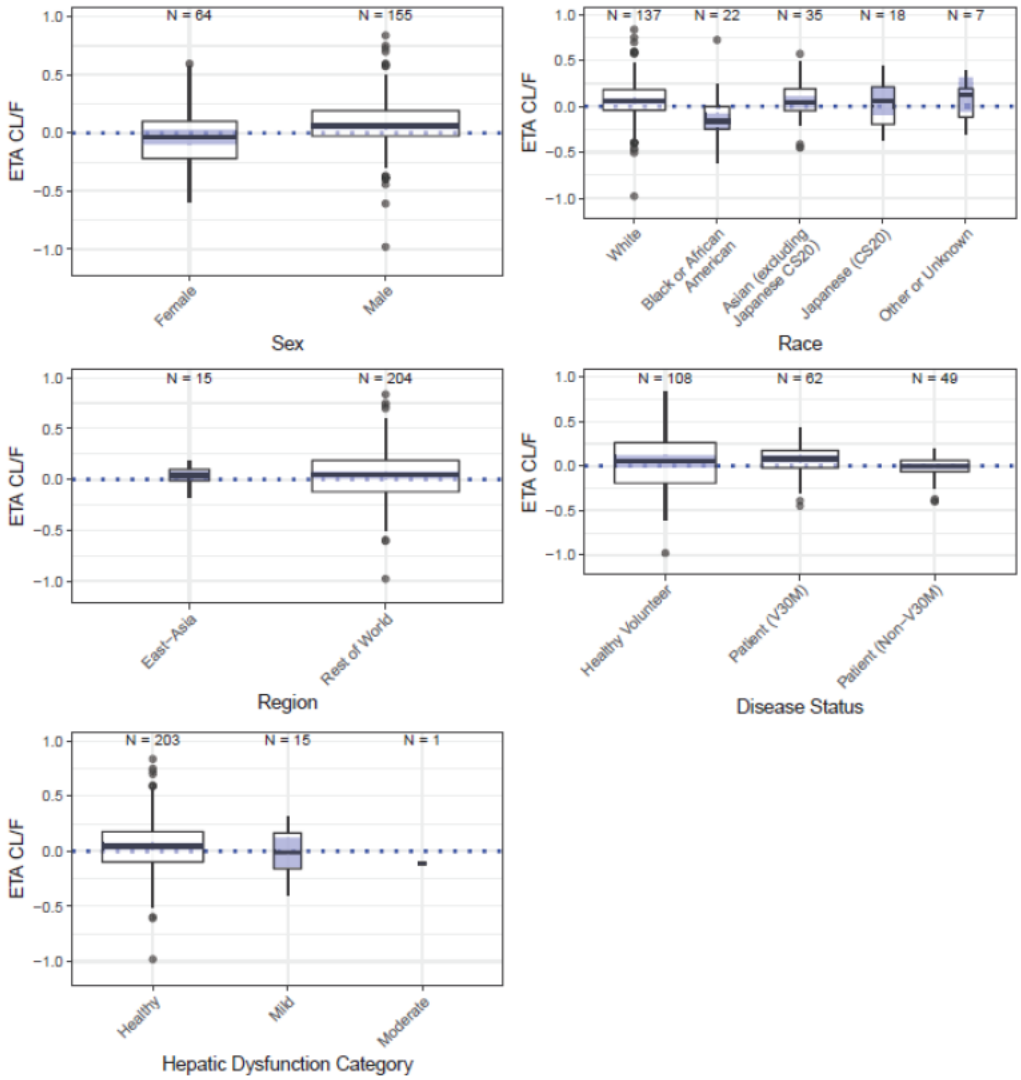
§ Additive on logit scale.

AI = auto-injector, CV = coefficient of variation, eGFR = estimated glomerular filtration rate, PFS = pre-filled syringe, RSE = relative standard error, WT = total body weight.

Individual estimates of shrinkage for CL/F, Vmax, KM, Q/F, Vc/F, Vp/F, FR1, ka1 and ka2, were 41.3%, 25.5%, 62.5%, 37.0%, 57.5%, 41.4%, 36.7%, 34.4% and 32.1%, respectively.

Figure 19 and Figure 20 show the relationship between ETACL and baseline covariates. The findings support the proposed labeling statement that eplontersen pharmacokinetics are not affected by age, body weight, sex, race, Val30Met mutation status, mild and moderate renal impairment (estimated glomerular filtration rate [eGFR]≥45 to <90 mL/min), or 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).

Figure 19. Base Model ETA-Covariate Plots: CL/F; Categorical Covariates

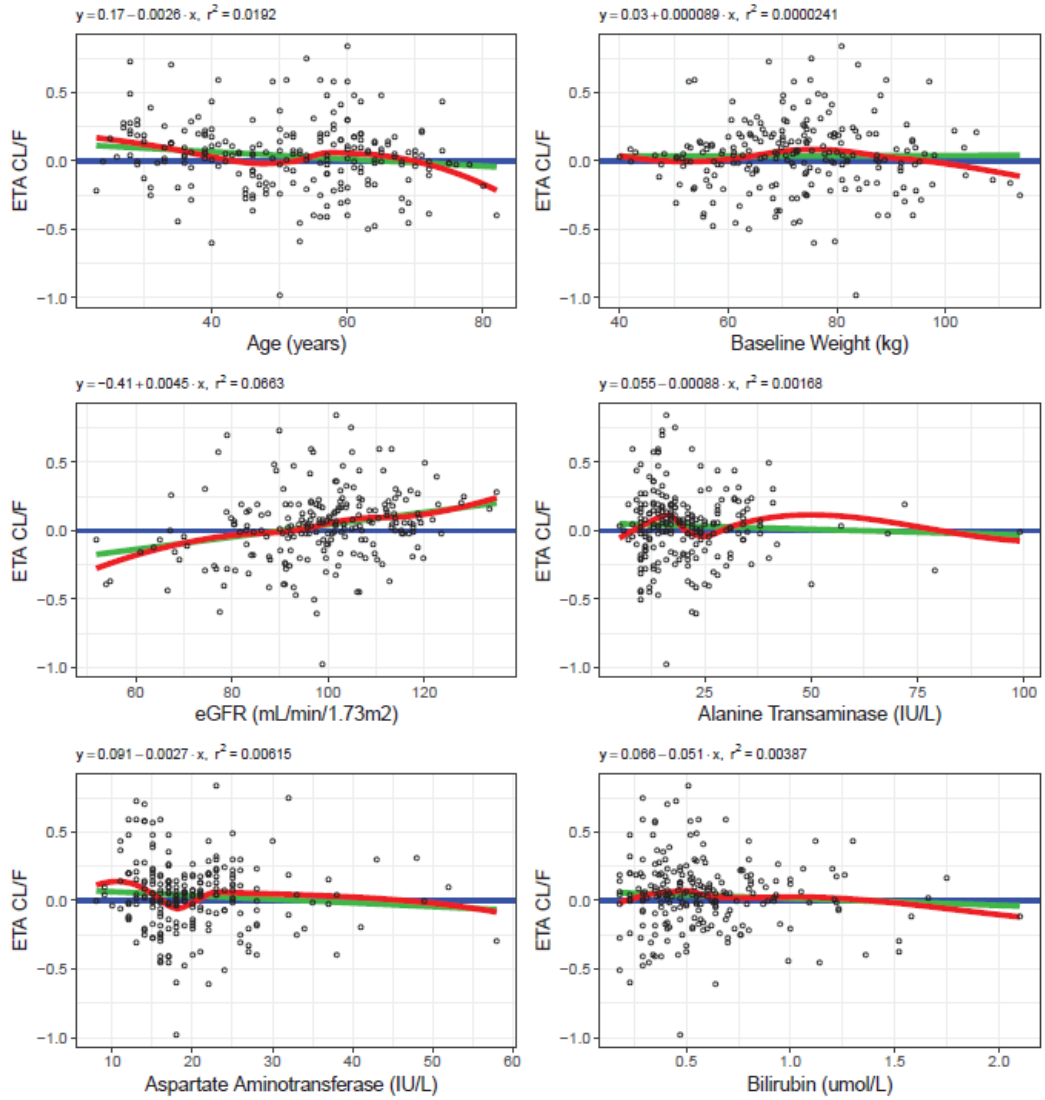


Source: Figure 63 on Page 197 of ppk01-final-report.pdf.

The dashed blue lines represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. The blue shaded region is the approximate 95% CI for the median, calculated as $\pm 1.58 \times IQR/\sqrt{n}$. Box widths are proportional to the square-roots of the number of observations in the groups. *N* denotes the number of subjects in each subcategory. Note: time-varying categorical covariates such as concomitant drug use is not included in the plots.

Abbreviations: CI, confidence interval; CL/F, apparent clearance; ETA, estimate of interindividual variability; IQR, interquartile range

Figure 20. Base Model ETA-Covariate Plots: CL/F; Continuous Covariates



Source: Figure 65 on Page 199 of ppk01-final-report.pdf.

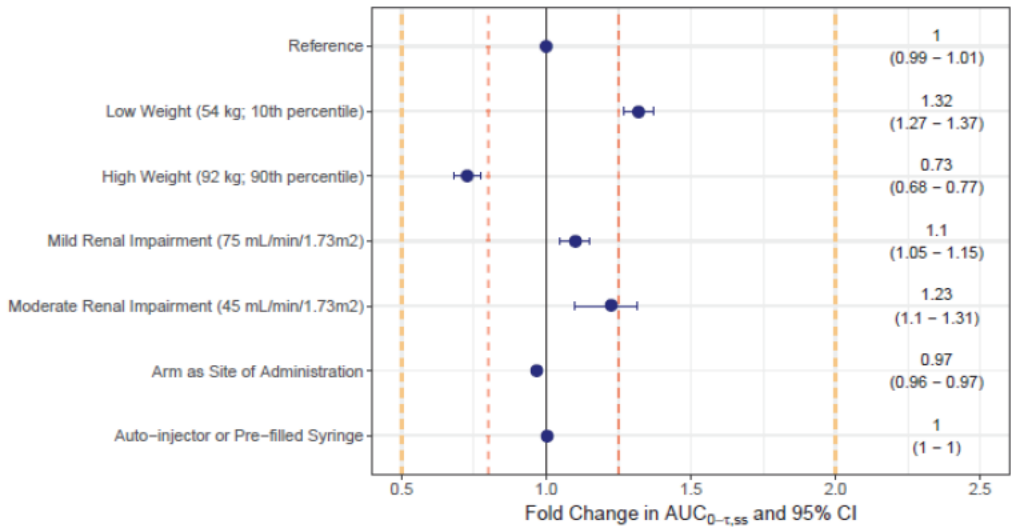
Note:

- The solid blue lines represent zero.
- The solid red lines represent the trend in the data (Loess smooth).
- The solid green lines represent a linear regression with the corresponding regression model shown above in each panel.

Abbreviations: CL/F, apparent clearance; ETA, estimate of interindividual variability

The impact of covariates on the exposure metrics (AUC0−τ,ss, C_{max},ss and C_{trough},ss) are summarized in Figure 21 and Figure 22. Overall, the median and 95% CI effect of covariates on AUC0−τ,ss, C_{max},ss and C_{trough},ss were within the 50-200% range of the reference subjects. The effect of low (54 kg, 10th percentile) and high (92 kg, 90th percentile) weight were 0.32-fold increase and 0.27-fold decrease in AUC0−τ,ss, respectively. Similarly, the effect of low and high weight were 0.67-fold increase and 0.40-fold decrease in C_{max},ss, respectively. The effect of moderate renal impairment (45 mL/min) was 0.29-fold increase in C_{trough},ss. The magnitude of the effect of covariate on AUC0−τ,ss, C_{max},ss and C_{trough},ss for mild renal impairment, arm as site of administration and auto-injector or prefilled syringe were within 0.78–1.25-fold range.

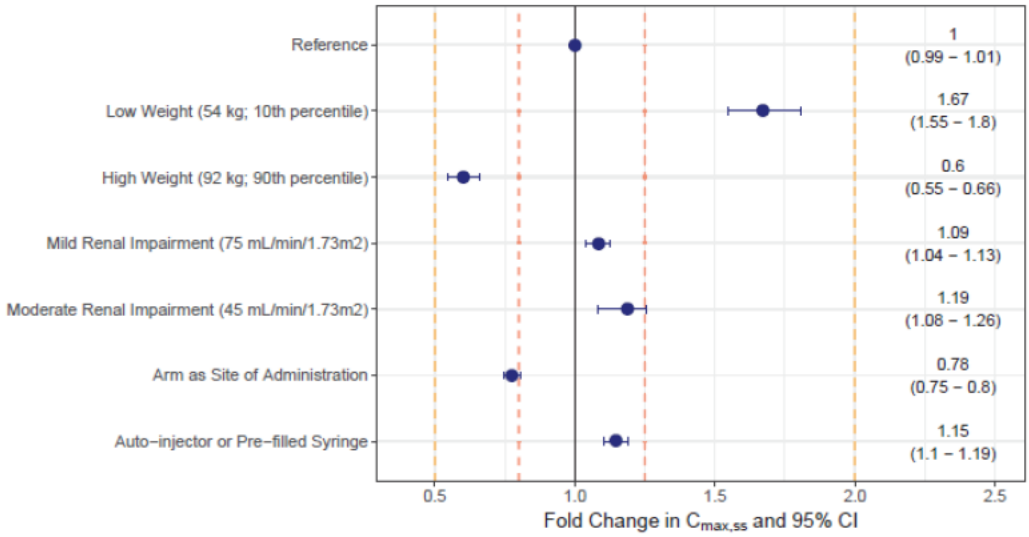
Figure 21. Model Predicted Effect of Covariate on Fold Change in Eplontersen $AUC_{0-\tau,ss}$



Source: Figure 33 on Page 105 of ppk01-final-report.pdf.

The solid black line represents the median of the simulated reference subject, defined as a subject (healthy volunteer or ATTRv-PN patient) receiving 45 mg eplontersen Q4W with a body weight of 70 kg, normal renal function (eGFR 105 mL/min/1.73m^2), abdomen or thigh as the site of administration and vial as the drug presentation. Dashed red lines represent the 80 – 125% range of the reference subject, and dashed orange lines represent the 50 – 200% range of the reference subject. The blue dots and error bars represent the median and 95% confidence interval (CI) based on 1000 simulated subjects within each group including uncertainty on the fixed effect.
Abbreviations: ATTRv-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; $AUC_{0-\tau}$, area under the concentration-time curve from 0 to time, t, at steady-state; eGFR, estimate glomerular filtration rate; CI, confidence interval; Q4W, once every four weeks

Figure 22. Model Predicted Effect of Covariate on Fold Change in Eplontersen $C_{max,ss}$



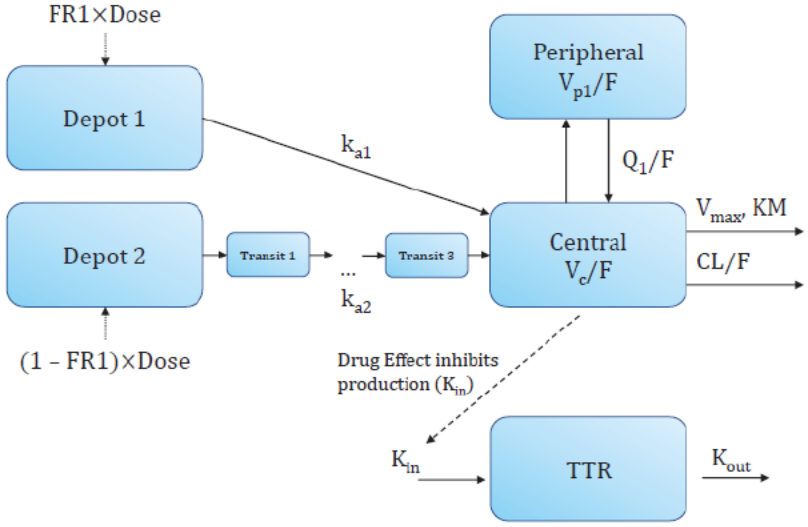
Source: Figure 35 on Page 107 of ppk01-final-report.pdf.

The solid black line represents the median of the simulated reference subject, defined as a subject (healthy volunteer or ATTRv-PN patient) receiving 45 mg eplontersen Q4W with a body weight of 70 kg, normal renal function (eGFR 105 mL/min/1.73m^2), abdomen or thigh as the site of administration and vial as the drug presentation. Dashed red lines represent the 80 – 125% range of the reference subject, and dashed orange lines represent the 50 – 200% range of the reference subject. The blue dots and error bars represent the median and 95% confidence interval (CI) based on 1000 simulated subjects within each group including uncertainty on the fixed effect.
Abbreviations: ATTRv-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; $C_{max,ss}$, maximum plasma concentration at steady-state; eGFR, estimate glomerular filtration rate; CI, confidence interval; Q4W, once every four weeks

Population Pharmacokinetic-Pharmacodynamic Analysis

A sequential approach was used where PK parameters were fixed to the final PK empirical Bayes estimates from the final PK model and the PD data were used to estimate the PD parameters. The PKPD model used the eplontersen concentration in the central compartment to drive the effect on TTR concentration, where the effect of eplontersen was modeled as a sigmoid maximum inhibitory effect (Imax) model inhibiting the production of TTR (Figure 23).

Figure 23. Schematic of the Final Population PKPD Model

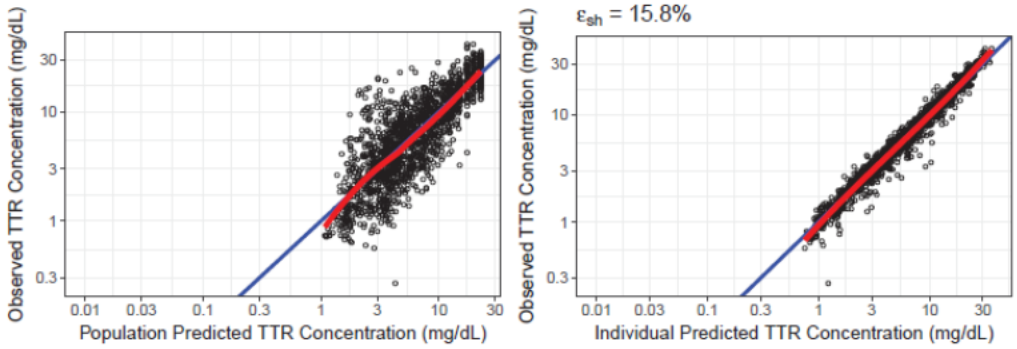


Source: Figure 38 on Page 111 of ppk01-final-report.pdf.

FR1 = fraction of the dose absorbed via the first pathway, k_{a1} = first-order absorption rate constant for the slow pathway, k_{a2} = first-order absorption rate constant for the fast pathway, CL/F = apparent clearance, V_{max} = maximum metabolic rate, K_M = Michaelis-Menten constant, Q/F = apparent inter-compartmental clearance, V_c/F = apparent volume of distribution for the central compartment, V_p/F = apparent volume of distribution for the peripheral compartment, K_{in} = zero-order production rate, K_{out} = first-order elimination rate, TTR = transthyretin protein.

Plots of observed versus population predicted TTR concentrations and observed versus individual predicted TTR concentrations are shown in Figure 24.

Figure 24. Observed vs. Predicted TTR Concentrations From the Final Population PKPD Model



Source: Figure 39 on Page 113 of ppk01-final-report.pdf.

Note:

- The solid blue lines represent the line of unity.
- The solid red lines represent the trend in the data (Loess smooth).
- ε_{sh} shows shrinkage for the residual variability.

Abbreviations: PKPD, pharmacokinetic-pharmacodynamic; TTR, transthyretin

Individual estimates of shrinkage for baseline TTR, IC_{50} and K_{out} were 11.7%, 8.8% and 17.9%, respectively. Parameter estimates from the PKPD model are shown in Table 91.

Table 91. Parameter Estimates From the Final Population PD Model

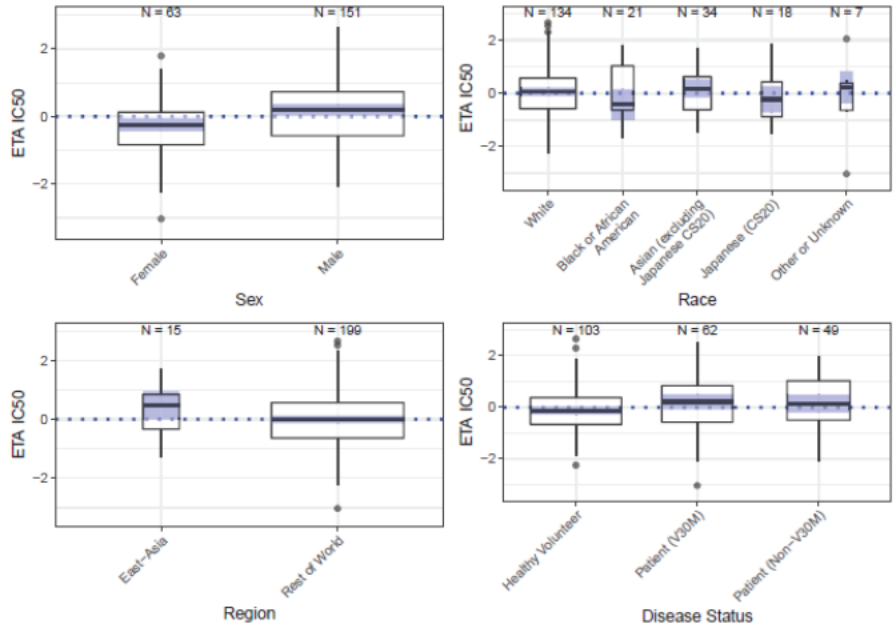
Parameter Name	Estimated Value (%RSE)
Baseline TTR (BLTTR, mg/dL)†	22.6 (2.5)
Covariate Effect of Sex on Baseline TTR (Fold)	0.864 (4.2)
Covariate Effect of Patient with Non-V30M Mutation on Baseline TTR (Fold)	0.767 (4.8)
First-order Elimination Rate of TTR (K_{out}, 1/h)‡	0.00313 (5.6)
Covariate Effect of Black or African American Race on K_{out} (Fold)	1.39 (11.1)
Covariate Effect of Japanese (CS20) Race on K_{out} (Fold)	1.41 (11.8)
Covariate Effect of Patient with V30M Mutation on K_{out} (Fold)	0.425 (8.5)
Covariate Effect of Patient with Non-V30M Mutation on K_{out} (Fold)	0.521 (9.2)
Maximum Inhibitory Effect (Imax, fraction)#	0.963 (0.1)
Exponent for Body Weight on I_{max}	1.24 (22.3)
Exponent for Baseline TTR on I_{max}	0.716 (22.1)
Half Maximal Inhibitory Concentration (IC_{50}, ng/mL)*	0.0343 (9.4)
Covariate Effect of Black or African American Race on IC_{50} (Fold)	0.363 (27.5)
Covariate Effect of Asian (excluding Japanese CS20) Race on on IC_{50} (Fold)	0.358 (22.5)
Hill Coefficient (γ)	0.822 (0.7)
Between Subject Variability for Baseline TTR (% CV)	25 (6.8)
Between Subject Variability for K_{out} (% CV)	40.5 (7.5)
Between Subject Variability for IC_{50} (% CV)	148 (6.3)
Residual Unexplained Variability (Proportional) (%)	17.1 (2.6)

Source: Table 9 on Page 112 of ppk01-final-report.pdf.

Note: PK parameters were fixed to the PK final EBE estimates (Table 8).
A reference subject, defined as a White male ATTRv-PN patient with V30M mutation receiving 45 mg eplontersen Q4W with a body weight of 70 kg, an observed baseline TTR of 21.4 mg/dL has model estimated baseline TTR = 22.6 mg/dl, K_{out} = 0.00133 1/h, I_{max} = 0.963, IC_{50} = 0.0343 ng/mL and γ = 0.822.
CV = coefficient of variation, RSE = relative standard error, TTR = transthyretin protein, WT = total body weight.
†BLTTR = 22.6 · 0.864 (if female) · 0.767 (if patient with non-V30M mutation)
‡K_{out} = 0.00313 · 1.39 (if Black or African American) · 1.41 (if Japanese (CS20)) · 0.425 (if patient with V30M mutation) · 0.521 (if patient with non-V30M mutation)
#logit(I_{max}) = ln (0.963/(1 - 0.963)) where, 'ln' is the natural logarithm.
I_{max} = exp(logit(I_{max}) + (1.24 * ln(WT/70)) + (0.716 * ln(BLTTR/21.4)))/(1 + exp(logit(I_{max}) + (1.24 * ln(WT/70)) + (0.716 * ln(BLTTR/21.4)))) where, 'exp' is the exponential function.
*IC_{50} = 0.0343 · 0.363 (if Black or African American) · 0.358 (if Asian (excluding Japanese CS20))

Figure 25 and Figure 26 show the relationship between $ETAIC_{50}$ and baseline covariates. The findings support the proposed labeling statement that eplontersen pharmacodynamics are not affected by age, body weight, sex, or race.

Figure 25. Final Model ETA-Covariate Plots: IC_{50}; Categorical Covariates

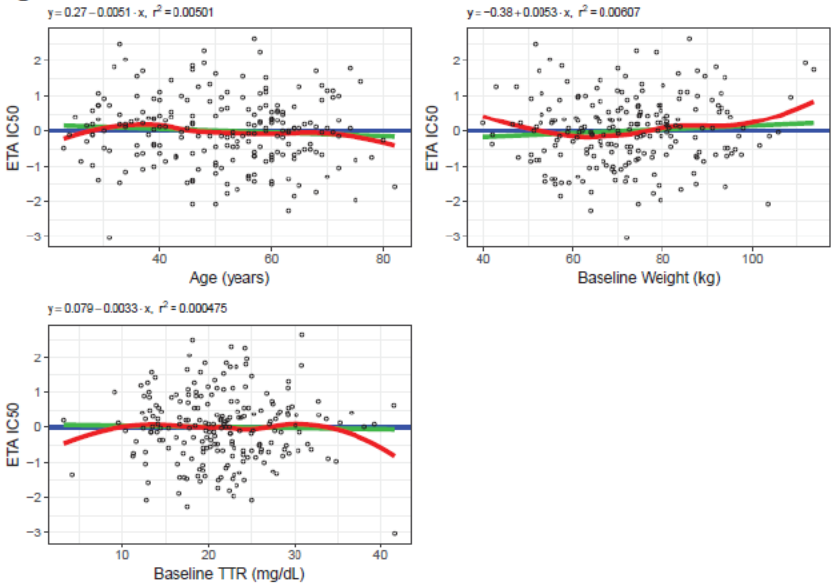


Source: Figure 116 on Page 255 of ppk01-final-report.pdf.

The dashed blue lines represent zero, the thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. The blue shaded region is the approximate 95% CI for the median, calculated as $\pm 1.58 \times IQR/\sqrt{n}$. Box widths are proportional to the square-roots of the number of observations in the groups. *N* denotes the number of subjects in each subcategory. Note: time-varying categorical covariates such as concomitant drug use is not included in the plots.

Abbreviations: CI, confidence interval; ETA, estimate of interindividual variability; IC_{50}, half-maximal inhibitory concentration; IQR, interquartile range; N, number of subjects

Figure 26. Final Model ETA-Covariate Plots: IC_{50}; Continuous Covariates



Source: Figure 117 on Page 256 of ppk01-final-report.pdf.

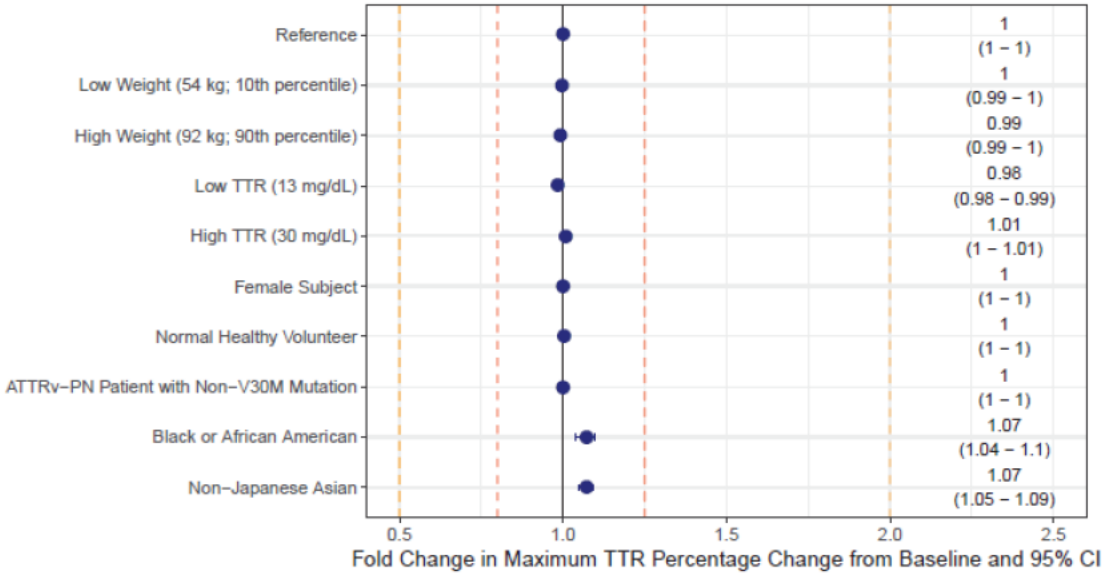
Note:

- The solid blue lines represent zero.
- The solid red lines represent the trend in the data (Loess smooth).
- The solid green lines represent a linear regression with the corresponding regression model shown above in each panel.

Abbreviations: ETA, estimate of interindividual variability; IC_{50}, half-maximal inhibitory concentration

The magnitude of covariate effects of the included covariates on reduction in TTR concentration was evaluated by deriving the fold change in maximum percentage change of TTR concentration from baseline over the steady-state dosing interval and fold change in percentage change from baseline at C_{trough},ss (i.e., 672 h post last dose at steady-state) for each covariate relative to a reference subject (Figure 27). The reference subject was defined as a white male hATTR-PN patient with V30M mutation receiving 45 mg eplontersen Q4W with a body weight of 70 kg and baseline TTR of 21.4 mg/dL.

Figure 27. Model Predicted Effect of Covariate on Fold Change in Maximum TTR Percentage Change From Baseline



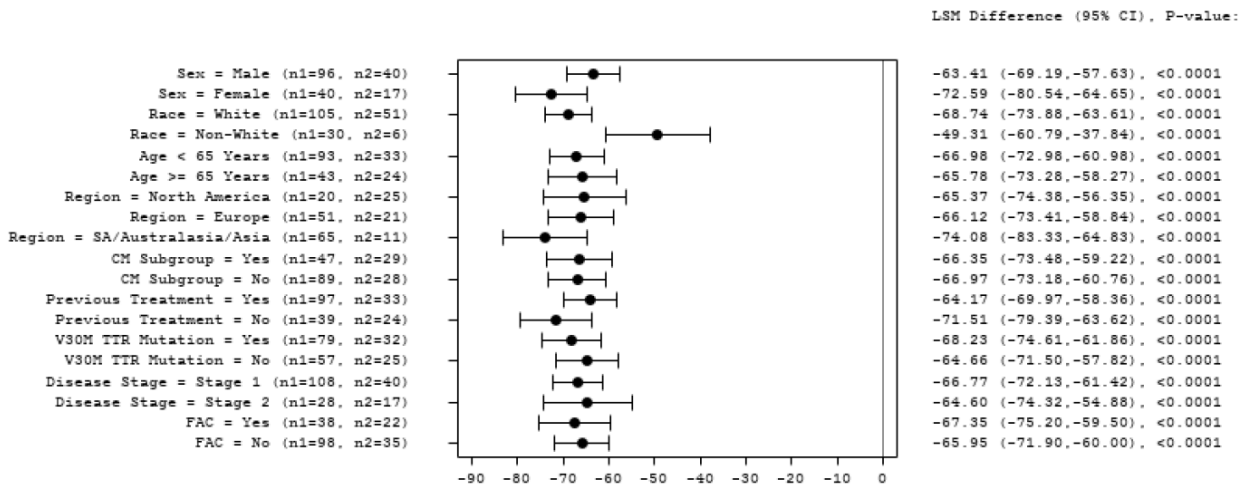
Source: Figure 46 on Page 120 of ppk01-final-report.pdf.

The solid black line represents the median of the simulated reference subject, defined as a White male ATTRv-PN patient with V30M mutation receiving 45 mg eplontersen Q4W with a body weight of 70 kg, baseline TTR of 21.4 mg/dL. Dashed red lines represent the 80 – 125% range of the reference subject, and dashed orange lines represent the 50 – 200% range of the reference subject. The blue dots and error bars represent the median and 95% confidence interval (CI) based on 1000 simulated subjects within each group including uncertainty on the fixed effect.

Abbreviations: ATTRv-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; CI, confidence interval; Q4W, once every four weeks; TTR, transthyretin

Percent change from baseline in serum TTR concentrations was examined in 9 subgroups: sex, race, age, region, CM subgroup, previous treatment, Val30Met TTR mutation, disease stage, and familial amyloid cardiomyopathy clinical diagnosis. In subjects receiving eplontersen, serum TTR concentrations were reduced consistently across subgroups (Figure 28). The observed difference in treatment differences (difference in LSMs) for percent change from baseline in TTR between white and non-white subgroups were mainly driven by a difference between white and non-white subgroups in the external placebo group (mean change of -8.84% [n =51] and -30.6% [n =6], respectively). In the eplontersen group, the TTR change from baseline for the white and non-white subgroups were similar (mean change -81.05% [n =105] and -85.31% [n =30], respectively), indicating no race effect.

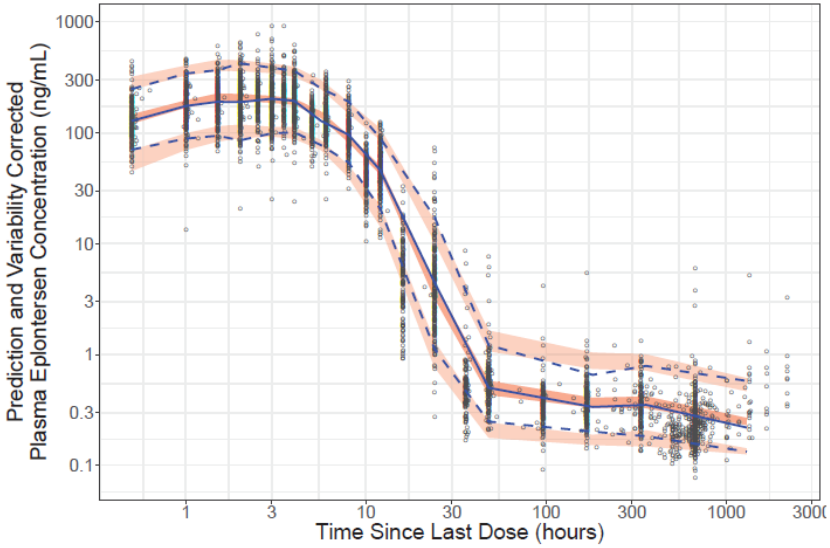
Figure 28. Forest Plot of Difference in LSM for Percent Change From Baseline in Serum TTR (g/L) (Eplontersen 45 mg Q4W - External Placebo) at Week 35 Interim Analysis (On-Treatment) Full Analysis Set



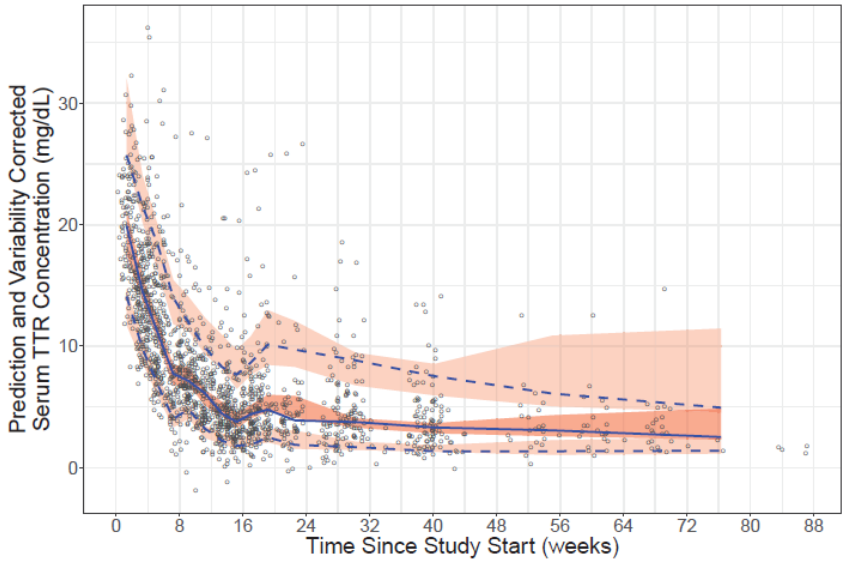
Source: Figure 8 on Page 46 of ppk01-final-report.pdf.
Note: Difference in LSMs, confidence intervals, and p-values are based on an MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, subgroup factors, treatment-by-time interaction, treatment-by-subgroup interaction, and treatment-by-time-by-subgroup interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline value of the endpoint and the baseline-by-time interaction. Only data up to Week 35 are included in the Week 35 interim analysis.
Abbreviations: CI, confidence interval; CM, cardiomyopathy; CRF, case report form; FAC, familial amyloid cardiomyopathy; LSM, least squares mean; MMRM, mixed effects model with repeated measures; n1, eplontersen 45 mg Q4W, n2, external placebo; Q4W, once every four weeks; SA, South America; TTR, transthyretin

The prediction and variability corrected visual predictive check for PK and PKPD model are shown in Figure 29, suggesting an acceptable description of the data by the model.

Figure 29. (Left) Prediction and Variability Corrected Visual Predictive Check of the Final Population (Right) PK Model PKPD Model Overall



Open circles = individual observed data, dashed blue lines = observed 5th & 95th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% confidence interval around the model predicted 5th, 50th, & 95th percentiles.
Note: Log-log scale is used.
Note data from studies and treatment regimens are pooled, including single and multiple dose regimens with differing duration of treatment and follow-up times.



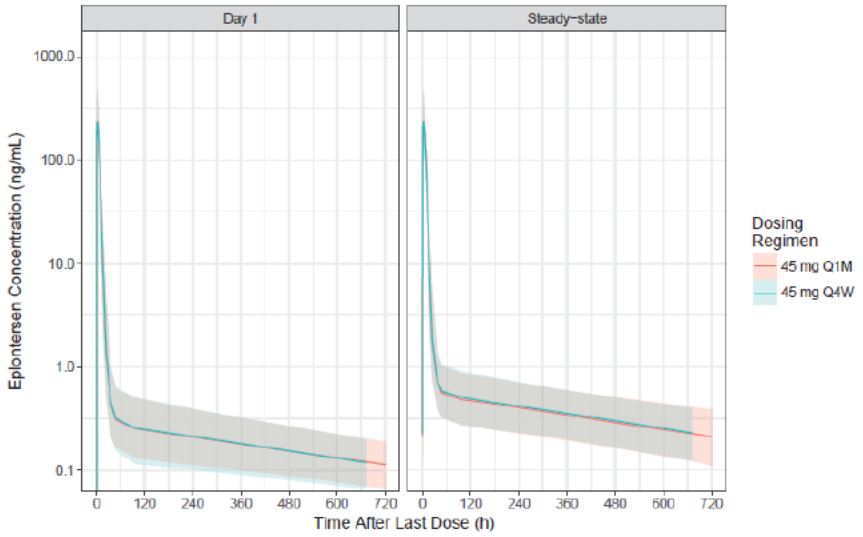
Open circles = individual observed data, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% confidence interval around the model predicted 10th, 50th, & 90th percentiles.
Note data from studies and treatment regimens are pooled, including single and multiple dose regimens with differing duration of treatment and follow-up times.

Source: Figure 29 on Page 101, Figure 42 on Page 116 of ppk01-final-report.pdf.
Abbreviations: PK, pharmacokinetic; PKPD, pharmacokinetic-pharmacodynamic

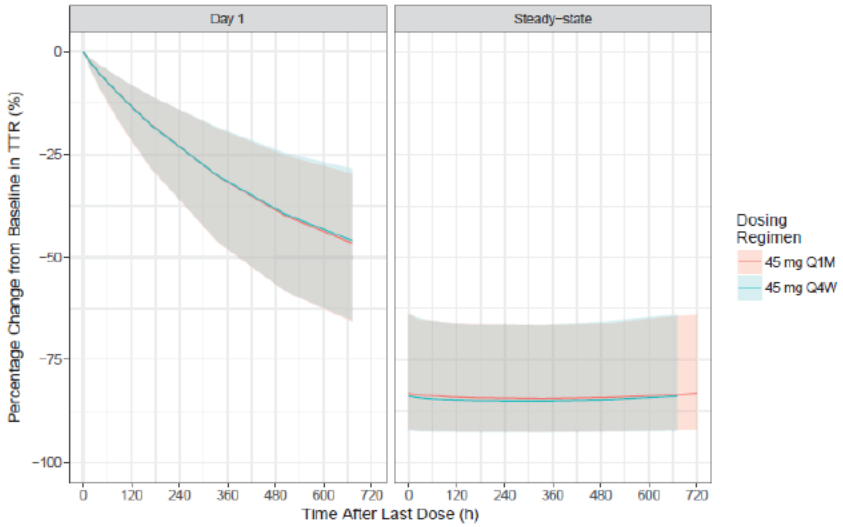
Also, the Applicant is seeking approval of a once every month (Q1M) dosing regimen in comparison to a Q4W dosing regimen evaluated in clinical program. The simulated PK and PD profiles following 45 mg eplontersen Q4W for 13 doses and 45 mg eplontersen Q1M for 12 doses are shown in Figure 30, respectively. Overall, both the PK and PD profiles following 45 mg Q4W and Q1M dosing overlap on Day 1 and at steady-state show only a marginal difference in median (and 80% prediction interval) eplontersen and TTR concentrations.

Figure 30. (A) Simulated PK Concentration-Time Profile (45 mg Q4W and Q1M Dosing Regimen) (B) Simulated Percent Change From Baseline in TTR Over Time (45 mg Q4W and Q1M Dosing Regimen)

(A)



(B)



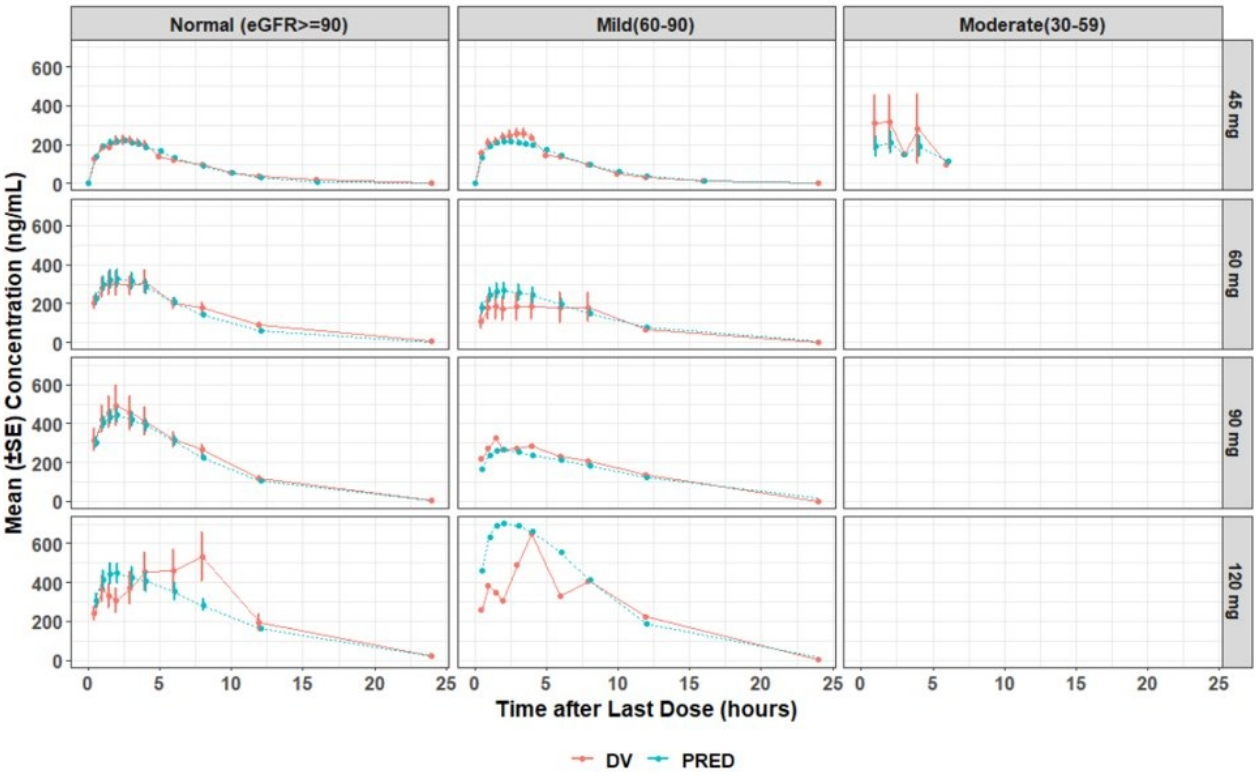
Source: Figure 49, 50 on Page 123, 124, Figure 42 on Page 116 of ppk01-final-report.pdf.
Note:

- (Panel A) Solid line shows the median concentration and shaded region is the 80% prediction interval for the median.
- (Panel B) Solid line shows the median percent change from baseline in TTR over time and the shaded region is the 80% prediction interval for the median.

Abbreviations: Q1M, once every month; Q4W, once every four weeks

The models and parameters were generated as reported by the Applicant. The Applicant's analysis was found to be reasonable. Figure 31 shows that eplontersen plasma concentrations in subjects with mild renal impairment are not significantly different from subjects with normal renal function. The data in subjects with moderate renal impairment is limited and the difference in plasma concentrations relative to normal subjects does not translate into the need for an alternate dosing regimen. Overall, the proposed labeling statements regarding eplontersen PK based on population PK and PKPD analysis are acceptable.

Figure 31. Observed and Population Predicted Plasma Eplontersen Concentrations in Subjects With Normal, Mild or Moderate Renal Impairment



Source: Reviewer's analysis.
Abbreviations: DV, dependent variable (observed); PRED, predicted; SE, standard error

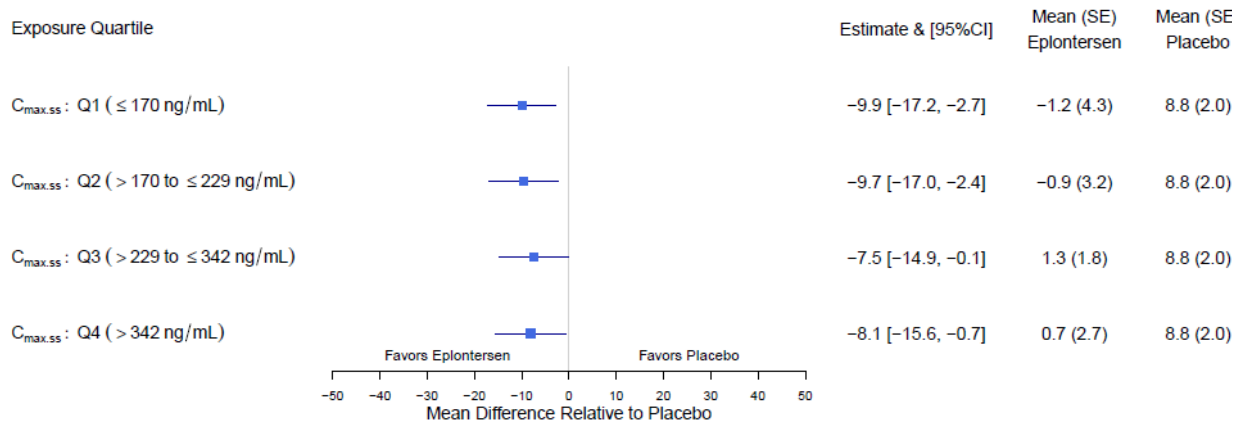
Exposure-Response Analysis

The analysis evaluated the exposure-response relationship on selected efficacy and safety endpoints at the target dose of eplontersen 45mg via SC administration Q4W in subjects with hATTR-PN using data from the pivotal Phase 3 Study ION-682884-CS3 with a data cut-off date of July 19, 2022.

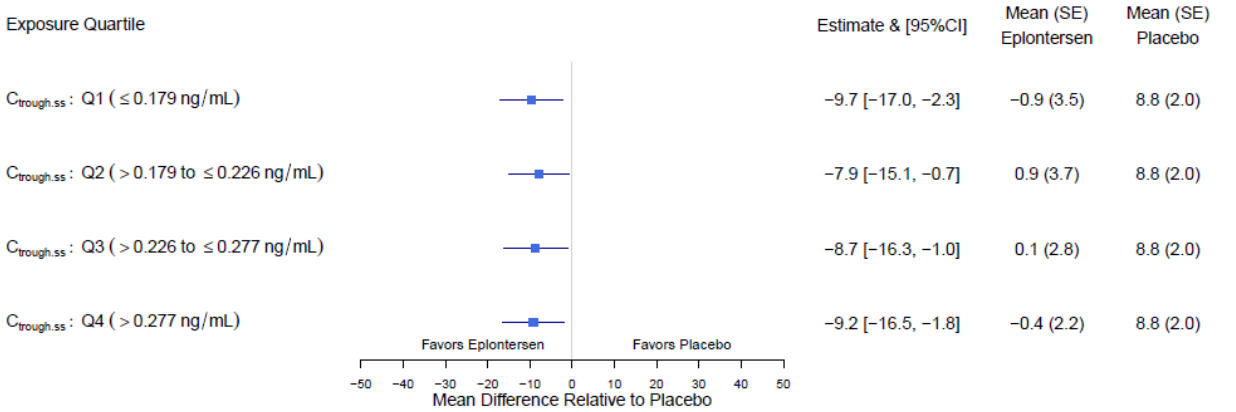
As showed in Figure 32, Figure 33, and Figure 34, the exposure-response relationships for efficacy endpoints and safety endpoints, showed no clear differences or trends across the exposure quartiles suggesting that there is no relationship between steady state C_{max} or C_{trough} and efficacy or safety.

Figure 32. mNIS+7 Change From Baseline at Week 35 – (A) Forest Plot by $C_{max,ss}$ Quartiles and (B) $C_{trough,ss}$ Quartiles

(A)



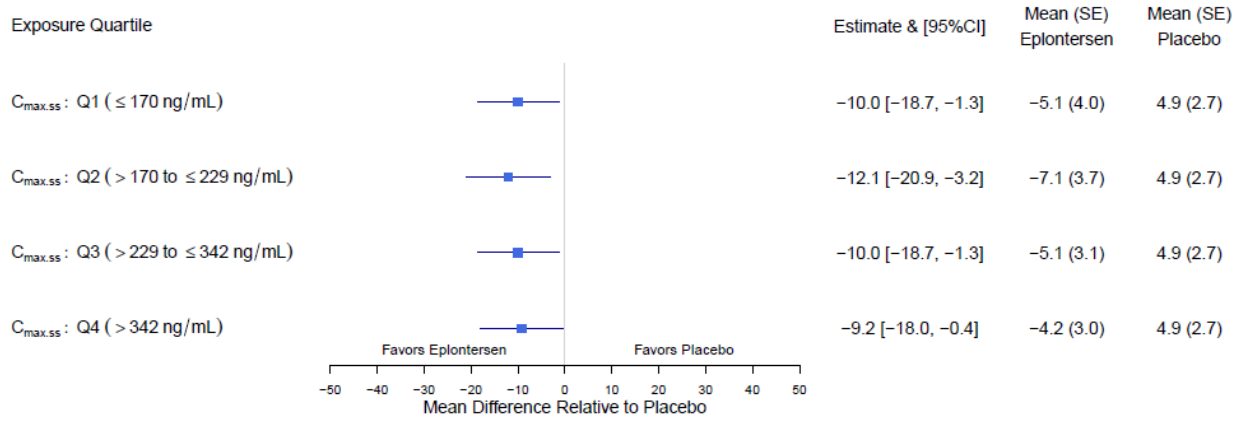
(B)



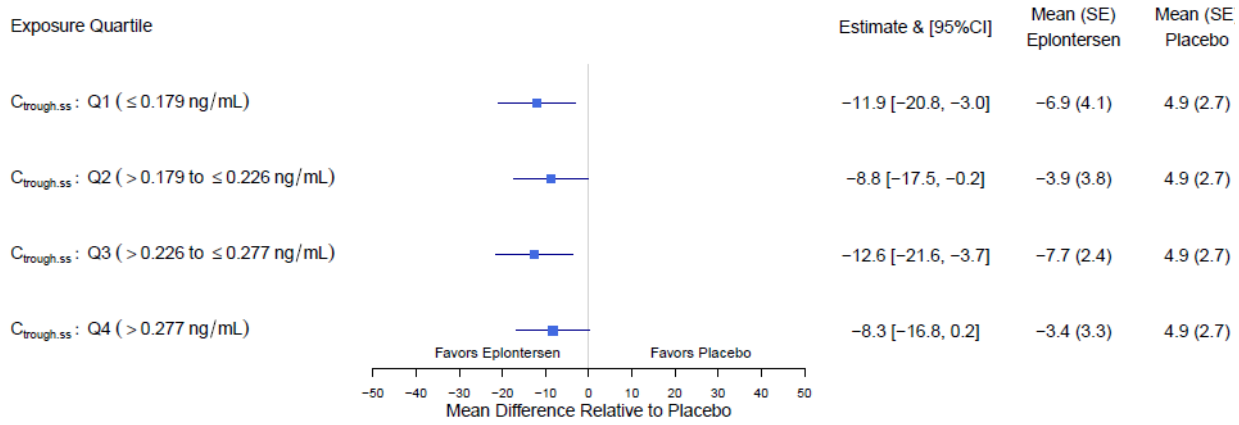
Source: Clinical Pharmacology Summary, Figure 24.
Abbreviations: CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady-state; $C_{trough,ss}$, lowest plasma concentration at steady-state; mNIS+7, modified Neuropathy Impairment Score +7; Q, quartile; SE, standard error

Figure 33. Norfolk QOL-DN Score Change From Baseline at Week 35 – (A) Forest Plot by $C_{max,ss}$ Quartiles and (B) $C_{trough,ss}$ Quartiles

(A)



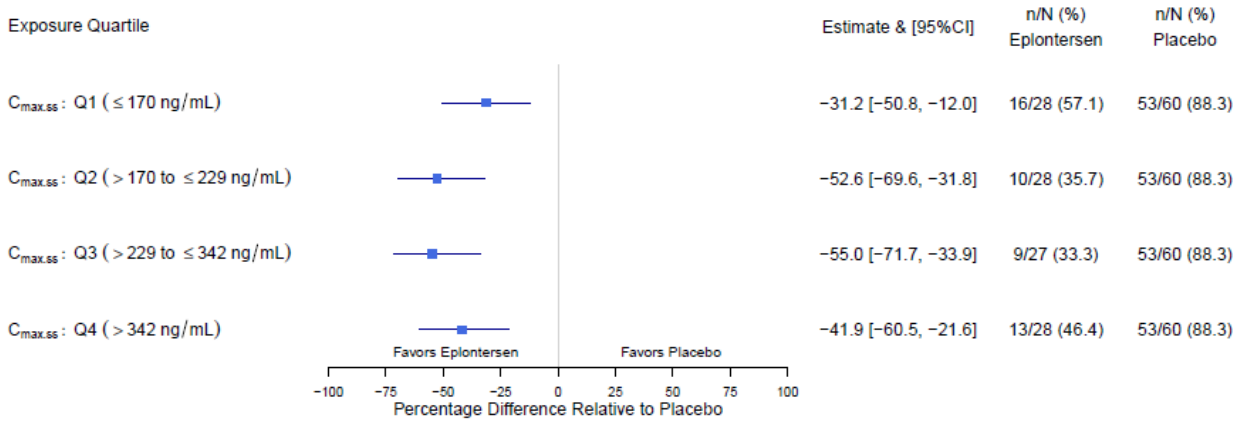
(B)



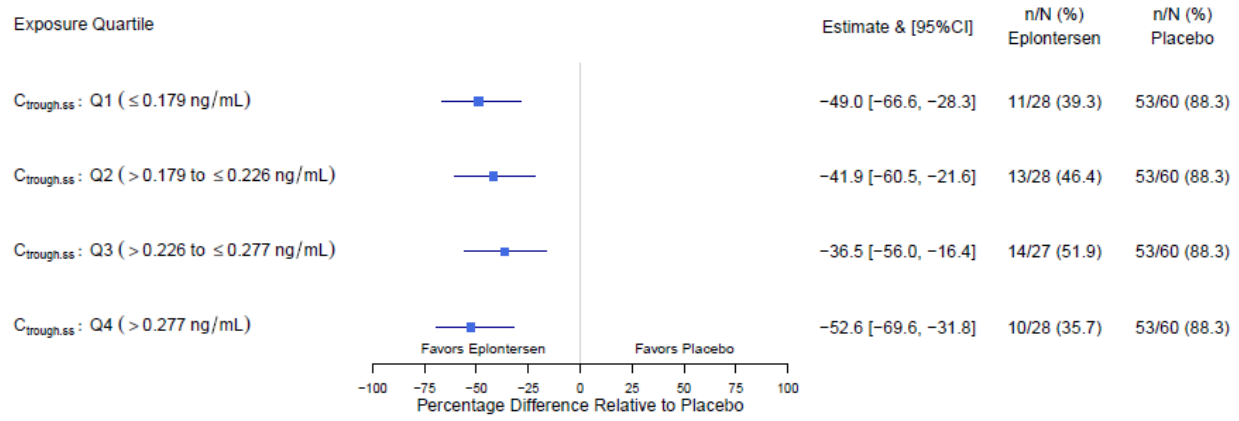
Source: Clinical Pharmacology Summary, Figure 25.
Abbreviations: CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady-state; $C_{trough,ss}$, lowest plasma concentration at steady-state; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire; Q, quartile; SE, standard error

Figure 34. Percentage Difference in Incidence of Moderate or Severe Treatment- Emergent Adverse Events Between Placebo and Treated Subjects – (A) Forest Plot by $C_{max,ss}$ Quartiles and (B) $C_{trough,ss}$ Quartiles

(A)



(B)



Source: Clinical Pharmacology Summary, Figure 26.
Abbreviations: CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady-state; $C_{trough,ss}$, lowest plasma concentration at steady-state; Q, quartile; SE, standard error

14.6. Pharmacogenetics

No pharmacogenomics data were submitted with this application.

15. Study/Trial Design

Please refer to Section 6.2 for further details related to study/trial design, eligibility criteria, the statistical analysis plan, and results of clinical studies intended to demonstrate efficacy.

Dose Selection

The eplontersen dose of 45 mg given once every 4 weeks was chosen based on the acceptable safety profile noted in the Phase 1/2 study (ION-682884-CS1) and a substantial PD effect in mean reduction in plasma TTR concentration. This dosing schedule is supported by the 4-week half-life noted in monkey liver. Please see Section 6.1 for further details on dose selection.

Concomitant Therapy

In ION-682884-CS3, concomitant therapy is defined as any nonprotocol-specified drug or substance administered between the signing of the informed consent and the last study visit. Subjects were required to take daily recommended dietary allowance supplemental doses of vitamin A during treatment (and post-treatment evaluation periods). In addition, any medications deemed necessary by the investigator were allowed except for tafamidis, inotersen, patisiran, or off-label use of diflunisal. Short courses of doxycycline (<15 days) were allowed.

Aside from vitamin A supplements, other frequently reported concomitant medications (≥10% of subjects in eplontersen group) were tozinameran (32.6%); paracetamol (29.2%); gabapentin (21.5%); pregabalin (20.1%); furosemide (14.6%); COVID-19 vaccine and elasomeran (13.2% each); domperidone and loperamide (12.5% each); COVID-19 vaccine NRVV Ad, clonazepam, ibuprofen, and calcium phosphate/colecalciferol/retinol (11.8% each); vitamins and minerals not otherwise specified (11.1%); and omeprazole, pantoprazole, and ascorbic acid with other vitamins (10.4% each).

16. Efficacy

Please refer to Section 6 for evaluation of efficacy on ION-682884-CS3.

17. Clinical Safety

Please refer to Section 7 for evaluation of safety of ION-682884-CS3.

Human Carcinogenicity or Tumor Development

There does not appear to be any increased risk of cancer with eplontersen treatment.

Overdose

An overdose was defined as the accidental or intentional use of a drug in an amount higher than the dose being studied. As of the cutoff date of July 19, 2022, two subjects ([(b) (6)] and [(b) (6)]) were identified as having experienced overdose; both received a dose of 120 mg at Week 17. Subject [(b) (6)] experienced a treatment-emergent adverse event (TEAE) of Hepatic enzyme increased approximately 2 weeks after the overdose (marginal increase in ALT [65 and 68 U/L, 1.3 x ULN]); dosing was not interrupted, and the elevations resolved spontaneously. Subject [(b) (6)] did not have any TEAEs reported within 30 days of the overdose.

Drug Abuse Potential

Eplontersen does not cross the blood-brain barrier. At the pre-NDA meeting dated August 23, 2022, it was stated that "ION-682884 appears to lack abuse potential, and therefore animal and human studies of abuse potential are not warranted at this time."

18. Clinical Virology

This section is not applicable.

19. Clinical Microbiology

This section is not applicable.

20. Mechanism of Action/Drug Resistance

Eplontersen is an antisense oligonucleotide GalNAc conjugate that causes hepatic-targeted degradation of TTR mRNA (for mutant variants and wild-type TTR) through direct binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.

21. Other Drug Development Considerations

This section is not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

This section is not applicable.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 92). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 92. Key Labeling Changes and Considerations

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
BOXED WARNING	Not applicable.
1 INDICATIONS AND USAGE	The applicant proposed (b) (4) which was removed for consistency with other Indications and Usage statements in the labeling of other drugs approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis.
2 DOSAGE AND ADMINISTRATION	Phrasing was added to align with 21 CFR 201.57(c)(3)(iv) regarding visually inspecting parental products. Revisions were made to clarify statements and recommendations regarding missed dose and the appropriate injection sites.
4 CONTRAINDICATIONS	No changes.
5 WARNINGS AND PRECAUTIONS	No major changes.
6 ADVERSE REACTIONS	In the Applicant proposed PI, (b) (4) The analysis by the Agency noted additional adverse reactions that met the cutoff of occurring in at least 5% of patients treated with WAINUA and reasonably likely cause by the drug. Therefore, Table 1, "Adverse Reactions Reported in at least 5% of Patients Treated with WAINUA (Study 1)", was added, which includes the adverse reactions of vitamin A decreased, vomiting, proteinuria, injection site reactions, blurred vision, and cataracts. The adverse reaction of injection site reactions includes a combination of terms (i.e., erythema, pain, and pruritis) that were proposed to be stated separately in the Applicant's draft PI. The Agency added information regarding less common but serious adverse reactions under the common adverse reaction table as recommended in the FDA guidance for industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006). The labeling language included is as follows: "Three serious adverse reactions of atrioventricular (AV) heart block (2%) occurred in WAINUA-treated patients, including 1 case of complete AV block."
7 DRUG INTERACTIONS	Not applicable.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Pregnancy (8.1) Revisions were made for consistency with current preferred labeling text; however, there were no conclusionary differences. Lactation (8.2) No major changes. Pediatric Use (8.4) No changes.

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
	Geriatric Use (8.5) No major changes. Renal Impairment (8.6) The estimated glomerular filtration rate for mild to moderate renal impairment was revised from [redacted] to 30 to <90 mL/min/1.73m^2 based on the range values for renal function provided in Table 1 of the draft FDA guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020). In addition, the Applicant proposed [redacted] This statement was deleted because [redacted] this statement could be misleading. Hepatic Impairment (8.7) No major changes.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Not applicable.
12 CLINICAL PHARMACOLOGY	Mechanism of Action (12.1) Terms [redacted] were removed to adhere to 21 CFR 201.56(a)(2). Pharmacodynamics (12.2) The QTc [redacted] comparison of the dose studied to the maximum recommended dose was included, and the language under the Cardiac Electrophysiology heading was rephrased consistent with the draft FDA guidance for industry *QTc Information in Human Prescription Drug and Biological Product Labeling* (August 2023). Pharmacokinetics (12.3) Revisions were made consistent with the FDA guidance for industry *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016). Information [redacted] was removed [redacted] Immunogenicity (12.6) The Applicant proposed [redacted] This was revised to note that although no effect of ADA on these parameters were noted, the available data are too limited to make definitive conclusions, which follows the recommendations in the draft FDA guidance for industry *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022).
13 NONCLINICAL TOXICOLOGY	Revisions were made for consistency with current preferred labeling text; however, there were no conclusionary differences.

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
14 CLINICAL STUDIES	The notation (b) (4) was removed (b) (4) (b) (4) (b) (4) However, limited TTR information is included in subsection 12.2.
17 PATIENT COUNSELING INFORMATION	No major changes.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	(b) (4) information was removed (b) (4) (b) (4) In addition, the following revisions were made: Dosage Forms and Strengths (3) The Applicant proposed (b) (4) that was deleted (b) (4) Description (11) The graphic of the structure was revised (b) (4) to eplontersen sodium. The excipient names were revised and alphabetized for consistency with USP nomenclature and recommendations. The quantitative ingredient information and declaration of ingredients used to adjust pH or tonicity was added per 21 CFR 201.56(c)(12)(i)(C) and 201.100(b)(5)(iii).

Source: Generated by the FDA review team.
[a] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[b] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): hATTR, hereditary transthyretin-mediated amyloidosis; AV, atrioventricular; CFR, code of federal regulations; PI, Prescribing Information; QTc, Interval from start of the Q wave to the end of the T wave, corrected for heart rate; TTR, transthyretin

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information
- Instructions for Use
- Container
- Carton

24. Postmarketing Requirements and Commitments

PMR 4564-1

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to eplontersen during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

- Draft Protocol Submission: 10/2024
- Final Protocol Submission: 08/2025
- Interim Study Report Submissions: 11/2026
  11/2027
  11/2028
  11/2029
  11/2030
  11/2031
  11/2032
  11/2033
  11/2034
  11/2035
- Study Completion: 12/2035
- Final Report Submission: 12/2036

PMR 4564-2

Perform a lactation study (milk only) in lactating women who have received a therapeutic dose of eplontersen using a validated assay to assess concentrations of eplontersen in breast milk.

- Draft Protocol Submission: 12/2024
- Final Protocol Submission: 07/2025
- Study Completion: 12/2026
- Final Report Submission: 05/2027

PMR 4564-3

Conduct a 26-week carcinogenicity study of eplontersen in Tg.rasH2 mouse.

- Draft Protocol Submission: 10/2021 (submitted)
- Final Protocol Submission: 01/2024

- Trial Completion: 04/2023
- Final Report Submission: 05/2024

PMR 4564-4

Evaluate the incidence and provide analyses of glomerulonephritis, thrombocytopenia, and atrioventricular block observed in the placebo-controlled study, ION-682884-CST, of eplontersen in adult hereditary and wild-type ATTR cardiomyopathy patients.

- Final Protocol Submission: 08/2019 (Submitted)
- Trial Completion: 11/2025
- Final Report Submission: 10/2026

25. Financial Disclosure

Table 93. Covered Clinical Studies: ION-682884-CS3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 206		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: IONIS PHARMACEUTICALS INC		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration; N/A, not applicable; Sponsor, Ionis Pharmaceuticals, Inc.

26. References

26.1. Literature

Benson, MD, M Waddington-Cruz, JL Berk, M Polydefkis, PJ Dyck, AK Wang, V Plante-Bordeneuve, FA Barroso, G Merlini, L Obici, M Scheinberg, TH Brannagan, 3rd, WJ Litchy, C Whelan, BM Drachman, D Adams, SB Heitner, I Conceicao, HH Schmidt, G Vita, JM Campistol, J Gamez, PD Gorevic, E Gane, AM Shah, SD Solomon, BP Monia, SG Hughes, TJ Kwoh, BW McEvoy, SW Jung, BF Baker, EJ Ackermann, MA Gertz, and T Coelho, 2018, Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis, N Engl J Med, 379(1):22-31, https://www.ncbi.nlm.nih.gov/pubmed/29972757.

Coutinho, P, A Martins da Silva, J Lopes Lima, and A Resende Barbosa, 1980, Forty years of experience with type I amyloid neuropathy. Review of 483 cases, Amyloid and amyloidosis:88-98.

John, RM, 2018, Arrhythmias in Cardiac Amyloidosis, J Innov Card Rhythm Manag, 9(3):3051-3057, https://www.ncbi.nlm.nih.gov/pubmed/32477799.

Schmidt, HH, M Waddington-Cruz, MF Botteman, JA Carter, AS Chopra, M Hopps, M Stewart, S Fallet, and L Amass, 2018, Estimating the global prevalence of transthyretin familial amyloid polyneuropathy, Muscle Nerve, 57(5):829-837, https://www.ncbi.nlm.nih.gov/pubmed/29211930.

Solomon, SD, D Adams, A Kristen, M Grogan, A Gonzalez-Duarte, MS Maurer, G Merlini, T Damy, MS Slama, TH Brannagan, 3rd, A Dispenzieri, JL Berk, AM Shah, P Garg, A Vaishnaw, V Karsten, J Chen, J Gollob, J Vest, and O Suhr, 2019, Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis, Circulation, 139(4):431-443, https://www.ncbi.nlm.nih.gov/pubmed/30586695.

Suanprasert, N, JL Berk, MD Benson, PJ Dyck, CJ Klein, JA Gollob, BR Bettencourt, V Karsten, and PJ Dyck, 2014, Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials, J Neurol Sci, 344(1-2):121-128, https://www.ncbi.nlm.nih.gov/pubmed/25012480.

Vinik, EJ, RP Hayes, A Oglesby, E Bastyr, P Barlow, SL Ford-Molvik, and AI Vinik, 2005, The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy, Diabetes Technol Ther, 7(3):497-508, https://www.ncbi.nlm.nih.gov/pubmed/15929681.

Vinik, EJ, AI Vinik, JF Paulson, IS Merkies, J Packman, DR Grogan, and T Coelho, 2014, Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy, J Peripher Nerv Syst, 19(2):104-114, https://www.ncbi.nlm.nih.gov/pubmed/24738700.

26.2. Guidance for Industry

FDA Draft Guidance for Industry *QTc Information in Human Prescription Drug and Biological Product Labeling* (August 2023), Food and Drug Adminsitration (FDA), https://www.fda.gov/media/170814/download.

FDA Guidance for Industry *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016), Food and Drug Administration (FDA), https://www.fda.gov/media/74346/download.

FDA Draft Guidance for Industry *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling - Content and Format* (February 2022), Food and Drug Administration (FDA), https://www.fda.gov/media/155871/download.

FDA Guidance for Industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006), Food and Drug Administration (FDA), https://www.fda.gov/media/72139/download.

ICH Guidance for Industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995), International Council for Harmonisation (ICH), https://www.fda.gov/media/71180/download.

FDA Draft Guidance for Industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020), Food and Drug Administration (FDA), https://www.fda.gov/media/78573/download.

26.3. Other

FDA *Standard Safety Tables and Figures: Integrated Guide* (August 2022), Food and Drug Administration (FDA)'s Office of New Drugs (OND): Center for Drug Evaluation and Research (CDER), https://downloads.regulations.gov/FDA-2022-N-1961-0046/attachment_1.pdf.

27. Review Team

Table 94. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Justine Kankam
Nonclinical reviewer	Chun-Ting (David) Lee
Nonclinical team leader	Lois Freed
OCP reviewer(s)	Ramakrishna Samala; Vishnu Sharma, Xiaohan Cai (secondary reviewer)
OCP team leader(s)	Atul Bhattaram; Bilal AbuAsal
Clinical reviewer	Monica Petluru; Gerard Boehm
Clinical team leader	Laura Jawidzik; Sally Yasuda
Biometrics reviewer	Jinnan Liu
Biometrics team leader	John P. Lawrence,
Cross-disciplinary team leader	Laura Jawidzik
Division director (pharm/tox)	Lois Freed
Division director (OCP)	Mehul Mehta
Division director (OB)	Hsien Ming (Jim) Hung
Division director (clinical)	Emily Freilich
Office director (or designated signatory authority)	Teresa Buracchio

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 95. Additional Reviewers of Application

Office or Discipline	Name(s)
Associate Director for Labeling	Tracy Peters
OPQ	Martha Heimann
OPDP	Aline Moukhtara; Samuel Fasanmi
OSI	Phillip Kronstein; Cara Alfaro
OSE/DEPI	Kira Leishear; Catherine Callahan
OSE/DMEPA2	Chad Morris; Stephanie DeGraw; Danielle Harris; Ila Srivastava; Colleen Little; Lolita Sterrett
OSE/DRISK	Jacqueline Sheppard; May Chanliston

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-96 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Laura Jawidzik ON DNI	Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Laura Jawidzik

Digitally signed by Laura Jawidzik

Date: 12/20/2023 5:36 PM EST
GUID: 2023122022366

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Chun Ting Lee ON DPTN	Sections: Sections 5.1, 7.1, 13.1, 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Chun Ting Lee

Digitally signed by Chun Ting Lee

Date: 12/20/2023 5:37 PM EST
GUID: 20231220223710

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Justine Kankam ORO DRON	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Justine Kankam

Digitally signed by Justine Kankam

Date: 12/20/2023 5:43 PM EST
GUID: 20231220224323

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Jinnan Liu OB DBI	Sections: 6.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jinnan Liu

Digitally signed by Jinnan Liu

Date: 12/20/2023 5:44 PM EST
GUID: 20231220224420

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Secondary Reviewer	Tracy Peters ON DNI	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Tracy Peters**

Digitally signed by Tracy Peters

Date: 12/21/2023 11:37 AM EST
GUID: 20231221163729

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Primary Reviewer	Tracy Peters ON DNI	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Tracy Peters**

Digitally signed by Tracy Peters

Date: 12/21/2023 11:38 AM EST
GUID: 20231221116389

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Monica Petluru ON DNI	Sections: 1-4, 6-8, 10, 15-19, 20, 23, 25, 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Monica Petluru

Digitally signed by Monica Petluru

Date: 12/21/2023 11:42 AM EST
GUID: 20231221164215

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Heather Bullock ORO DRON	Sections: Summary of Regulatory History	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Heather Bullock

Digitally signed by Heather Bullock

Date: 12/21/2023 12:05 PM EST
GUID: 20231221175540

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Ramakrishna Samala OCP DNP	Sections: 5.2, 6.1, 6.2, 8, and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Ramakrishna Samala**

Digitally signed by Ramakrishna San

Date: 12/21/2023 12:20 PM EST
GUID: 20231221172026

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Supervisor / Team Lead	Bilal Abuasal OCP DNP	Sections: 5.2, 6.1, 6.2, 8, and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Bilal Abuasal**

Digitally signed by Bilal Abuasal

Date: 12/21/2023 12:34 PM EST
GUID: 20231221173421

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Primary Reviewer	Bruce Huang OBP DBRRII	Sections: 14.4 Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Bruce Huang

Digitally signed by Bruce Huang

Date: 12/21/2023 12:44 PM EST
GUID: 20231221174414

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Deputy Director for Safety Discipline Secondary Reviewer	Sally Yasuda ON DNI	Sections: 7.7.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sally Yasuda

Digitally signed by Sally Yasuda

Date: 12/21/2023 12:44 PM EST
GUID: 20231221174443

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Lois Freed ON DPTN	Sections: 5, 7, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Lois Freed

Digitally signed by Lois Freed

Date: 12/21/2023 12:51 PM EST
GUID: 20231221175514

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Deputy Director for Safety Discipline Primary Reviewer	Sally Yasuda ON DNI	Sections: 7.7.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sally Yasuda

Digitally signed by Sally Yasuda

Date: 12/21/2023 12:54 PM EST
GUID: 20231221175429

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Venkatesh Bhattaram OCP DPM	Sections: 5.2, 6.1, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Venkatesh Bhattaram**

Digitally signed by Venkatesh Bhatta

Date: 12/21/2023 1:08 PM EST
GUID: 2023122118839

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
12/20/2023 05:36:42 PM

TERESA J BURACCHIO
12/21/2023 02:28:38 PM
;