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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Rainer W. Paine, MD, PhD
NDA 215515
Amvuttra (vutrisiran)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
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Reviewer Name(s)	Rainer W. Paine, MD, PhD
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Established/Proper Name	vutrisiran
(Proposed) Trade Name	Amvuttra
Applicant	Alnylam Pharmaceuticals Inc.
Dosage Form(s)	Injection
Applicant Proposed Dosing Regimen(s)	25 mg administered by subcutaneous injection once every 3 months (quarterly)
Applicant Proposed Indication(s)/Population(s)	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SUR	safety update report
TEAE	treatment emergent adverse event

1.1. Product Introduction

In hereditary transthyretin amyloidosis (hATTR amyloidosis), misfolding of the transthyretin (TTR) protein leads to its aggregation and the formation of amyloid fibrils, which interfere with the normal function of affected organ systems, including the peripheral nervous system, which was evaluated for this product.

Vutrisiran is a chemically modified double-stranded small interfering ribonucleic acid (siRNA) that targets variant and wild-type transthyretin (TTR) messenger RNA (mRNA) and is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes. It is related to patisiran, approved for the same indication in 2018, but vutrisiran has been chemically modified for greater metabolic stability, prolonged liver residence time, and less frequent dosing (every 3 months) compared to the dosing every 3 weeks for patisiran.

Note that reviewer commentary throughout the text is presented in *italics*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study HELIOS-A is a single adequate and well-controlled study that can support approval of vutrisiran for the treatment of adults with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), also known as transthyretin familial amyloid polyneuropathy (TTR-FAP).

The HELIOS-A study was a well-designed, multinational, 18-month study that has provided reliable, clinically meaningful, and statistically strong evidence of an effect of vutrisiran on polyneuropathy in subjects with hATTR. The placebo group from the approved patisiran NDA 210922 phase 3 APOLLO study, which enrolled a similar subject population and incorporated similar endpoints to HELIOS-A, was used as an external control group for the efficacy analyses of vutrisiran. The mean scores on the HELIOS-A study's primary efficacy endpoint in vutrisiran-treated subjects were notably improved from baseline, which is inconsistent with the known course of the condition. Although the trial was not designed to demonstrate that subjects statistically improved on treatment, it is clear that treatment with vutrisiran resulted in at least the stability of polyneuropathy in many subjects. The results of the primary analyses from this trial were also supported by highly statistically significant positive results on the trial's pre-specified secondary efficacy endpoints at Month 9.

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Confirmatory evidence is provided by data that provide strong mechanistic support (i.e., reduction in serum TTR) and scientific knowledge about the effectiveness of another drug in the same pharmacological class (i.e., patisiran for the treatment of hATTR-PN).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Vutrisiran (Amvuttra™, called ALN-TTRSC02 in clinical trials) is a chemically modified double-stranded small interfering ribonucleic acid (siRNA) that targets transthyretin (TTR) messenger ribonucleic acid (mRNA) in order to suppress the production of TTR protein. Clinical studies evaluated subjects with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). Based on the positive results of a single adequate and well-controlled study (Study HELIOS-A) and confirmatory evidence from pharmacodynamic/mechanistic data of transthyretin reduction with vutrisiran and other drugs in the class (i.e., patisiran, inotersen), it is the conclusion of this reviewer that the effectiveness of vutrisiran has been established for the treatment of adults with hATTR-PN.

Hereditary transthyretin amyloidosis (hATTR amyloidosis) 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 2500 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).

Patisiran and inotersen are the two drugs approved for the treatment of the neuropathy of hATTR amyloidosis in the U.S. Vutrisiran is related to patisiran, approved for the same indication in 2018, but vutrisiran has been chemically modified for less frequent subcutaneous dosing (every 3 months) compared to the intravenous dosing every 3 weeks for patisiran. Inotersen is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Inotersen is administered by weekly subcutaneous injection. Inotersen is available only through a restricted distribution program called the TEGSEDI REMS Program because of the risks of thrombocytopenia and glomerulonephritis. Liver transplant may be an option for some patients. Tafamidis (approved for treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults, but not for the treatment of hATTR-PN) and diflunisal are reported to be used off-label.

An 18-month external placebo-controlled multinational study of vutrisiran in adults with hATTR-PN (122 vutrisiran, 77 external placebo control) evaluated polyneuropathy through clinical neurological examinations and tests of nerve conduction, sensation, and postural blood pressure. The placebo-treated subjects worsened on these measures during the course of the trial, as would be expected from disease progression. In contrast, the average scores in the vutrisiran-treated subjects improved modestly from baseline. Whereas only approximately 18% of placebo-

treated subjects improved by month 9, approximately 50% of vutrisiran-treated subjects demonstrated numerical improvements of polyneuropathy scores during the trial. There was a similar pattern of positive results on a subject-reported subjective assessment of the clinical impact of polyneuropathy on their quality of life. Vutrisiran-treated subjects had a mean serum TTR reduction of 81% from baseline at treatment Month 9, compared to a 1.5% serum TTR reduction in the external placebo control group.

The most commonly observed ($\geq 5\%$) adverse events associated with the use of vutrisiran in the 18-month external placebo-controlled study were arthralgia, vitamin A decreased, and dyspnea. The proportion of subjects experiencing serious adverse reactions was 24% in the vutrisiran group and 40% in the external placebo group. The adverse events that caused the most subjects to stop taking vutrisiran across all clinical studies were cardiac failure or cardiac death (3 subjects, 2.5%).

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 vutrisiran for the treatment of polyneuropathy in adults with hATTR.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Hereditary transthyretin amyloidosis (hATTR amyloidosis) is a genetic disease that causes 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 symptom onset, most often due to cardiac dysfunction, infection, or cachexia. - The incidence of hATTR amyloidosis is 1/100,000 in U.S. Caucasians.	hATTR amyloidosis is a serious and life-threatening disease that can lead to disability and death.
Current Treatment Options	- Patisiran 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 3 weeks and	There remains a significant unmet clinical need for effective treatments for hATTR amyloidosis polyneuropathy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	carries a warning for infusion-related reactions. • Tafamidis is approved for treatment of the cardiomyopathy of hATTR amyloidosis, but is not approved for the treatment of hATTR-PN. • Other treatment options for hATTR amyloidosis include liver transplant and medical management of associated symptoms. • Diflunisal, a non-steroidal anti-inflammatory drug, is sometimes used off-label to treat the disease.	
<u>Benefit</u>	• In the 18-month external placebo-controlled multinational study of vutrisiran in adults with hATTR-PN (122 vutrisiran, 77 external placebo control) there was an average treatment-effect at Month 9 of 17 points (baseline ~60; 304-point scale) on the Modified Neurological Impairment Score +7 (mNIS+7), an objective evaluation of a range of signs and symptoms related to polyneuropathy, for subjects in the vutrisiran group compared to placebo (p<0.0001). • There was an average treatment-effect at Month 9 of 16 points (baseline ~47; 141-point scale) on the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score, a subject-reported assessment of the impact of their polyneuropathy, for subjects in the vutrisiran group compared to placebo (p<0.0001). • There was statistically significant treatment benefit in the vutrisiran group compared to placebo on the secondary endpoint of gait speed (10-MWT). • Vutrisiran-treated subjects had a mean serum TTR reduction of 81% from baseline at treatment Month 9, compared to a 1.5% serum TTR reduction in the external placebo control group.	The results of the 18-month external placebo-controlled multinational study of vutrisiran in adults with hATTR-PN provide reliable, clinically meaningful, and statistically strong evidence that vutrisiran is effective for the treatment of polyneuropathy in the subjects. Confirmatory evidence is provided by data that provide strong mechanistic support (i.e., reduction in serum TTR) and scientific knowledge about the effectiveness of another drug in the same pharmacological class (i.e., patisiran for the treatment of hATTR-PN).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety database for vutrisiran includes all subjects from the Phase 3 externally controlled study and the open-label extension study. • The most commonly observed ($\geq 5\%$ and at least 2% more frequently in the vutrisiran group than in the placebo group) adverse events associated with the use of vutrisiran in the 18-month external placebo-controlled study were arthralgia, vitamin A decreased, and dyspnea. • The adverse events that caused the most subjects to stop taking vutrisiran across all clinical studies were cardiac failure or cardiac death (3 subjects, 2.5%). • Mortality was numerically lower in the vutrisiran group (2.5%) than in the external placebo group (8%) or concurrent comparator patisiran group (7%). However, the Phase 3 clinical study was not designed to statistically evaluate an effect on survival and no conclusion regarding a potential long-term survival effect can be made. • Vutrisiran reduces vitamin A levels in the body. All subjects received the recommended daily amount of vitamin A as a supplement.	The safety profile of vutrisiran is acceptable to support an approval. WARNINGS and PRECAUTIONS should be included in labeling to describe the need for vitamin A supplementation to avoid possible vitamin A deficiency.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	6.1.1
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	6.1.1
☒	Performance outcome (PerfO)	6.1.1
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) 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. TTR is a tetrameric protein primarily produced in hepatocytes. The disease is caused by genetic mutations in the TTR gene that lead the tetrameric TTR protein to break into monomeric units that misfold and aggregate as amyloid fibril deposits.

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 [TTRFAP]), 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.

The exact incidence of hATTR is unknown and varies geographically, but is estimated to be 1/100,000 in U.S. Caucasians. Between approximately 100 to 2500 individuals are estimated to have hATTR-PN in the United States (Schmidt et al., 2018).

Symptom onset occurs between 20 and 70 years of age. Death usually occurs within 5 to 12 years after diagnosis, most often due to cardiac dysfunction, infection, or cachexia. The disease is often misdiagnosed if there is no family history to increase clinical suspicion. The diagnosis can be confirmed by histopathology and genetic analysis.

2.2. Analysis of Current Treatment Options

Patisiran and inotersen are the two drugs approved for the treatment of the neuropathy of hATTR amyloidosis in the U.S. Patisiran is a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Patisiran is administered by IV infusion every 3 weeks. It carries warnings and precautions of infusion-related reactions and reduced serum vitamin A levels. Inotersen is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Inotersen is administered by weekly subcutaneous injection. Inotersen is available only through a restricted distribution program called the TEGSEDI REMS Program because of the risks of thrombocytopenia and glomerulonephritis. Liver transplant may also be a treatment option for some patients. Tafamidis (approved in the U.S. in 2019 for treatment of the heart disease

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(cardiomyopathy) caused by transthyretin mediated amyloidosis (ATTR-CM) in adults, but not for the treatment of hATTR-PN) and diflunisal are reported to be used off-label.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Vutrisiran is a new molecular entity (NME) that is not currently marketed in the United States or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The FDA granted vutrisiran Orphan Drug (May 25, 2018) and Fast Track (April 3, 2020) designations.

A pre-IND meeting was held on 17 July 2018. The Division stated that it was willing to consider the use of an external control based on the placebo arm of the Apollo study for patisiran in the Applicant's proposed Phase 3 study, with the expectation that there would be a large magnitude of effect with vutrisiran that was comparable to the effects observed with patisiran. The Division recommended a concurrent active comparator to provide a descriptive assessment of comparative efficacy and safety to available therapies, which would be important for future risk-benefit comparison. The sponsor proposed co-primary endpoints of TTR reduction (evaluating non-inferiority to patisiran-LNP) and mNIS+7 (evaluating superiority to placebo from the patisiran-LNP Phase 3 APOLLO study), with a primary efficacy analysis after 9 months of treatment. The Division indicated that clinical outcomes should be assessed as a primary endpoint, with TTR reduction as a secondary endpoint. Because the mNIS+7 includes elements that are of uncertain clinical meaningfulness (e.g., electrophysiologic measures), the Division stated that the mNIS+7 would not be acceptable as a primary endpoint alone but would require another clinically meaningful outcome (such as the Norfolk-QOL-DN) as a co-primary. The Division encouraged the Applicant to conduct an 18-month study with an interim efficacy analysis at 9 months, rather than the planned 9-month study. The Division also recommended evaluating additional dosing regimens to allow for the evaluation of dose-response relationships.

An IND (139086) for vutrisiran was submitted to the Division of Neurology Products on October 19, 2018.

(b) (4)

(b) (4)
The sponsor was notified of this determination in the Study May Proceed letter dated December 7, 2018.

A pre-NDA teleconference was held on March 26, 2021, that discussed the format and content of the future NDA submission. The Agency agreed that there was no need to include an assessment of the abuse potential of vutrisiran because the drug does not affect the CNS, it is not chemically or pharmacologically similar to other drugs with known abuse potential, and it does not produce psychoactive effects such as sedation, euphoria, and mood changes.

3.3. Foreign Regulatory Actions and Marketing History

Vutrisiran is not approved in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

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

Inspections found that subject (b) (6), randomized to vutrisiran in the HELIOS A study, experienced “recurrent syncope” (b) (6). This SAE occurred after the 120-day safety update cut-off date was not included in the 120-day safety update. This SAE is discussed in Section 8.4.2.

4.2. Product Quality

Vutrisiran drug product (DP) is a sterile, preservative-free, colorless to yellow solution of 50 mg/mL vutrisiran (equivalent to 53 mg/mL vutrisiran sodium), in (b) (4). The DP formulation has been developed for the SC route of administration and was supplied in 2 primary container closure systems during Phase 3 clinical development:

- Vial: a single-use (b) (4) glass vial with (b) (4) stopper and flip-off seal. This presentation was used in the Phase 1 Study 001 and the 9-month primary efficacy period of HELIOS-A, the Phase 3 study.

- Prefilled syringe (PFS): a single-use Type I glass PFS equipped with a passive needle safety system (PFS-S). This PFS-S presentation was introduced in HELIOS-A after completion of the 9-month primary efficacy period.

Both the vial with syringe and PFS-S presentations contain the same DP formulation and are designed to deliver 0.5 mL vutrisiran DP solution (equivalent to 25 mg of vutrisiran). The PFS-S presentation is the intended to-be-marketed presentation.

During the review, it was determined that vutrisiran was initially supplied for the HELIOS-A study (ALN-TTRSC02-002) in a vial and later in a pre-filled syringe, and that subjects received various combinations of vial and syringe administrations. The volume of vutrisiran administered by syringe is variable (with a range of (b) (4) mL) and some subjects may have received up to (b) (4) mg of vutrisiran instead of the 25 mg specified in the protocol. An information request was sent to the Applicant on September 23, 2021, requesting adverse and serious adverse event data as a function of administration with pre-filled syringe or vial. The Applicant submitted the requested data and responded that during the engineering study as well as from the manufacture of clinical batches of drug product the expelled volume of vutrisiran was consistently no more than 0.553 mL. These data are discussed in the safety review in Section 8.4.5.

Analysis and discussion of the acceptability of product quality is deferred to the chemistry, manufacturing, and controls (CMC) reviewer.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The following are among the relevant findings related to the pharmacokinetic properties of vutrisiran in animals:

- In vivo studies included evaluation of vutrisiran pharmacology in transgenic mice expressing the hTTR V30M variant in which reduction of TTR serum protein was demonstrated after single- and repeat-dose administration.
- Vutrisiran pharmacology was evaluated in monkey studies, in which reduction of TTR serum and TTR plasma protein was observed following single- and repeat-

The following are the key findings from safety pharmacology and toxicology studies:

- An in vitro human ether-à-go-go-related gene (hERG) assay with vutrisiran was not conducted because vutrisiran is a relatively large molecule (approximately 17 kDa), which would preclude interaction with ion channels.
- Vutrisiran is not taken up by cardiac tissue, and is unable to access, interact with, or block the inner pore of the hERG channel.
- A GLP-compliant safety pharmacology study was conducted in monkeys using the intended SC clinical route of administration at 30 or 300 mg/kg vutrisiran. All animals survived until study termination.
- Foci of hepatocellular alteration were a rat-specific finding and were not observed in any of the other nonclinical species tested.
- Repeated administration of vutrisiran at ≥ 30 mg/kg resulted in sustained reductions from baseline in circulating TTR (up to 99%) and vitamin A (up to 89%) in both the 13-week and 9-month monkey studies that were maintained throughout the 12-week recovery period in the 13-week study. There were no apparent toxicological findings associated with the reductions in TTR or vitamin A. Ophthalmic exams, electroretinograms, and histopathology of the eye were normal.
- There was no evidence of genotoxicity or chromosomal damage at all doses evaluated: 500, 1000, and 2000 mg/kg.

Refer to the separate nonclinical review for further details and analysis.

4.5. Clinical Pharmacology

Vutrisiran is absorbed from the injection site and cleared from plasma through uptake into hepatocytes. The distribution of vutrisiran in monkey liver was evaluated following an IV dose of 10 mg/kg, single SC doses of 0.3, 1, 3 and 30 mg/kg, and after qM $\times$ 4 SC doses of 0.3 and 1 mg/kg. Liver $t_{1/2}$ ranged from 16 to 74 days across the dose range. No accumulation of vutrisiran was observed in liver after repeat dosing.

Refer to the full review of the Office of Clinical Pharmacology (OCP) for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

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4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies submitted to support the safety and efficacy of vutrisiran are summarized in the table below.

Table 1: Listing of Clinical Trials Relevant to this NDA, copied from submission.

	Vutrisiran Studies		External Control/Reference Population
	Study 001 (Phase 1)	HELIOS-A	APOLLO
Study Status	Completed (12 January 2018)	Ongoing (primary analysis data cutoff date, 10 November 2020)	Completed (17 August 2017)
Patient Population	Healthy adult volunteers 18-65 years old	Adult patients with hATTR amyloidosis with polyneuropathy	Adult patients with hATTR amyloidosis with polyneuropathy
Study Design	Phase 1, randomized, single-blind, placebo-controlled, single-ascending dose study	Phase 3, randomized (3:1), OL study with reference comparator patisiran group, with 2 parts: 18-month Treatment Period (vutrisiran or patisiran); primary analysis at M9 for efficacy 18-month Treatment Extension Period; all patients receive vutrisiran	Phase 3, randomized (2:1), DB, placebo-controlled study. Primary analysis at M18.
Countries	UK	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Greece, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, UK, US	Argentina, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Italy, Japan, Korea, Mexico, Netherlands, Portugal, Spain, Sweden, Taiwan, Turkey, UK, US
No. of Patients	80 subjects: 60 vutrisiran and 20 placebo	164 patients: 122 vutrisiran and 42 patisiran	225 patients: 148 patisiran and 77 placebo patients
Dose Regimen	Single dose of SC vutrisiran: 5, 25, 50, 100, 200 or 300 mg	Vutrisiran 25 mg q3M (SC) or patisiran 0.3 mg/kg q3w (IV). Premedication with corticosteroid, anti-histamines and paracetamol 60 minutes prior to the infusion (patisiran group only)	q3w IV dose of patisiran 0.3 mg/kg (patisiran group) or placebo (placebo group). All patients received premedication with corticosteroid, anti-histamines and paracetamol 60 minutes prior to the infusion
Key Disease-specific Eligibility Criteria	Not applicable	- Diagnosis of hATTR amyloidosis with documented <i>TTR</i> variant - NIS 5-130, inclusive - PND score of $\leq 3b$ - NYHA HF classification $\leq II$ - KPS of $\geq 60\%$	- Diagnosis of hATTR amyloidosis with documented <i>TTR</i> variant^a - NIS of 5-130, inclusive - PND score of $\leq 3b$ - NYHA HF classification $\leq II^b$ - KPS of $\geq 60\%$

	Vutrisiran Studies		External Control/Reference Population
	Study 001 (Phase 1)	HELIOS-A	APOLLO
Primary Objective	Safety and tolerability	Efficacy of vutrisiran on mNIS+7 (neuropathy impairment)	Efficacy of patisiran on mNIS+7 (neuropathy impairment)

5.2. Review Strategy

Effectiveness and safety were assessed by evaluating the results from the Phase 3, randomized, open-label, active comparator, and externally controlled HELIOS-A (ALN-TTRSC02-002) study in adult subjects with hATTR amyloidosis with polyneuropathy. The effectiveness assessment focused on the clinical interpretability of the trial endpoints and the Applicant's reported results. Confirmation of the efficacy analyses themselves 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. This reviewer acknowledges the data analyses of FDA analyst Rui Li.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. ALN-TTRSC02-002 (HELIOS-A)

6.1.1. Study Design

Overview and Objective

The HELIOS-A study is a Phase 3 global, randomized, open-label, externally controlled study to evaluate the efficacy and safety of vutrisiran (ALN-TTRSC02) in subjects with polyneuropathy caused by hereditary transthyretin amyloidosis (hATTR Amyloidosis).

The objectives of the study are described by the Applicant as follows:

- The primary objective of the study is to determine the efficacy of vutrisiran in subjects with hATTR amyloidosis by evaluating the effect on neurologic impairment relative to an external control group.
- The secondary objectives of the study are to determine the efficacy of vutrisiran on quality of life, gait speed, neurologic impairment, nutritional status, and disability; and to demonstrate the noninferiority of vutrisiran compared to patisiran with respect to serum transthyretin (TTR) levels.
- The exploratory objectives of the study are to determine the effect of vutrisiran on the following clinical parameters:
 - o Disability and nutritional status
 - o Manifestations of cardiac amyloid involvement
 - o Other assessment of neurologic impairment
 - o Other assessments of quality of life
 - o Disease stage
 - o Performance of daily activities

Additional exploratory objectives are

- To characterize the pharmacodynamic (PD) effect of vutrisiran and patisiran on serum TTR and vitamin A levels

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- To characterize plasma pharmacokinetic (PK) of vutrisiran and patisiran
- To assess presence of antidrug antibodies (ADAs) to vutrisiran and patisiran.

The safety objective is to determine the safety and tolerability of vutrisiran in subjects with hATTR amyloidosis.

Trial Design

This is an ongoing, global, Phase 3, randomized, open-label, externally controlled study designed to evaluate efficacy, safety, PK, and PD of vutrisiran in adult subjects with hATTR amyloidosis with polyneuropathy. The study is being conducted in 2 parts: an 18-month treatment period, with the primary efficacy analysis at Month 9 and efficacy analyses at Month 18, followed by an 18-month treatment extension period, in which subjects initially treated with patisiran are switched to vutrisiran. The placebo group of the APOLLO study (the pivotal Phase 3 study from the approved patisiran NDA 210922) is used as an external control for the primary and most secondary and exploratory efficacy analyses of vutrisiran.

- Choice of control group:
The placebo group of the APOLLO (ALN-TTR02-004) study is used as an external control for the primary, most secondary, and most exploratory efficacy analyses. This external placebo group consists of subjects with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) who are comparable to the hATTR-PN subjects enrolled in the HELIOS-A study. There were no clinically significant differences in the enrollment criteria for the APOLLO and HELIOS-A studies. The HELIOS-A study also includes an active control group receiving the approved treatment patisiran.

Reviewer Comment: Given the life-threatening nature of hATTR amyloidosis and the existence of approved therapies, it would not be ethical to use a concurrent placebo control group in the HELIOS-A study; therefore, it is reasonable to consider the use of external control, if feasible.

- Key Eligibility Criteria:
The criteria listed below from the submitted protocol appear adequate to enroll adult subjects with hATTR amyloidosis with polyneuropathy representative of the U.S. population.

Key Inclusion Criteria

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

- Male or female age 18 (or age of legal consent, whichever is older) to 85 years of age
- Have a diagnosis of hATTR amyloidosis with documented TTR mutation

- Have a neuropathy impairment score (NIS) of 5 to 130 (inclusive; this criterion must be met at the Screening Visit 2). 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.
- Have a Polyneuropathy Disability (PND) score of ≤ 3 (this criterion must be met at the Screening Visit 2). The PND scale is shown in the following figure, copied from the HELIOS-A study protocol.

Figure 1: Polyneuropathy Disability Score. Source: HELIOS-A Study Protocol

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA	Walking with the help of one stick or crutch
IIIB	Walking with the help of two sticks or crutches
IV	Confined to a wheelchair or bedridden

- Have a Karnofsky Performance Status (KPS) of $\geq 60\%$

Key Exclusion Criteria

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

- Has had a liver transplant or is likely, in the opinion of the Investigator, to undergo liver transplantation during the 18-month Treatment Period of the study
- Has known other (non-hATTR) forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis
- Has a New York Heart Association heart failure classification >2
- Has other known causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy) that the treating physician believes to be contributing to the neuropathy
- Had acute coronary syndrome within the past 3 months
- Has uncontrolled clinically significant cardiac arrhythmia or unstable angina
- Female patient is pregnant or breastfeeding

Study Endpoints

Primary Efficacy Endpoint

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The primary efficacy endpoint for the HELIOS-A study is the change from baseline in the modified neuropathy impairment score +7 (mNIS+7; Suanprasert et al., 2014) compared to the placebo group of the APOLLO study at Month 9.

The mNIS+7 is a 304-point composite measure of neurologic impairment that includes the following measures and components. 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:
 - o NIS-weakness (NIS-W)
 - o NIS-reflexes (NIS-R)
- Electrophysiologic measures of small and large nerve fiber function in order to determine the sum of 5 NCS component scores that included assessment of the ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, and peroneal CMAP
- Sensory testing to determine the QST score included assessing touch pressure by body surface area (QST-BSATP) and heat pain by body surface area (QST-BSAHP)
- Postural blood pressure was measured to assess autonomic function.

Reviewer Comment:

The primary endpoint, mNIS+7, is composed of a clinical exam-based neuropathy impairment score (NIS) combined with electrophysiologic measures of small and large nerve fiber function (+7) such as nerve conduction studies (NCS), quantitative sensory testing (QST), 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 as that is an assessment of patient function. Note that the mNIS+7 and Norfolk QOL-DN were also the efficacy endpoints for the APOLLO clinical study of patisiran, which was approved for the treatment of hATTR amyloidosis in 2018.

Secondary Efficacy Endpoints

The study evaluated the change from baseline in the following parameters compared to the placebo group of the APOLLO study:

- o Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score at Month 9

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- o Timed 10-meter walk test (10-MWT) at Month 9
- o mNIS+7 at Month 18
- o Norfolk QoL-DN total score at Month 18
- o 10-MWT at Month 18
- o Modified body mass index (mBMI) at Month 18
- o Rasch-built Overall Disability Scale (R-ODS) at Month 18

The study also evaluated the percent reduction in serum TTR levels in the vutrisiran group compared to the within-study patisiran group through Month 18.

Reviewer Comment: This NDA submission only includes the primary analysis of efficacy at Month 9 and cumulative safety data through the data cutoff date. Data to support listed objectives that relate to endpoints analyzed at Month 18 are not included in this NDA submission. Data for mBMI and R-ODS are instead presented as exploratory endpoints at Month 9.

Norfolk QoL-DN

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.

Reviewer Comment: The Norfolk QoL-DN, evaluated in Vinik et al., 2005 and 2014, is a clinically meaningful endpoint that assesses patient function and is appropriate for use in this study. The remaining secondary and exploratory endpoints described below are acceptable.

Ten-meter Walk Test

Ability to ambulate (gait speed) was assessed through the 10-meter walk test (10-MWT). The walk had to be completed without assistance from another person; ambulatory aids such as canes and walkers were permitted.

Rasch-built Overall Disability Scale

An assessment of the disability each subject experienced was measured using the RODS. The R-ODS is comprised of a 24-item linearly weighted scale that captures activity and social participation limitations in subjects. The best possible score is 48. Lower scores indicate greater disability.

Modified Body Mass Index

The nutritional status of subjects was evaluated using the mBMI; calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

The study also evaluated the following exploratory endpoints.

- Change from baseline in the following parameters compared to the placebo group of the APOLLO study at Month 9: R-ODS and mBMI
- Change from baseline over time: N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters, troponin I and T levels, New York Heart Association class; NIS; EuroQol of Life-5 Dimensions 5-Levels (EQ-5D-5L) questionnaire and the EuroQol-Visual Analog Scale (EQ-VAS); Familial Amyloid Polyneuropathy (FAP) stage and PND score; and KPS
- Change from baseline in technetium scintigraphy cardiac parameters at Month 18
- Percent reduction in serum TTR and vitamin A levels over time
- PK profile of vutrisiran and patisiran
- Incidence and titers of ADA to vutrisiran and patisiran

Statistical Analysis Plan

Reviewer Comment: Please refer to the statistical review for detailed evaluation of the Applicant's planned statistical analysis.

The approach to multiple comparisons used by the Applicant is shown in the following table, copied from the submission.

Table 2: Multiple Comparisons Procedure. Source: HELIOS-A Statistical Analysis Plan table 1.

MCP Step ^a	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
Evaluated at the Month 9 analysis timepoint			
1	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value $\leq \alpha$
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 9	Placebo (APOLLO)	Nominal P value $\leq \alpha$
3	10-MWT gait speed change from baseline at Month 9	Placebo (APOLLO)	Nominal P value $\leq \alpha$
Evaluated at the Month 18 analysis timepoint			

MCP Step ^a	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
4	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value $\leq \alpha$
5	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 18	Placebo (APOLLO)	Nominal P value $\leq \alpha$
6	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value $\leq \alpha$
7	mBMI (BMI [kg/m ²] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value $\leq \alpha$
8	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value $\leq \alpha$
9	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference $> -10\%$

Results for both the primary endpoint, mNIS+7 change from baseline at Month 9, and key secondary endpoint, Norfolk QoL-DN total score change from baseline at Month 9, must be statistically significant to declare a positive trial. The overall familywise error rate will be controlled at $\alpha=0.05$ for the primary and secondary endpoint hypothesis tests. Per serial gatekeeping multiple comparisons procedure (MCP), if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant, and the next step will be evaluated; otherwise, all hypotheses in the given and subsequent steps are deemed not statistically significant.

Protocol Amendments

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The original protocol was finalized on 11 October 2018. Since then, there have been 3 global protocol amendments and 12 country-specific protocol amendments.

See Appendix 13.3 for a table of all protocol amendments, copied from the submission.

6.1.2. Study Results

Compliance with Good Clinical Practices

All clinical studies were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and local requirements, and in consideration of applicable regulatory Guidance.

Financial Disclosure

The Applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Subject Disposition

Of the 122 subjects in the vutrisiran group, 3 (2.5%) subjects discontinued study drug prior to Month 9: 2 study drug discontinuations were due to death of the subject and 1 study drug discontinuation was due to physician decision for a subject who did not comply with study visits and was considered lost to follow up. None of the subjects in the vutrisiran group discontinued study drug after Month 9.

Of the 42 subjects in the patisiran group, 2 (4.8%) subjects discontinued study drug prior to Month 9, both due to the death of the subject. In addition, 2 (4.8%) subjects in the patisiran group discontinued study drug after Month 9: 1 (2.4%) due to the death of the subject and 1 (2.4%) due to an adverse event.

In the external placebo group 37.7% of subjects discontinued treatment.

Overall, there were low rates of discontinuation in the study that would not substantially affect the ability to interpret the efficacy data.

Protocol Violations/Deviations

A summary of major protocol deviations is listed below.

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Table 3: List of Major Protocol Deviations: 37 deviations in 14 subjects. Source: HELIOS-A CSR

Subject ID	Protocol Deviation Category	Summary
(b) (6)	Key Study Procedures	missing Month 9 Norfolk data
	Key Study Procedures	missed Month 9 efficacy visit due to COVID-19
	Key Study Procedures	missed Month 9 efficacy visit due to COVID-19
	Key Study Procedures	missing Month 9 mNIS+7 and Norfolk data
	Key Study Procedures	missed pregnancy test
	Key Study Procedures	missed pregnancy tests [2 deviations (Day 1 and Day 85)]
	Key Study Procedures	NIS assessments not being performed by certified staff [2 deviations]
	Key Study Procedures	missing baseline Norfolk data
	SAE Reporting timeline	SAE reported within 24 hours [2 deviations]
	SAE Reporting timeline	SAE reported within 24 hours [3 deviations]
	SAE Reporting timeline	SAE reported within 24 hours
	Missing or Wrong Treatment	approximately 25% overdosing of patisiran due to the incorrect information in the site's internal system [10 deviations]
	Missing or Wrong Treatment	approximately 25% overdosing of patisiran due to the incorrect information in the site's internal system [10 deviations]
	Informed Consent	study visits were performed by a home healthcare professional without documentation that the subject had consented to home healthcare services

These deviations do not compromise the efficacy and safety results of the study.

Table of Demographic Characteristics

Study subject demographics relevant to the efficacy analysis are described in the following table copied from the submission. Study subject demographics relevant to the safety analysis are described in Section 8.2.2.

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Table 4: Baseline Values for Study Endpoint Parameters (mITT Population). Source: HELIOS-A CSR, table 6

Demographic	APOLLO	HELIOS-A		
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Modified Neuropathy Impairment Score +7 (mNIS+7)				
Mean (SD)	74.61 (37.04)	60.55 (35.99)	57.69 (33.71)	59.82 (35.34)
Median (min, max)	71.50 (11.0, 153.5)	63.50 (2.5, 158.0)	53.44 (7.0, 137.6)	59.94 (2.5, 158.0)
Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score				
Mean (SD)	55.5 (24.3)	47.1 (26.3)	47.3 (29.9)	47.2 (27.2)
Median (min, max)	53.5 (8, 111)	44.0 (-1, 105)	41.0 (1, 125)	42.0 (-1, 125)
10-meter Walk Test (10-MWT, m/s)				
Mean (SD)	0.790 (0.319)	1.006 (0.393)	1.011 (0.400)	1.007 (0.393)
Median (min, max)	0.800 (0.00, 1.53)	1.049 (0.08, 1.87)	1.000 (0.11, 1.93)	1.025 (0.08, 1.93)
Modified Body Mass Index (mBMI, kg/m²)				
Mean (SD)	989.9 (214.2)	1057.5 (234.0)	1060.3 (226.6)	1058.2 (231.4)
Median (min, max)	959.7 (569, 1508)	1047.2 (589, 1723)	1029.1 (646, 1636)	1038.1 (589, 1723)
Rasch-built Overall Disability Scale (R-ODS)				
Mean (SD)	29.8 (10.8)	34.1 (11.0)	34.0 (10.4)	34.1 (10.8)
Median (min, max)	30.5 (3, 48)	35.0 (5, 48)	35.0 (9, 47)	35.0 (5, 48)
Polyneuropathy Disability (PND) Score				
I	20 (26.0)	44 (36.1)	15 (35.7)	59 (36.0)
II	23 (29.9)	50 (41.0)	17 (40.5)	67 (40.9)
IIIA	22 (28.6)	16 (13.1)	7 (16.7)	23 (14.0)
IIIB	11 (14.3)	12 (9.8)	3 (7.1)	15 (9.1)
IV	1 (1.3)	0	0	0
Neuropathy Impairment Score (NIS)				
Mean (SD)	57.02 (32.04)	43.02 (28.63)	43.11 (28.23)	43.04 (28.44)
Median (min, max)	53.88 (7.0, 125.5)	36.00 (5.0, 127.0)	38.00 (5.5, 115.6)	36.50 (5.0, 127.0)
Serum TTR (mg/L)				
Mean (SD)	198.84 (58.08)	206.11 (61.03)	206.47 (65.28)	206.20 (61.94)

Demographic	APOLLO	HELIOS-A		
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Median (min, max)	196.43 (58.5, 320.1)	203.25 (58.4, 343.2)	203.90 (71.0, 353.2)	203.25 (58.4, 353.2)

Reviewer comment: As seen in the above table, there is an imbalance in baseline disease severity between the HELIOS-A vutrisiran group and the external placebo group from the APOLLO study, with greater disease severity in the external placebo group as measured by baseline mNIS+7 (mean 75 placebo vs. 61 vutrisiran), Norfolk QoL-DN (mean 56 placebo vs. 47 vutrisiran), 10-MWT (mean 0.8 placebo vs. 1 vutrisiran), and R-ODS (mean 30 placebo vs. 34 vutrisiran). The analysis of efficacy will need to take into account this worse baseline disease severity in the placebo group, which could potentially amplify the appearance of benefit in the vutrisiran group. However, note that the vutrisiran and active comparator patisiran groups have more similar baseline disease severity as seen in the above table, which will facilitate the interpretation of the efficacy analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In the vutrisiran group, 121 (99.2%) subjects had no missed doses of study drug and 1 (0.8%) subject had 1 missed dose; no subjects missed more than 1 dose of vutrisiran as of the data cutoff date. In the external placebo group, 51 (66.2%) subjects did not miss any doses between the first and last dose and no placebo subjects missed 3 or more consecutive doses.

The most frequently used medications ($\geq 20\%$ of vutrisiran-treated subjects) were vitamin A and D, including combinations of the two (71.3%), antiepileptics (44.3%), other analgesics and antipyretics (35.2%), antidepressants (32.8%), drugs for peptic ulcer and gastro-esophageal reflux disease (32.0%), antithrombotic agents (29.5%), multivitamins, combinations (29.5%), lipid modifying agents, plain (28.7%), high-ceiling diuretics (27.0%), and anti-inflammatory and antirheumatic products (non-steroids) (21.3%).

There were no applicable rescue medications for this trial.

Efficacy Results – Primary Endpoint: mNIS+7, Change from Baseline to Month 9

The primary endpoint was the difference between vutrisiran (HELIOS-A) and placebo (APOLLO) treatment in the change from baseline at Month 9 in mNIS+7.

The table and figures below show the Applicant's analysis of the primary endpoint. Note that

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higher mNIS+7 scores indicate greater impairment. There is a statistically significant difference in mNIS+7 scores between the vutrisiran and external placebo groups, indicating an improvement of neurological function in the vutrisiran group and a worsening in the placebo group. *The FDA statistical reviewer agrees that the result is positive.*

Table 5: mNIS+7, ANCOVA/Multiple Imputation Model, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A CSR, table 10.

Statistic ^a	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
Month 9 LS mean (SE)	14.76 (2.00)	-2.24 (1.43)
95% CI	(10.84, 18.68)	(-5.04, 0.57)
LS mean difference (SE) (vutrisiran – placebo)	-	-17.00 (2.44)
95% CI	-	(-21.78, -12.22)
p-value	-	3.542E-12

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Table 6: mNIS+7, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A CSR, table 11

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
Baseline	Actual	n	77	122	42
		Mean (SD)	74.61 (37.04)	60.55 (35.99)	57.69 (33.71)
		Median	71.50	63.50	53.44
		Min, Max	11.0, 153.5	2.5, 158.0	7.0, 137.6
Month 9	Actual	n	67	114	37
		Mean (SD)	90.99 (41.31)	57.50 (37.98)	52.56 (33.25)
		SE	5.05	3.56	5.47
		Median	91.50	57.00	50.25
		Min, Max	19.0, 167.5	1.0, 160.1	6.0, 152.3
	Change from baseline	n	67	114	37
		Mean (SD)	15.22 (17.18)	-1.70 (13.22)	-1.41 (17.23)
		SE	2.10	1.24	2.83
		Median	13.00	-0.44	-2.00
		Min, Max	-16.6, 72.0	-35.0, 26.0	-47.0, 62.9

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Figure 2: mNIS+7, Change from Baseline Over Time (mITT Population). Source: Helios-A CSR, figure 3

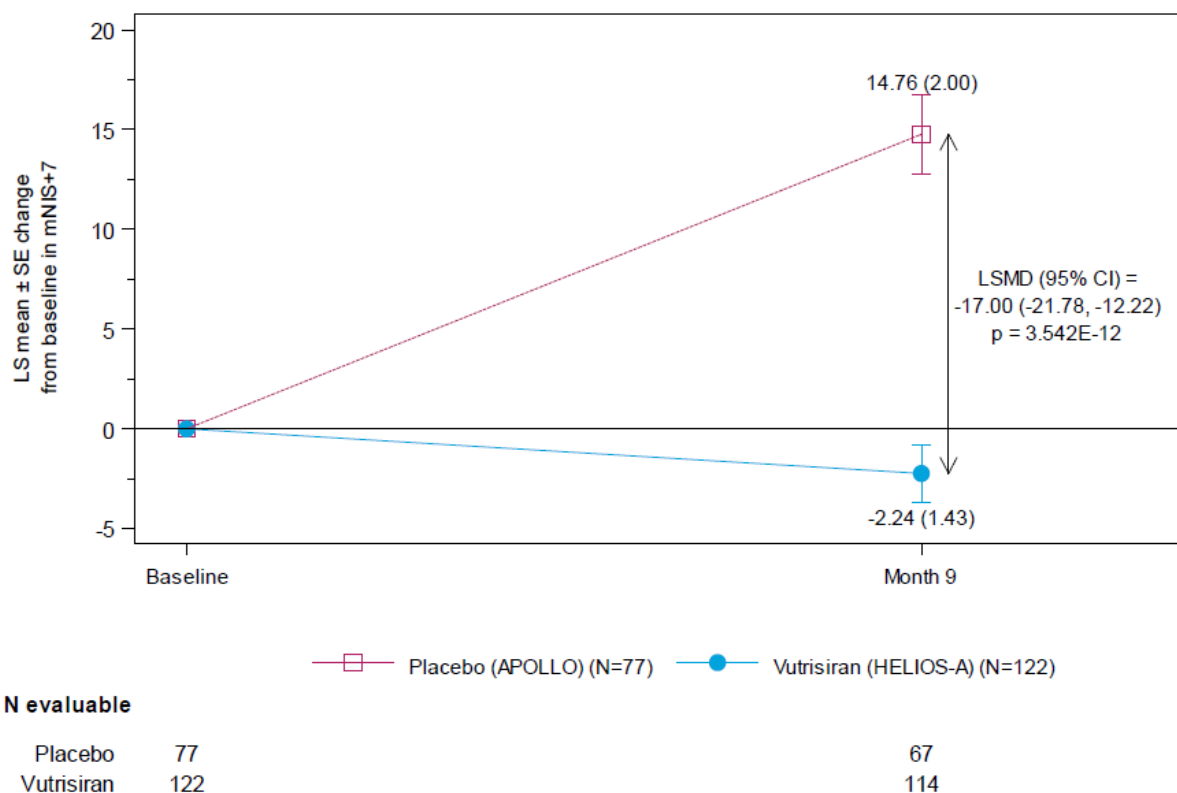
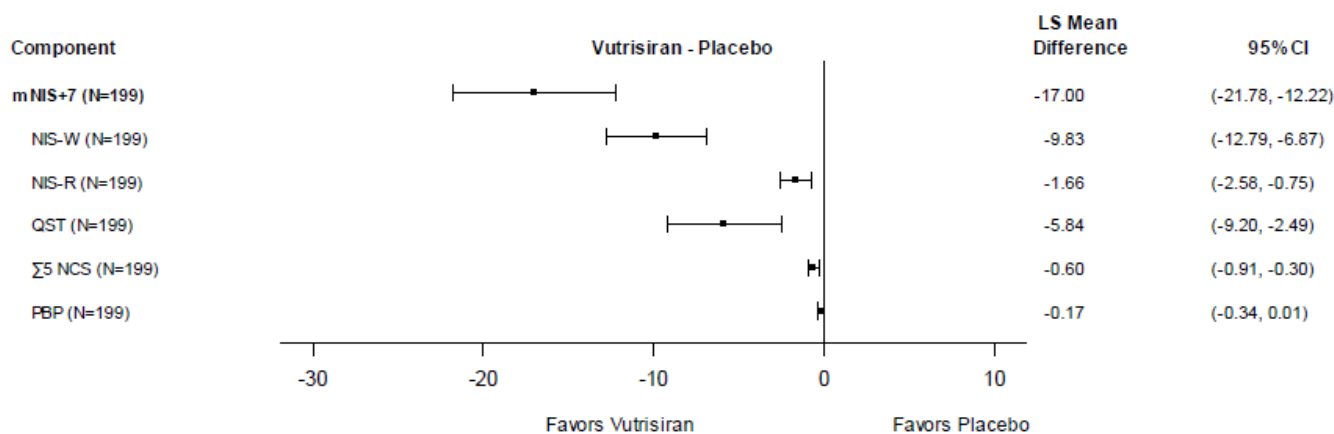


Figure 3: mNIS+7, ANCOVA/Multiple Imputation Model Component Analysis Forest Plot, Change from Baseline to Month 9, (mITT Population). Source: Helios-A CSR, figure 4



Reviewer Comment: The observed improvement of neuropathy as evidenced by the reduction in mNIS+7 score is not consistent with the natural history of hereditary TTR amyloidosis

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polyneuropathy and supports the efficacy of vutrisiran. The effect on the mNIS+7 appears to be driven primarily by an effect on muscle strength and QST. Although strength testing can potentially be affected by subject motivation in cases of unblinding, motivation would be unlikely to have an effect on QST. These results have been independently verified by the Agency biometrics reviewer for this application. Although there was an imbalance in baseline disease severity between the vutrisiran and external placebo groups (worse disease in the placebo group at baseline) as seen in the table of baseline demographics above, the magnitude of the difference between the vutrisiran group and external placebo control, with improvement in the vutrisiran group and worsening in the placebo group, is sufficient to overcome concerns about potential biases due to baseline differences and supports the efficacy of vutrisiran.

Data Quality and Integrity

No clinical research sites were identified by OSI as potentially fraudulent. There is no detectable data duplication in variables.

Efficacy Results – Secondary and other relevant endpoints

The results of the analyses of the secondary efficacy measures have been independently verified by the biometrics reviewer for this application.

Norfolk QoL-DN, Key Secondary Endpoint, Change from Baseline to Month 9

The key secondary endpoint was the difference between vutrisiran (HELIOS-A) and placebo (APOLLO) treatment in the change from baseline at Month 9 in the Norfolk QoL-DN.

The tables and figure below show the Applicant's analysis of the key secondary endpoint. Note that higher Norfolk QoL-DN scores indicate worse quality of life. There is a statistically significant difference in Norfolk QoL-DN scores between the vutrisiran and external placebo groups, indicating an improvement of quality of life in the vutrisiran group and a worsening in the placebo group.

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Table 7: Norfolk QoL-DN, ANCOVA/Multiple Imputation Model, Change from Baseline to Month 9, (mITT Population). Source: HELIOS-A CSR, table 15

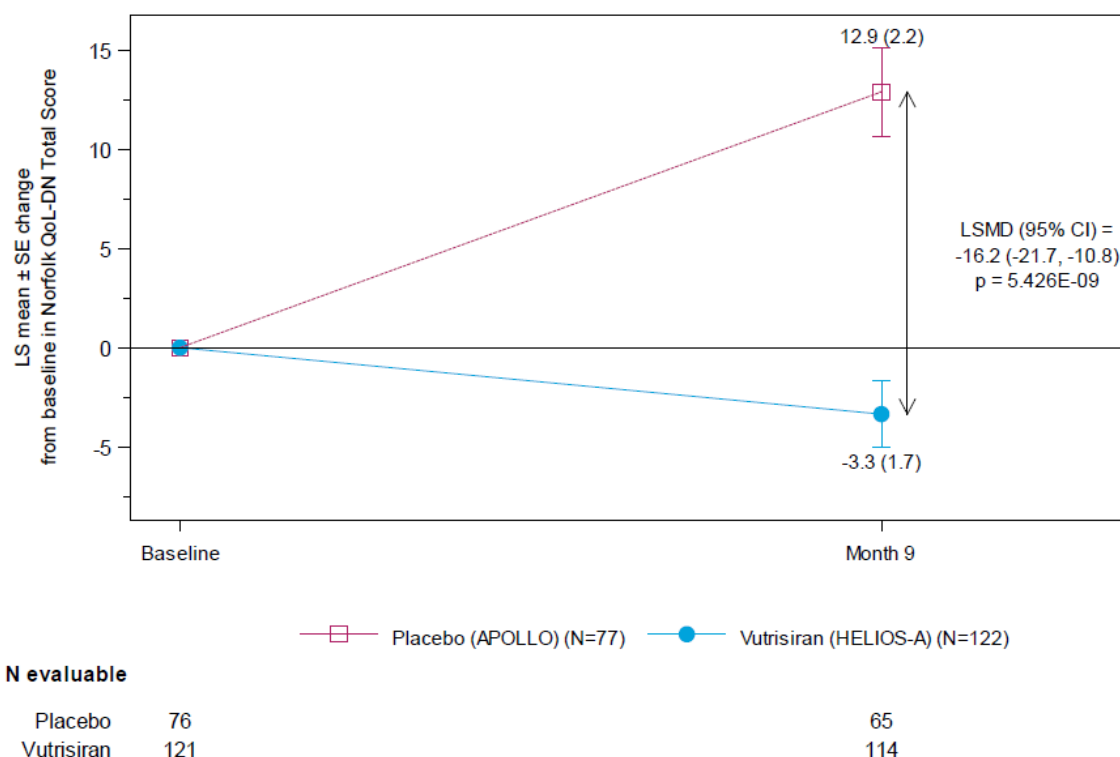
Statistic ^a	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
Month 9 LS mean (SE)	12.9 (2.2)	-3.3 (1.7)
95% CI	(8.5, 17.3)	(-6.6, -0.1)
LS mean difference (SE) (vutrisiran – placebo)	-	-16.2 (2.8)
95% CI	-	(-21.7, -10.8)
p-value	-	5.426E-09

Table 8: Norfolk QoL-DN, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A CSR, table 16

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
Baseline	Actual	n	76	121	42
		Mean (SD)	55.5 (24.3)	47.1 (26.3)	47.3 (29.9)
		Median	53.5	44.0	41.0
		Min, Max	8, 111	-1, 105	1, 125
Month 9	Actual	n	66	115	38
		Mean (SD)	66.2 (27.6)	41.8 (26.6)	44.2 (27.1)
		SE	3.4	2.5	4.4
		Median	68.0	40.0	39.0
		Min, Max	5, 109	-4, 102	1, 115

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
	Change from baseline	n	65	114	38
		Mean (SD)	11.5 (19.2)	-3.9 (18.3)	0.1 (18.0)
		SE	2.4	1.7	2.9
		Median	10.0	-2.5	-4.0
		Min, Max	-36, 58	-59, 52	-26, 54

Figure 4: Norfolk QoL-DN, Change from Baseline Over Time (mITT Population). Source: HELIOS-A CSR, figure 5



Reviewer Comment: The observed improvement of quality of life as evidenced by the Norfolk QoL-DN score supports the efficacy of vutrisiran.

Secondary Endpoint: Timed 10-meter walk test (10-MWT) at Month 9

The 10-meter walk test (10-MWT) is a measure of walking ability and gait speed expressed as a rate in meters/second. An increase in gait speed from baseline indicates improvement, and a

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decrease from baseline indicates worsening. The following tables and figure, copied from the submission, show the changes in 10-MWT in the external placebo and vutrisiran groups.

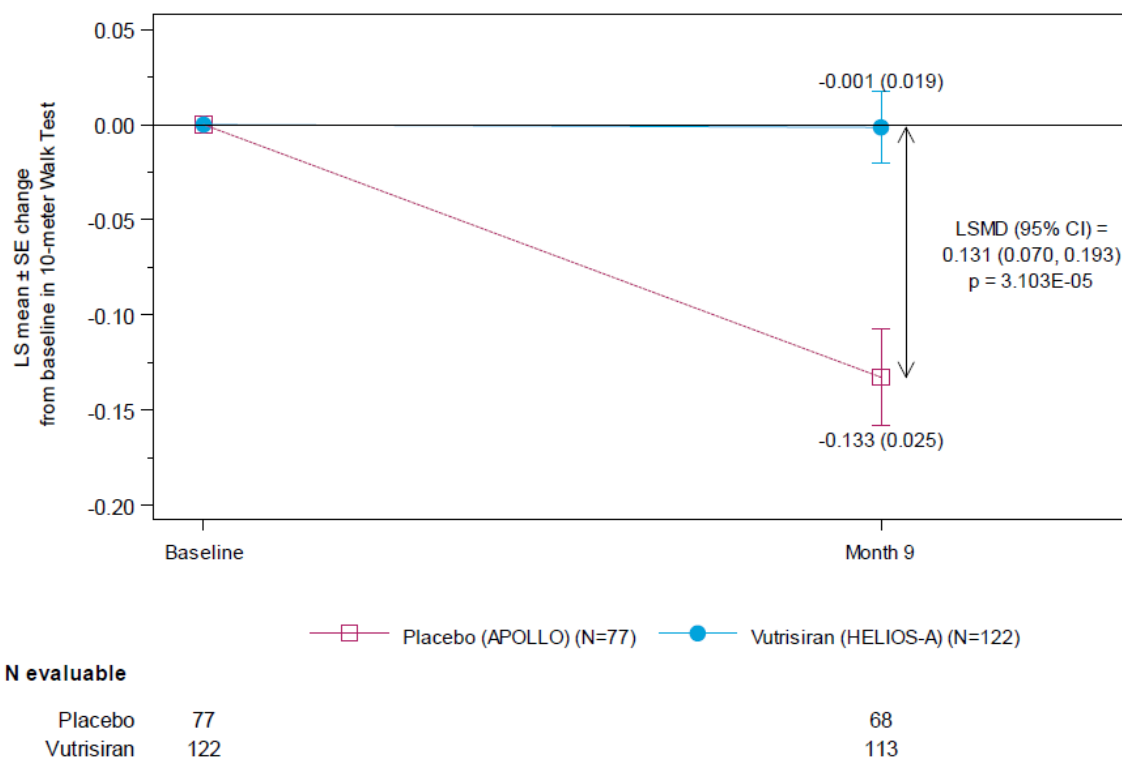
Table 9: 10-MWT, ANCOVA/Multiple Imputation Model, Change from Baseline to Month 9, (mITT Population). Source: HELIOS-A CSR, table 20

Statistic ^a	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
Month 9 LS mean (SE)	-0.133 (0.025)	-0.001 (0.019)
95% CI	(-0.182, -0.083)	(-0.038, 0.036)
LS mean difference (SE) (vutrisiran – placebo)	-	0.131 (0.031)
95% CI	-	(0.070, 0.193)
p-value	-	3.103E-05

Table 10: 10-MWT, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A CSR, table 21

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
Baseline	Actual	n	77	122	42
		Mean (SD)	0.790 (0.319)	1.006 (0.393)	1.011 (0.400)
		Median	0.800	1.049	1.000
		Min, Max	0.00, 1.53	0.08, 1.87	0.11, 1.93
Month 9	Actual	n	68	113	37
		Mean (SD)	0.662 (0.366)	1.022 (0.445)	1.003 (0.484)
		SE	0.044	0.042	0.080
		Median	0.667	1.053	1.026
		Min, Max	0.00, 1.47	0.09, 2.32	0.00, 2.31

Figure 5: 10-MWT, Change from Baseline Over Time (mITT Population). Source: HELIOS-A CSR, figure 7



As seen above, there was maintenance of gait speed in the vutrisiran group compared to mean worsening in the placebo group at 9 months. *This result is consistent with the positive finding of the primary endpoint and is appropriate for inclusion in the prescribing information.*

Exploratory Endpoints

Results of exploratory endpoints are presented descriptively.

Exploratory Endpoint: Modified body mass index (mBMI) change from baseline over time

The mBMI is the product of BMI multiplied by the concentration of serum albumin. An increase in mBMI from baseline suggests improvement in nutritional status, and a decrease from baseline suggests worsening of nutritional status. The mBMI has been found to be a more accurate measure of malnutrition status than conventional BMI (Oh et al. 2018).

The following table, copied from the submission, describes the change from baseline in mBMI over 9 months in the vutrisiran and external placebo groups as well as in the active patisiran comparator.

Table 11: mBMI, Change from Baseline to Month 9 (mITT Population).

Source: HELIOS-A CSR, table 25

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
Baseline	Actual	N	77	122	42
		Mean (SD)	989.9 (214.2)	1057.5 (234.0)	1060.3 (226.6)
		Median	959.7	1047.2	1029.1
		Min, Max	569, 1508	589, 1723	646, 1636
Month 9	Actual	N	68	112	36
		Mean (SD)	932.3 (226.3)	1067.4 (235.4)	1071.2 (270.9)
		SE	27.4	22.2	45.1
		Median	905.7	1043.4	1057.1
		Min, Max	543, 1557	587, 1747	584, 1634
	Change from baseline	N	68	112	36
		Mean (SD)	-63.6 (82.6)	2.9 (74.6)	-6.2 (106.0)
		SE	10.0	7.1	17.7
		Median	-76.7	-5.3	-12.4
		Min, Max	-295, 175	-218, 198	-369, 169

As seen in the above table, there was a mean increase in the mBMI in the vutrisiran group compared to a mean decrease in the external placebo group. This result is consistent with the positive finding of the primary endpoint.

Exploratory Endpoint: Rasch-built Overall Disability Scale (R-ODS) score change from baseline over time

The R-ODS is a patient-reported measure of level of disability on a scale of 0-48, with 0 being the worst and 48 the best. The following table, copied from the submission, shows the change from baseline in R-ODS to Month 9 for the vutrisiran, patisiran, and external placebo groups.

Table 12: R-ODS, Change from Baseline to Month 9, (mITT Population).

Source: HELIOS-A CSR, table 27

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
Baseline	Actual	n	76	122	42
		Mean (SD)	29.8 (10.8)	34.1 (11.0)	34.0 (10.4)
		Median	30.5	35.0	35.0
		Min, Max	3, 48	5, 48	9, 47
Month 9	Actual	n	67	113	38
		Mean (SD)	24.9 (11.4)	34.1 (11.8)	33.9 (12.0)
		SE	1.4	1.1	2.0
		Median	25.0	37.0	36.0
		Min, Max	4, 48	3, 48	5, 48
	Change from baseline	n	66	113	38
		Mean (SD)	-4.7 (4.9)	-0.3 (5.5)	-1.8 (6.5)
		SE	0.6	0.5	1.0

Visit	Actual/ Change	Statistic	APOLLO	HELIOS-A	
			Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
		Median	-4.0	0.0	0.0
		Min, Max	-17, 4	-18, 25	-21, 10

As seen in the above table, there was worsening in the disability scale for the external placebo group and stability in the vutrisiran group. This result is consistent with the positive findings of the primary endpoint.

Exploratory Endpoints: Serum Transthyretin (TTR) and Vitamin A

At baseline, the median TTR level in the vutrisiran group was 203.2 mg/L (range, 58.4 to 343.2 mg/L). A median TTR reduction of 64.2% from baseline was observed at Day 22 with near to steady state median TTR reduction of 74.2% at Week 6.

The following figure, copied from the submission, shows the serum TTR change from baseline over time for vutrisiran and patisiran.

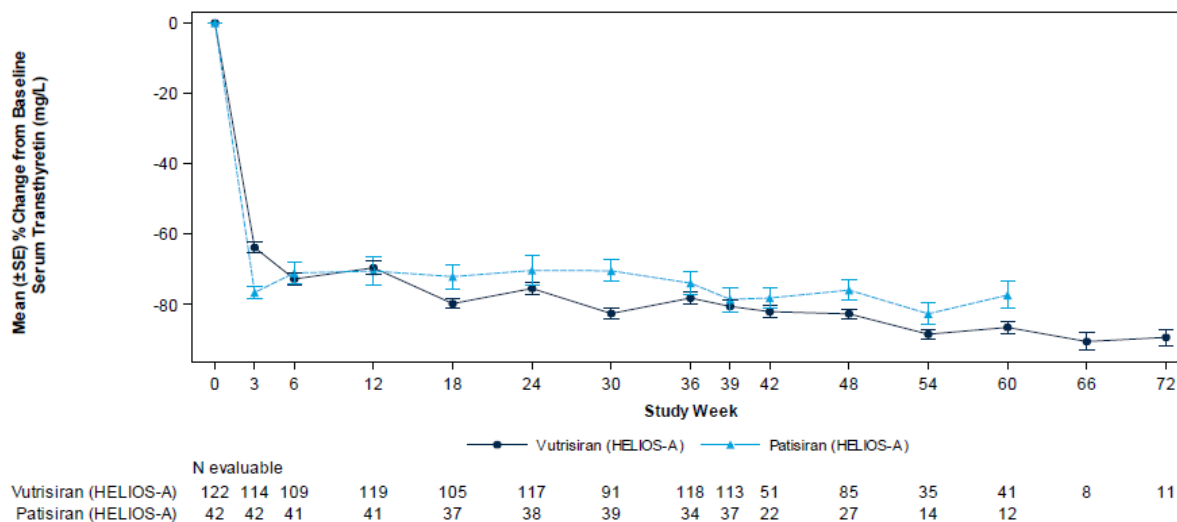
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Figure 6: Mean ($\pm$ SE) TTR Percent Change from Baseline Over Time During the Study (mITT Population). Source: HELIOS-A CSR, figure 14



The observed reduction in TTR in the vutrisiran group is consistent with the reported mechanism of action for vutrisiran.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Effectiveness was assessed by evaluating the results from the Phase 3, randomized, open-label, externally controlled HELIOS-A (ALN-TTRSC02-002) study in adult subjects with hATTR amyloidosis with polyneuropathy.

7.1.1. Primary Endpoints

The change from baseline to Month 9 on the mNIS+7 in vutrisiran-treated patients compared to the external placebo control was the primary endpoint used for the HELIOS-A study. As discussed in Section 6.1.1, 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 functional endpoint, the Norfolk QOL-DN.

As seen in Section 6.1.2, there was worsening of neurological impairment in the external placebo group and improvement in the vutrisiran group, as measured by the change in mNIS+7 score at 9 months ($p < 0.0001$).

These results show a clinically meaningful benefit, with a reduction of neurological impairment that is inconsistent with the natural history of hATTR neuropathy.

7.1.2. Secondary and Other Endpoints

Note that only 9 months of efficacy data for the HELIOS-A study were included with this application. Therefore, only the first two secondary endpoints at Month 9 for the HELIOS-A study, Norfolk QoL-DN and 10-MWT, were evaluated statistically for this application. The remaining pre-specified Month 18 secondary endpoints (mBMI, R-ODS) were evaluated at Month 9 as exploratory endpoints.

The key secondary endpoint for the HELIOS-A study is the change in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score at 9 months. It is a clinically meaningful functional endpoint that is appropriate for use in this study. As discussed in Section 6.1.2, there was an improvement in the Norfolk QOL-DN score in the vutrisiran group, compared to a worsening in the external placebo group.

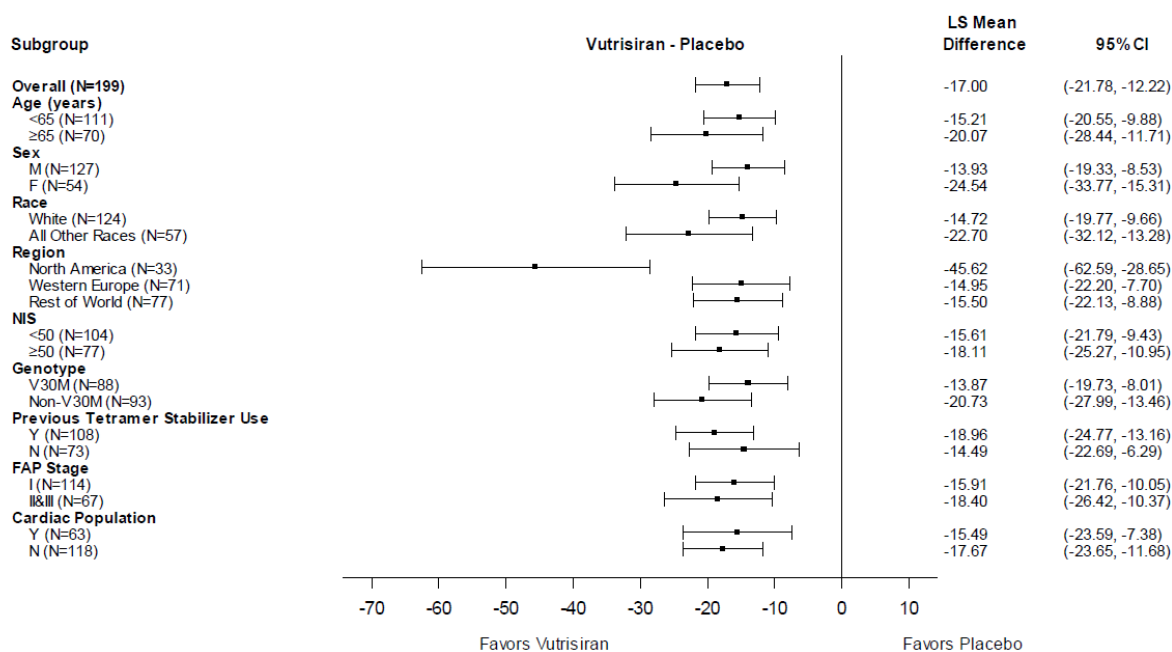
The next secondary endpoint, the change from baseline at Month 9 in the 10-meter walk test (10-MWT), showed maintenance of gait speed in the vutrisiran group compared to mean worsening in the external placebo group at 9 months.

Both Month 9 secondary efficacy endpoints for the HELIOS-A study had statistically significant results that support the efficacy of vutrisiran.

7.1.3. Subpopulations

Subgroup data are summarized in the following figures, copied from the submission, for age, sex, race, region, baseline NIS score, genotype, previous tetramer stabilizer use, disease stage, and cardiac subpopulation (subjects with preexisting cardiac amyloidosis).

Figure 7: mNIS+7, ANCOVA Model Subgroup Analysis Forest Plot, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A study CSR, figure 8



Abbreviations: ANCOVA=analysis of variance; CI=confidence interval; FAP=Familial Amyloid Polyneuropathy; LS=least squares; mITT=modified intent-to-treat; mNIS+7=modified neuropathy impairment score +7; NIS=neuropathy impairment score; V30M=valine to methionine variant at amino acid 30.

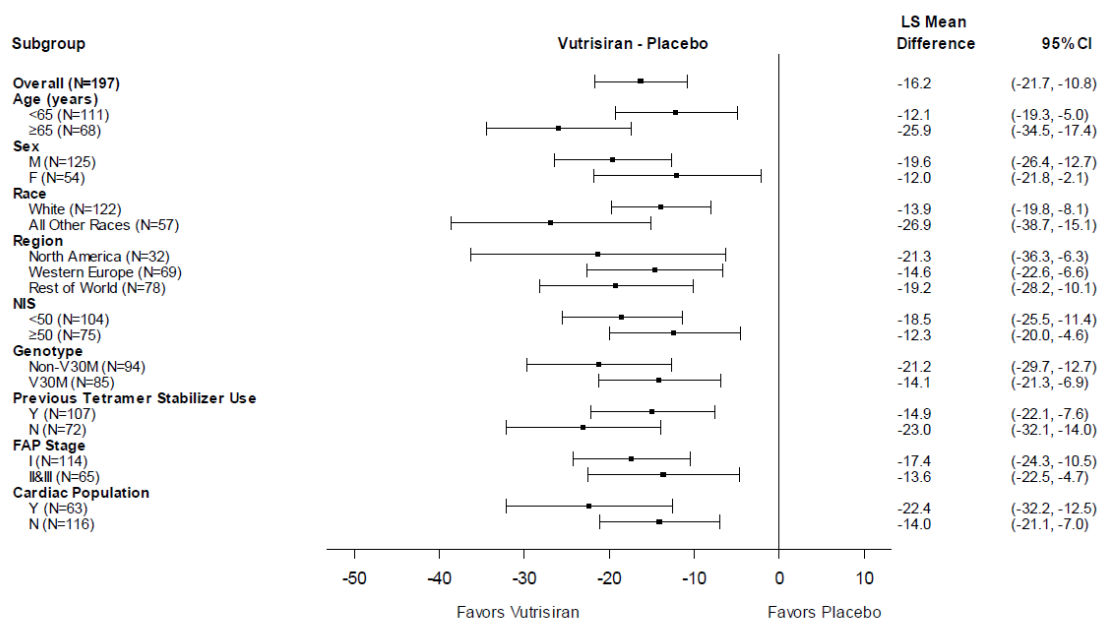
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Figure 8: Norfolk QoL-DN, ANCOVA Model Subgroup Analysis Forest Plot, Change from Baseline to Month 9 (mITT Population). Source: HELIOS-A study CSR, figure 11



Abbreviations: ANCOVA=analysis of variance; CI=confidence interval; FAP=Familial Amyloid Polyneuropathy; LS=least squares; mITT=modified intent-to-treat; NIS=neuropathy impairment score; Norfolk QoL-DN=Norfolk Quality of Life-Diabetic Neuropathy; V30M=valine to methionine variant at amino acid 30.

The effect of vutrisiran relative to placebo was similar across subgroups for both the primary (mNIS+7) and key secondary (Norfolk QoL-DN) efficacy endpoints.

7.1.4. Dose and Dose-Response

The Applicant's recommended dose for vutrisiran is 25 mg administered by subcutaneous injection once every 3 months. This recommendation is based on the dose-dependent reduction of TTR levels observed in previous clinical studies, including studies of the approved drug patisiran, which reflects the mechanism of action of vutrisiran. At steady state, which is achieved by approximately 6 months, the 25 mg SC q3M regimen of vutrisiran was predicted to achieve median trough TTR reductions of 86%, which is similar to patisiran (mean 82% TTR reduction over 24 months). In the HELIOS-A study approximate steady state median TTR reduction was 74.2% at Week 6.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

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Vutrisiran showed an onset of effect on serum TTR levels with a median TTR reduction of 64.2% from baseline by Day 22, compared to 79.5% in the patisiran group. Key efficacy endpoints (mNIS+7, Norfolk QoL-DN) were only evaluated at month 9 when efficacy was demonstrated relative to the external placebo control group.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional postmarketing considerations with respect to the established benefit on the treatment of polyneuropathy in subjects with hATTR amyloidosis.

7.2.2. Other Relevant Benefits

Based on the mechanism of action of vutrisiran, it is theoretically possible that it might be beneficial for the non-polyneuropathy symptoms in subjects with hATTR. However, any such benefits have not been established in the current development program.

7.3. Integrated Assessment of Effectiveness

The external placebo-controlled HELIOS-A Study is the one adequate and well-controlled efficacy study, with confirmatory evidence from pharmacodynamic/mechanistic data of transthyretin reduction, that can support approval of vutrisiran for the treatment of hATTR polyneuropathy. It is a single well-designed multicenter study that has provided reliable and statistically strong ($p < 0.0001$) evidence of an important clinical benefit, an effect on polyneuropathy as measured by the Modified Neurological Impairment Score +7 (mNIS+7). Vutrisiran-treated subjects demonstrated a numerical improvement on mNIS+7 scores from baseline, which is inconsistent with the natural course of the disease. The study has also shown a clinically meaningful and statistically strong ($p < 0.0001$) improvement in quality of life, as measured by the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) score as a key secondary endpoint. Further, vutrisiran showed statistically significant improvement on the secondary endpoint of gait speed (10-MWT). Additionally, the inclusion of an active comparator arm showed that efficacy on clinical outcomes with vutrisiran appeared to be comparable to the available therapy, patisiran.

The pathophysiology of hATTR amyloidosis and the mechanism of action of vutrisiran are well understood. Mutant TTR protein causes amyloid deposition, which damages the involved organ systems. Prior to the approvals of patisiran and inotersen for hATTR polyneuropathy and

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tafamidis for hATTR cardiomyopathy, only liver transplant was effective at treating hATTR amyloidosis by reducing mutant TTR production. Pharmacodynamics data for vutrisiran show a reduction in TTR levels that mirrors the efficacy assessments in a manner consistent with the drug's mechanism of action. These data provide confirmatory evidence to support the substantial evidence of effectiveness of vutrisiran.

8. Review of Safety

8.1. Safety Review Approach

Safety was assessed by evaluating the results from the Phase 3, randomized, open-label, externally controlled HELIOS-A (ALN-TTRSC02-002) study in adult subjects with hATTR amyloidosis with polyneuropathy, including both the treatment and extension periods. The study also included a smaller active control arm with patisiran to allow for relative comparisons for safety. The available narratives for deaths, serious adverse events, laboratory studies, and vital signs were reviewed. Reviewer analyses were conducted on the submitted datasets for the HELIOS-A trial, including adverse events, serious adverse events, deaths, and laboratory value assessments. The medical scientific literature was searched where appropriate for additional information. The Phase 1 study (Study 001) had a small population, short treatment duration, and small drug doses, yielding correspondingly limited safety information and therefore forms only a small part of the safety review. Additional blinded safety reports from the ongoing Phase 3 HELIOS-B study in hATTR cardiomyopathy subjects have also been submitted for review.

Note that the safety analysis incorporates the additional safety data from the 120-Day Safety Update to this NDA submission.

It is also important to note that there are marked limitations to the ability to make safety comparisons between the vutrisiran treatment arm and the external placebo control group. The two groups are not concurrent, not randomized, and the APOLLO study that provides the placebo arm was conducted before the COVID pandemic. Therefore, there are limitations that preclude direct comparison of the two groups; however, the placebo group serves as a useful comparator to assess relative risks of adverse events for vutrisiran. Similarly, there are limitations in the ability to make direct comparisons to the patisiran arm. Although the patisiran arm is a concurrent arm, it enrolled fewer patients. However, as with the placebo arm, it provides important context for a relative comparison to the safety of patisiran.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

For the all vutrisiran-treated population, which includes subjects originally randomized to vutrisiran (N=122) that continued to receive vutrisiran in the extension period as well as subjects who switched from patisiran to vutrisiran in the extension period (N=11), the overall mean duration of vutrisiran exposure was 16.4 months (range: 0.1-24.8 months), with a cumulative treatment exposure of 181.6 person years. The size and subject duration of exposure for the vutrisiran safety population are described in the following table, copied from the submission, and verified from the submitted data. At the initial filing, a total of 118 patients were exposed to vutrisiran for ≥ 9 months, 74 for ≥ 12 months, and 34 for ≥ 15 months. At the time of the 120-day safety update, 119 patients had ≥ 12 months of exposure, 101 had ≥ 15 months, and 56 had ≥ 18 months.

Table 13: Exposure to Vutrisiran During Study HELIOS-A (All Vutrisiran-Treated Population).
Source: HELIOS-A 120-Day SUR, table 14.1.9.1.2

Parameter Statistics/Category	Vutrisiran/Vutrisiran (N=122)	Patisiran/Vutrisiran (N=11)	Total (N=133)
Cumulative treatment duration, patient-years	179.9	1.7	181.6
<u>Treatment duration (months)</u>			
n	122	11	133
Mean (SD)	17.69 (3.46)	1.82 (1.23)	16.38 (5.51)
Median	17.58	1.68	17.31
Min, Max	1.7, 24.8	0.1, 4.4	0.1, 24.8
<u>Treatment duration group (months), n (%)</u>			
<3 Months	2 (1.6)	9 (81.8)	11 (8.3)

≥3 to <6 Months	0	2 (18.2)	2 (1.5)
≥6 to <9 Months	1 (0.8)	0	1 (0.8)
≥9 to <12 Months	0	0	0
≥12 to <15 Months	18 (14.8)	0	18 (13.5)
≥15 to <18 Months	45 (36.9)	0	45 (33.8)
≥18 to <21 Months	36 (29.5)	0	36 (27.1)
≥21 to <24 Months	18 (14.8)	0	18 (13.5)
≥24 to <27 Months	2 (1.6)	0	2 (1.5)

Given the prevalence of hATTR-PN (100 to 2500 individuals in the U.S.), the exposure is deemed adequate to support a reasonable assessment of safety. It was agreed at the Type B Pre-NDA meeting of 26 March 2021 that the Applicant would have 74 subjects with at least 1 year of safety data in the initial NDA submission and approximately 100 subjects with 1 year of safety data at the 120-day safety update.

8.2.2. Relevant characteristics of the safety population:

There were 122 subjects in the vutrisiran safety population of study HELIOS-A, enrolled from 57 sites in 22 countries. Demographic and important baseline characteristics are summarized in the following tables.

Table 14: Demographic and Baseline Characteristics in the HELIOS-A Study Population and the External APOLLO Study Control Group. Source: FDA analysis of submitted data

Characteristic	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Sex, n (%)			
Female	43 (35.2)	15 (35.7)	19 (24.7)
Male	79 (64.8)	27 (64.3)	58 (75.3)
Age, years			
N	122	42	77

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Characteristic	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Mean (SD)	57.80(13.19)	58.00(10.52)	62.17(10.76)
Median (Min, Max)	60.00(26.0, 85.0)	60.00(31.0, 81.0)	63.00(34.0, 80.0)
Age groups (years), n (%)			
65-<75	39 (32.0)	9 (21.4)	24 (31.2)
<65	76 (62.3)	31 (73.8)	44 (57.1)
>= 75	7 (5.7)	2 (4.8)	9 (11.7)
Race, n (%)			
ASIAN	21 (17.2)	8 (19.0)	25 (32.5)
BLACK OR AFRICAN AMERICAN	4 (3.3)	4 (9.5)	1 (1.3)
MULTIPLE	1 (0.8)	0 (0.0)	0 (0.0)
OTHER	10 (8.2)	1 (2.4)	0 (0.0)
UNKNOWN	0 (0.0)	0 (0.0)	1 (1.3)
WHITE	86 (70.5)	29 (69.0)	50 (64.9)
Ethnicity, n (%)			
HISPANIC OR LATINO	12 (9.8)	4 (9.5)	11 (14.3)
NOT HISPANIC OR LATINO	109 (89.3)	38 (90.5)	65 (84.4)
UNKNOWN	1 (0.8)	0 (0.0)	1 (1.3)
Country of participation, n (%)			
Argentina	2 (1.6)	1 (2.4)	0 (0.0)
Australia	12 (9.8)	0 (0.0)	0 (0.0)
Belgium	2 (1.6)	0 (0.0)	0 (0.0)
Brazil	3 (2.5)	0 (0.0)	2 (2.6)
Bulgaria	9 (7.4)	4 (9.5)	1 (1.3)
Canada	1 (0.8)	1 (2.4)	1 (1.3)
Cyprus	3 (2.5)	0 (0.0)	2 (2.6)
France	13 (10.7)	7 (16.7)	12 (15.6)
Germany	3 (2.5)	0 (0.0)	2 (2.6)
Greece	1 (0.8)	0 (0.0)	0 (0.0)

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Characteristic	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Italy	2 (1.6)	3 (7.1)	2 (2.6)
Japan	4 (3.3)	3 (7.1)	9 (11.7)
Korea	6 (4.9)	3 (7.1)	2 (2.6)
Malaysia	6 (4.9)	0 (0.0)	0 (0.0)
Mexico	5 (4.1)	1 (2.4)	4 (5.2)
Netherlands	1 (0.8)	0 (0.0)	1 (1.3)
Portugal	10 (8.2)	3 (7.1)	4 (5.2)
Spain	6 (4.9)	1 (2.4)	10 (13.0)
Sweden	1 (0.8)	4 (9.5)	4 (5.2)
Taiwan	2 (1.6)	2 (4.8)	10 (13.0)
Turkey	0 (0.0)	0 (0.0)	1 (1.3)
United Kingdom	4 (3.3)	2 (4.8)	1 (1.3)
United States	26 (21.3)	7 (16.7)	9 (11.7)

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Table 15: Baseline Disease Characteristics (Safety Populations). Source: HELIOS-A CSR, table 5

Demographic	APOLLO	HELIOS-A		
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Time since hATTR diagnosis (years)				
Mean (SD)	2.60 (3.24)	3.35 (3.69)	3.59 (3.16)	3.41 (3.55)
Median (min, max)	1.41 (0.0, 16.5)	1.94 (0.0, 15.3)	2.39 (0.1, 12.5)	2.22 (0.0, 15.3)
Age (years) at hATTR symptom onset, n (%)				
<50	20 (26.0)	48 (39.3)	12 (28.6)	60 (36.6)
≥50	57 (74.0)	74 (60.7)	30 (71.4)	104 (63.4)
Neuropathy impairment score ^{a,b} , n (%)				
<50	35 (45.5)	78 (63.9)	27 (64.3)	105 (64.0)
≥50 to <100	33 (42.9)	39 (32.0)	13 (31.0)	52 (31.7)
≥100	9 (11.7)	5 (4.1)	2 (4.8)	7 (4.3)
Genotype ^a , n (%)				
V30M	40 (51.9)	54 (44.3)	20 (47.6)	74 (45.1)
Non-V30M	37 (48.1)	68 (55.7)	22 (52.4)	90 (54.9)
Early onset V30M (<50 years of age at onset), n (%)				
Yes	10 (13.0)	25 (20.5)	8 (19.0)	33 (20.1)
No	67 (87.0)	97 (79.5)	34 (81.0)	131 (79.9)
Previous tetramer stabilizer use ^a , n (%)				
No	36 (46.8)	47 (38.5)	9 (21.4)	56 (34.1)
Yes	41 (53.2)	75 (61.5)	33 (78.6)	108 (65.9)
Time since discontinuation of previous tetramer stabilizer use (days)				
Mean (SD)	31.39 (29.32)	58.08 (179.59)	28.48 (30.56)	49.04 (150.90)

Demographic	APOLLO	HELIOS-A		
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Median (min, max)	22.00 (6.0, 148.0)	18.00 (4.0, 1210.0)	19.00 (4.0, 122.0)	18.00 (4.0, 1210.0)
Previous tetramer stabilizer, n (%)				
Tafamidis	27 (35.1)	53 (43.4)	25 (59.5)	78 (47.6)
Diflunisal	14 (18.2)	22 (18.0)	8 (19.0)	30 (18.3)
Karnofsky Performance Status (KPS), n (%)				
60	22 (28.6)	17 (13.9)	5 (11.9)	22 (13.4)
70-80	45 (58.4)	73 (59.8)	27 (64.3)	100 (61.0)
90-100	10 (13.0)	32 (26.2)	10 (23.8)	42 (25.6)
New York Heart Association (NYHA) classification, n (%)				
No heart failure ^c	-	68 (55.7)	21 (50.0)	89 (54.3)
I	40 (51.9)	11 (9.0)	5 (11.9)	16 (9.8)
II	36 (46.8)	43 (35.2)	16 (38.1)	59 (36.0)
III	0	0	0	0
IV	0	0	0	0
Missing	1 (1.3)	0	0	0
NT-proBNP, n (%)				
≤3000 ng/L	66 (85.7)	112 (91.8)	37 (88.1)	149 (90.9)
>3000 ng/L	9 (11.7)	10 (8.2)	5 (11.9)	15 (9.1)
Missing	2 (2.6)	0	0	0
Cardiac subpopulation, n (%) ^d				
Yes	36 (46.8)	35 (28.7)	13 (31.0)	48 (29.3)
No	41 (53.2)	87 (71.3)	29 (69.0)	116 (70.7)

Based on the characteristics in the above demographics table, 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 US patient population.

8.2.3. Adequacy of the safety database:

For chronically administered drugs, the International Conference on Harmonisation (ICH) E-1 guidelines recommend having studied drug exposure in 1500 subjects overall, 300-600 subjects

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for six months, and 100 subjects for one year.

When compared to the ICH guidelines, the overall number of exposed subjects is less than the usual recommendation. However, because hATTR amyloidosis is a serious and life-threatening rare disease, there is no specific minimum number of subjects that should be studied to establish clinical safety. The number of subjects exposed ≥ 1 year exceeds the ICH recommendation.

Because hATTR amyloidosis is a rare and serious and life-threatening illness, the overall subject exposure in the clinical development program is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The NDA submission was well-organized. The submission quality with respect to the Applicant's clinical safety assessments was acceptable.

8.3.2. Categorization of Adverse Events

The Applicant's process for recording AEs was appropriate. The Applicant categorized adverse events as mild, moderate, or severe. A subject that experienced the same event more than once was counted only once and at the highest severity for that event. Adverse events were coded to MedDRA 23.0 for the HELIOS-A study. 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 potential safety areas of interest based on the therapeutic class, observations from nonclinical studies, mechanism of action of vutrisiran, route of administration, disease-related pathophysiology of hATTR amyloidosis, or general interest: injection site reactions (ISRs), hepatic events, cardiac events, renal disorders, malignancies, ocular events, depression and suicidality, and COVID-19. Safety assessments of these events are discussed in Section 8.4.5.

8.3.3. Routine Clinical Tests

In addition to queries for adverse events, assessments of vital signs and laboratory monitoring were performed in the pivotal safety/efficacy study HELIOS-A. Laboratory monitoring included assessments of serum chemistry, hematology, urinalysis, coagulation, viral hepatitis, liver

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function testing, FSH, pregnancy testing, cardiac biomarkers (NT-proBNP, troponin T, and troponin I), TTR protein, vitamin A, ECG, and anti-drug antibodies.

The schedule of key safety assessments for the HELIOS-A Study is presented in the following table, based on the submitted protocol.

Table 16: HELIOS-A Study Schedule of Key Safety Assessments and External Placebo Control APOLLO Study Safety Assessments. Sources: HELIOS-A Study Protocol and APOLLO Study Protocol

	To Month 9			Months 9-18	
	APOLLO Study	HELIOS-A Study		APOLLO Study	HELIOS-A Study
Physical Exam	Week 36	Weeks 12, 24, 36		Weeks 78, 81	Weeks 48, 60, 72
Vital Signs	Every 3 weeks	Every 3 weeks		Every 3 weeks	Every 3 weeks
Electrocardiogram	Week 18, 36	Weeks 12, 36		Weeks 57, 79	Weeks 48, 79
Blood Chemistry	Week 12, 27	Weeks 12, 24, 36		Weeks 51, 66, 78	Weeks 48, 60, 72, 79
Hematology	Week 36	Weeks 12, 24, 36		Week 78	Weeks 48, 60, 72

8.4. Safety Results

8.4.1. Deaths

There were three deaths (2.5%) in the vutrisiran group in the HELIOS-A study: two deaths in the main study and one death in the extension period. The deaths were related to 1) Covid-19 with cardiac amyloidosis, heart failure, and pneumonia; 2) cardiac amyloidosis, cardiac failure, and iliac artery occlusion; and 3) sudden cardiac death (in a subject with a history of cardiac amyloidosis and congestive heart failure), respectively.

In the patisiran active comparator group there were three deaths (7%) related to cardiac arrhythmia, Covid-19 infection, and ischemic heart disease, respectively.

There were 6 deaths (8%) in the external placebo control group from the APOLLO study.

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Reviewer Comment: Subjects in all of these studies were quite ill, with complex, chronic multisystem diseases and complicated courses. It is not possible to attribute the deaths to the investigational drug; conversely, it is not possible to be confident that the drug was not in some way contributory.

The death rates are similar to rates that have been reported in the literature for the hATTR amyloidosis. In conclusion, it appears unlikely that these deaths were caused by the investigational drug.

Although mortality was numerically lower in the vutrisiran group (2.5%) than in the external placebo group (8%) or concurrent comparator patisiran (7%), the HELIOS-A study was not designed to statistically evaluate an effect on survival and no conclusion regarding a potential long-term survival effect can be made.

8.4.2. Serious Adverse Events

Inspections found that subject (b) (6), randomized to vutrisiran in the HELIOS-A study, experienced “recurrent syncope.” This SAE occurred after the 120-day safety update cut-off date and was not included in the 120-day safety update. Review of the submitted discharge summary found that the subject had a history of cardiac amyloidosis and cardiac conduction disturbance with trifascicular block on ECG. The subject received an implantable cardioverter-defibrillator (ICD) and was discharged without any changes to medical therapy. *Note that cardiac conduction disease is known to be associated with cardiac amyloidosis.*

In the externally controlled HELIOS-A Study, the proportion of subjects experiencing serious AEs was 24% in the vutrisiran group and 40% in the external placebo group. The following table lists the serious adverse events that occurred at least 0.5% more frequently in the vutrisiran group than in the external placebo group. There was more pyelonephritis in the vutrisiran group (1.6%) than in patisiran (0%) or placebo (0%). The other SAEs in the table below occurred in one subject each in the vutrisiran group and in no subjects in the placebo group. Serious adverse events by system organ class reported in $\geq 5\%$ of patients were infections and infestations (7.4% vutrisiran vs. 12% placebo) and cardiac disorders (9% vutrisiran vs. 13% placebo). Note that cardiac disease (conduction disorders, infiltrative cardiomyopathy) and renal disease (leading to renal failure) are all features of ATTR amyloidosis.

COVID-19 did not exist at the time that the external placebo control group was evaluated so the COVID-19 preferred term comparison with the vutrisiran group is not valid.

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Table 17: Serious Adverse Events listed by Preferred Terms in the HELIOS-A study and external placebo control group that occurred at least 0.5% more frequently in the vutrisiran group. Source: FDA Analysis

Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Total Subjects with any Adverse Events	29 (23.8%)	18 (42.9%)	31 (40.3%)
COVID-19	2 (1.6%)	0 (0.0%)	0 (0.0%)
COVID-19 pneumonia	2 (1.6%)	1 (2.4%)	0 (0.0%)
Pyelonephritis	2 (1.6%)	0 (0.0%)	0 (0.0%)
Acute myocardial infarction	1 (0.8%)	0 (0.0%)	0 (0.0%)
Adenocarcinoma of the cervix	1 (0.8%)	0 (0.0%)	0 (0.0%)
Ankle fracture	1 (0.8%)	1 (2.4%)	0 (0.0%)
Atrioventricular block complete	1 (0.8%)	0 (0.0%)	0 (0.0%)
Atrioventricular block second degree	1 (0.8%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (0.8%)	0 (0.0%)	0 (0.0%)
Dyslipidemia	1 (0.8%)	0 (0.0%)	0 (0.0%)
Endometrial neoplasm	1 (0.8%)	0 (0.0%)	0 (0.0%)
Endoscopy	1 (0.8%)	0 (0.0%)	0 (0.0%)
Escherichia urinary tract infection	1 (0.8%)	0 (0.0%)	0 (0.0%)
Femur fracture	1 (0.8%)	0 (0.0%)	0 (0.0%)
Fractured sacrum	1 (0.8%)	0 (0.0%)	0 (0.0%)
Hypotension	1 (0.8%)	1 (2.4%)	0 (0.0%)
Iliac artery occlusion	1 (0.8%)	0 (0.0%)	0 (0.0%)
Metabolic encephalopathy	1 (0.8%)	0 (0.0%)	0 (0.0%)
Myocardial ischemia	1 (0.8%)	1 (2.4%)	0 (0.0%)
Neuralgia	1 (0.8%)	0 (0.0%)	0 (0.0%)
Osteoarthritis	1 (0.8%)	0 (0.0%)	0 (0.0%)
Pericarditis	1 (0.8%)	0 (0.0%)	0 (0.0%)
Post procedural complication	1 (0.8%)	0 (0.0%)	0 (0.0%)
Renal failure	1 (0.8%)	1 (2.4%)	0 (0.0%)

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Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Skin laceration	1 (0.8%)	0 (0.0%)	0 (0.0%)
Syncope	1 (0.8%)	0 (0.0%)	0 (0.0%)
Tachycardia paroxysmal	1 (0.8%)	0 (0.0%)	0 (0.0%)
Upper gastrointestinal hemorrhage	1 (0.8%)	0 (0.0%)	0 (0.0%)

The all vutrisiran-treated population includes subjects originally randomized to vutrisiran (N=122) that continued to receive vutrisiran in the extension period as well as subjects who switched from patisiran to vutrisiran in the extension period (N=11). In the all vutrisiran-treated population, SAEs were reported in 23% (31 of 133) of subjects. SAEs occurring in at least 1% of subjects are shown in the following table. Note that the patisiran-vutrisiran group includes subjects who received patisiran in the main HELIOS-A study and then switched to vutrisiran in the open-label extension study. System organ classes with a frequency of SAEs of $\geq 5\%$ were cardiac disorders (8%) and infections and infestations (7%).

Table 18: Serious Adverse Events in the All Vutrisiran-Treated Population listed by Preferred Terms that occurred in at least 1% of subjects. Source: FDA Analysis

Preferred Terms	Vutrisiran-Vutrisiran (N = 122)	Patisiran-Vutrisiran (N = 11)	Total (N = 133)
Total Subjects with any Adverse Events	30 (24.6%)	1 (9.1%)	31 (23.3%)
Acute kidney injury	2 (1.6%)	0 (0.0%)	2 (1.5%)
COVID-19	2 (1.6%)	0 (0.0%)	2 (1.5%)
COVID-19 pneumonia	2 (1.6%)	0 (0.0%)	2 (1.5%)
Fall	2 (1.6%)	0 (0.0%)	2 (1.5%)
Orthostatic hypotension	2 (1.6%)	0 (0.0%)	2 (1.5%)
Pneumonia	2 (1.6%)	0 (0.0%)	2 (1.5%)
Pyelonephritis	2 (1.6%)	0 (0.0%)	2 (1.5%)
Sepsis	2 (1.6%)	0 (0.0%)	2 (1.5%)

An analysis of serious adverse events in the externally controlled HELIOS-A study was also conducted using custom FDA groupings of preferred terms in order to detect additional possible safety signals. The results of this analysis are shown in the following table.

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Table 19: Treatment Emergent Serious Adverse Events in the HELIOS-A Study Grouped by Similar Preferred Terms that occurred at least 1% more frequently in the Vutrisiran group than in the External Placebo group. Source: FDA Analysis of submitted data.

Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Total Subjects with any Adverse Events	26 (21.3%)	18 (42.9%)	30 (39.0%)
AV block	2 (1.6%)	0 (0.0%)	0 (0.0%)
CAD, myocardial ischemia, (includes acute coronary syndrome)	2 (1.6%)	1 (2.4%)	0 (0.0%)
Myocardial ischemia FDA N	2 (1.6%)	1 (2.4%)	0 (0.0%)
Arrhythmia FDA B	5 (4.1%)	1 (2.4%)	2 (2.6%)
Syncope FDA B	3 (2.5%)	1 (2.4%)	1 (1.3%)

*Myocardial ischemia FDA N includes acute myocardial infarction and myocardial ischemia. Arrhythmia FDA B includes ventricular tachycardia, tachycardia paroxysmal, and atrial fibrillation. Syncope FDA B includes dizziness, hypotension, and syncope.

Small imbalances (<2% difference) were noted in the grouped cardiac SAEs favoring the external placebo group. Note that the rates of these cardiac SAE groupings were similar to those observed in the concurrent active patisiran comparator. Further analysis of cardiac AEs and SAEs is presented in Section 8.5.2.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the externally controlled HELIOS-A Study, 3 (2.5%) subjects in the vutrisiran group and 11 subjects (14.3%) in the external placebo group had an AE leading to treatment discontinuation. Two of these subjects discontinued treatment due to fatal events (COVID-19 pneumonia and cardiac failure with iliac artery occlusion) during the treatment period as described in Section 8.4.1. The third subject ((b) (6)) discontinued treatment with vutrisiran because of an adverse event of cardiac failure on study day 467 that resolved on study day 478. Study drug was discontinued and the subject discontinued the study. This subject had a medical history of coronary arterial stent insertion, coronary artery disease, cardiac failure congestive, acute myocardial infarction, first degree atrioventricular heart block, cardiac amyloidosis, cardiomyopathy, left anterior fascicular block, and non-sustained ventricular tachycardia. Because of these prior cardiac conditions it is not possible to conclude a causal association with the vutrisiran treatment.

In addition to the AEs leading to treatment discontinuation described above, 1 subject ((b) (6)) discontinued vutrisiran treatment during the extension period due to a fatal event of sudden cardiac death on study day 602. The subject had received the eighth dose of vutrisiran on study day 589. The subject's medical history included cardiac amyloidosis and congestive cardiac failure.

8.4.4. Significant Adverse Events

Adverse events that occurred during the studies were assessed by the Investigators for severity (mild, moderate, or severe). A subject that experienced the same event more than once was counted only once and at the highest severity for that event.

In the externally controlled HELIOS-A Study, 14.8% of subjects in the vutrisiran group had severe AEs compared to 36.4% in the external placebo group. Severe AEs by preferred term (PT) that were reported in more than a single subject were sepsis (2 subjects) and atrial fibrillation (2 subjects).

In the pooled HELIOS-A Study and open-label extension, 14.3% of subjects that received vutrisiran had severe AEs. Severe AEs by preferred term (PT) that were reported in more than a single subject were fall (2 subjects) and pain in extremity (2 subjects).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Results of the FDA analysis of TEAEs are shown in the following table. In the externally controlled HELIOS-A Study, the proportion of subjects experiencing treatment emergent AEs was 97.5% in the vutrisiran group and 97.4% in the external placebo group. The following table lists the treatment emergent adverse events that occurred at least 2% more frequently in the vutrisiran group than in the external placebo group.

TEAEs that occurred at least 5% more frequently in the vutrisiran group than in the external placebo control include arthralgia, vitamin A decreased, and dyspnea. Note that a decrease in vitamin A levels is an expected adverse event given vutrisiran's mechanism of action and that all subjects were taking vitamin A supplements. Although there

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was more “vision blurred” in the vutrisiran group (4.1%) than in the external placebo control (1.3%), the AE of night blindness, which can be associated with low vitamin A levels, was similar in both the vutrisiran (1 subject, 0.8%) and external placebo (1 subject, 1.3%) groups.

Treatment emergent adverse events by system organ class that occurred at least 1% more frequently in the vutrisiran group than in the external placebo group were reproductive system and breast disorders (9.8% vutrisiran vs. 5.2% placebo), musculoskeletal and connective tissue disorders (41.8% vutrisiran vs. 37.7% placebo), and eye disorders (27% vutrisiran vs. 26% placebo). The difference in reproductive system and breast disorders was driven by three subjects with erectile dysfunction (2.5%) in the vutrisiran group (vs. 0% in placebo) and 4 subjects (3.2%) with menstrual abnormalities (dysmenorrhea, menorrhagia, metrorrhagia, vaginal hemorrhage, respectively) compared to 0% in the external placebo group.

COVID-19 did not exist at the time that the external placebo control group was evaluated so the COVID-19 preferred term comparison with the vutrisiran group is not valid.

Table 20: Treatment-emergent Adverse Events that Occurred at least 2% more frequently in the Vutrisiran group than in the External Placebo group During the 18-Month Treatment Period

Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Total Subjects with any Adverse Events	119 (97.5%)	40 (95.2%)	75 (97.4%)
Arthralgia	12 (9.8%)	4 (9.5%)	0 (0.0%)
Abdominal pain	11 (9.0%)	0 (0.0%)	1 (1.3%)
Vitamin A decreased	8 (6.6%)	2 (4.8%)	0 (0.0%)
Dyspnoea	7 (5.7%)	0 (0.0%)	0 (0.0%)
COVID-19	5 (4.1%)	0 (0.0%)	0 (0.0%)
Injection site reaction	5 (4.1%)	0 (0.0%)	0 (0.0%)
Troponin T increased	5 (4.1%)	0 (0.0%)	0 (0.0%)
Joint injury	5 (4.1%)	0 (0.0%)	1 (1.3%)
Vision blurred	5 (4.1%)	1 (2.4%)	1 (1.3%)
Pain in extremity	16 (13.1%)	4 (9.5%)	8 (10.4%)
COVID-19 pneumonia	3 (2.5%)	1 (2.4%)	0 (0.0%)
Chest pain	3 (2.5%)	1 (2.4%)	0 (0.0%)
Dyspnoea exertional	3 (2.5%)	0 (0.0%)	0 (0.0%)

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Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Erectile dysfunction	3 (2.5%)	0 (0.0%)	0 (0.0%)
Eye pain	3 (2.5%)	0 (0.0%)	0 (0.0%)
Sinusitis	3 (2.5%)	0 (0.0%)	0 (0.0%)
Tachycardia	3 (2.5%)	0 (0.0%)	0 (0.0%)
Visual impairment	3 (2.5%)	0 (0.0%)	0 (0.0%)
Muscle spasms	4 (3.3%)	1 (2.4%)	1 (1.3%)
Osteoarthritis	4 (3.3%)	0 (0.0%)	1 (1.3%)

In the pooled population of all subjects who received vutrisiran in the externally controlled HELIOS-A Study and the open-label extension study, the proportion of subjects experiencing treatment emergent AEs was 92%. The following table lists the treatment emergent adverse events that occurred in at least 5% of subjects.

Table 21: Pooled Treatment Emergent Adverse Events listed by Preferred Terms in the HELIOS-A study and open-label extension that occurred in at least 5% of subjects. Source: FDA Analysis

Preferred Terms	Vutrisiran-Vutrisiran (N = 122)	Patisiran-Vutrisiran (N = 11)	Total (N = 133)
Total Subjects with any Adverse Events	120 (98.4%)	2 (18.2%)	122 (91.7%)
Fall	21 (17.2%)	0 (0.0%)	21 (15.8%)
Pain in extremity	16 (13.1%)	0 (0.0%)	16 (12.0%)
Diarrhea	15 (12.3%)	0 (0.0%)	15 (11.3%)
Urinary tract infection	15 (12.3%)	0 (0.0%)	15 (11.3%)
Oedema peripheral	14 (11.5%)	0 (0.0%)	14 (10.5%)
Arthralgia	12 (9.8%)	0 (0.0%)	12 (9.0%)
Abdominal pain	11 (9.0%)	0 (0.0%)	11 (8.3%)
Dizziness	11 (9.0%)	0 (0.0%)	11 (8.3%)
Nausea	11 (9.0%)	0 (0.0%)	11 (8.3%)

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Preferred Terms	Vutrisiran-Vutrisiran (N = 122)	Patisiran-Vutrisiran (N = 11)	Total (N = 133)
Headache	10 (8.2%)	0 (0.0%)	10 (7.5%)
Cough	9 (7.4%)	0 (0.0%)	9 (6.8%)
Upper respiratory tract infection	9 (7.4%)	0 (0.0%)	9 (6.8%)
Nasopharyngitis	8 (6.6%)	0 (0.0%)	8 (6.0%)
Syncope	8 (6.6%)	0 (0.0%)	8 (6.0%)
Vitamin A decreased	8 (6.6%)	0 (0.0%)	8 (6.0%)
Vomiting	8 (6.6%)	0 (0.0%)	8 (6.0%)
Atrial fibrillation	7 (5.7%)	0 (0.0%)	7 (5.3%)
Dyspnoea	7 (5.7%)	0 (0.0%)	7 (5.3%)
Neuralgia	7 (5.7%)	0 (0.0%)	7 (5.3%)
Rash	7 (5.7%)	0 (0.0%)	7 (5.3%)
Thermal burn	7 (5.7%)	0 (0.0%)	7 (5.3%)

Note that digestive symptoms due to autonomic neuropathy (diarrhea, constipation), cardiac disease (conduction disorders, infiltrative cardiomyopathy), and renal disease (leading to renal failure) are all features of ATTR amyloidosis.

An analysis of treatment emergent adverse events in the externally controlled HELIOS-A study was also conducted using custom FDA groupings of preferred terms in order to detect additional possible safety signals. The results of this analysis are shown in the following table.

Table 22: Treatment Emergent Adverse Events in the HELIOS-A Study Grouped by Similar Preferred Terms that occurred at least 1% more frequently in the Vutrisiran group than in the External Placebo group (FDA Custom Grouping of Terms)

Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Total Subjects with any Adverse Events	112 (91.8%)	39 (92.9%)	75 (97.4%)
arthralgia, arthritis, arthrosis	13 (10.7%)	4 (9.5%)	1 (1.3%)
Arthralgia FDA N	11 (9.0%)	4 (9.5%)	0 (0.0%)
Arthritis FDA B	18 (14.8%)	5 (11.9%)	6 (7.8%)
Dyspnoea FDA B	8 (6.6%)	0 (0.0%)	0 (0.0%)

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Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Dyspnoea FDA N	8 (6.6%)	0 (0.0%)	0 (0.0%)
dyspnea, SOB, respiratory distress	8 (6.6%)	0 (0.0%)	0 (0.0%)
Arthralgia FDA B	14 (11.5%)	4 (9.5%)	4 (5.2%)
Bronchospasm FDA B	9 (7.4%)	0 (0.0%)	1 (1.3%)
Acute coronary syndrome FDA B	8 (6.6%)	2 (4.8%)	1 (1.3%)
injection site reaction (all)	5 (4.1%)	0 (0.0%)	0 (0.0%)
Myocardial infarction FDA B	9 (7.4%)	2 (4.8%)	3 (3.9%)
Myocardial ischemia FDA B	9 (7.4%)	2 (4.8%)	3 (3.9%)
Abnormal uterine bleeding FDA B	3 (2.5%)	0 (0.0%)	0 (0.0%)
Abnormal uterine bleeding FDA N	3 (2.5%)	0 (0.0%)	0 (0.0%)
DOE	3 (2.5%)	0 (0.0%)	0 (0.0%)
Myocardial ischemia FDA N	3 (2.5%)	1 (2.4%)	0 (0.0%)
Sexual dysfunction	3 (2.5%)	0 (0.0%)	0 (0.0%)
Sexual dysfunction FDA B	3 (2.5%)	0 (0.0%)	0 (0.0%)
Sexual dysfunction FDA N	3 (2.5%)	0 (0.0%)	0 (0.0%)
cramps, muscle spasm	4 (3.3%)	1 (2.4%)	1 (1.3%)
chest pain (non-cardiac or unknown)	7 (5.7%)	1 (2.4%)	3 (3.9%)
CAD, myocardial ischemia, (includes ACS)	2 (1.6%)	2 (4.8%)	0 (0.0%)
Confusional state FDA N	2 (1.6%)	1 (2.4%)	0 (0.0%)
Dysgeusia FDA N	2 (1.6%)	1 (2.4%)	0 (0.0%)
Erectile dysfunction FDA B	2 (1.6%)	0 (0.0%)	0 (0.0%)
Erectile dysfunction FDA N	2 (1.6%)	0 (0.0%)	0 (0.0%)
Gynecomastia FDA B	2 (1.6%)	0 (0.0%)	0 (0.0%)
Gynecomastia FDA N	2 (1.6%)	0 (0.0%)	0 (0.0%)
dysfunctional uterine bleeding, menometrorrhagia	2 (1.6%)	0 (0.0%)	0 (0.0%)

Preferred Terms	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
erectile dysfunction	2 (1.6%)	0 (0.0%)	0 (0.0%)
tendonitis, synovitis	2 (1.6%)	0 (0.0%)	0 (0.0%)
Arthritis FDA N	5 (4.1%)	1 (2.4%)	2 (2.6%)
GOT, GPT, GGTP, LFTs	5 (4.1%)	6 (14.3%)	2 (2.6%)

Overall, the findings of the above grouping of preferred terms are similar to the standard table of preferred terms. Note that there is an imbalance of cardiac AE groupings (acute coronary syndrome, myocardial infarction, myocardial ischemia) that favors the external placebo group, although the rates were similar to those observed in the concurrent active patisiran comparator. Further analysis of cardiac AEs and SAEs is presented in Section 8.5.2.

Multiple similar terms for abdominal pain were reported and are grouped together, as shown in the following table.

Table 23: Abdominal Pain Grouping of Preferred Terms in the HELIOS-A Study and External Placebo Group from the APOLLO Study. Source: FDA Analysis

Abdominal Pain Grouped Terms		
Preferred Term	n (%) in Vutrisiran Group (N=122)	n (%) in external Placebo Group (N=77)
Abdominal pain	11 (9)	1 (1.3)
Abdominal pain upper	3 (2.5)	6 (7.8)
Abdominal discomfort	3 (2.5)	3 (3.9)
Abdominal distension	0 (0)	1 (1.3)
Grouping of all terms	12/122 (9.8)	10/77 (13)

The above grouping of abdominal pain terms shows that there was more abdominal pain overall in the external placebo group than in the vutrisiran group. *This reviewer therefore recommends that abdominal pain not be included in the list of the most common treatment emergent adverse events in the prescribing information.*

8.4.6. Laboratory Findings

Laboratory findings for subjects who received vutrisiran in the externally controlled HELIOS-A study and for the open-label extension study are summarized. The evaluations included

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hematology, renal function, liver function tests (LFTs), blood chemistry, thyroid function, and coagulation parameters.

Hematology:

There were no notable changes in hematological parameters (hemoglobin, leukocytes, lymphocytes, neutrophils, or platelet count) in drug-treated subjects compared to the external placebo subjects, as seen in the following tables.

In the vutrisiran group, one subject had a Common Terminology Criteria for Adverse Events (CTCAE) category Grade 3 hematology abnormality (neutrophil count of $<1.0 \times 10^9/L$), which occurred once and was likely related to the administration of paclitaxel and carboplatin for the treatment of endometrial neoplasm.

Post-baseline shift tables of hematology laboratory parameters are shown below, based on FDA analysis of the submitted data.

Table 24: Post-baseline shift table of Platelets in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	$>150 \times 10^9/L$	$>100-150 \times 10^9/L$	$>50-100 \times 10^9/L$
Vutrisiran (N = 122)	$>150 \times 10^9/L$	99 (82.5%)	12 (10.0%)	0 (0.0%)
	$>100-150 \times 10^9/L$	3 (2.5%)	4 (3.3%)	0 (0.0%)
	$>50-100 \times 10^9/L$	0 (0.0%)	1 (0.8%)	1 (0.8%)
Patisiran (N = 42)	$>150 \times 10^9/L$	35 (85.4%)	3 (7.3%)	0 (0.0%)
	$>100-150 \times 10^9/L$	0 (0.0%)	2 (4.9%)	0 (0.0%)
	$>50-100 \times 10^9/L$	0 (0.0%)	1 (2.4%)	0 (0.0%)
APOLLO (Placebo) (N = 77)	$>150 \times 10^9/L$	52 (85.2%)	4 (6.6%)	0 (0.0%)
	$>100-150 \times 10^9/L$	2 (3.3%)	1 (1.6%)	0 (0.0%)
	$>50-100 \times 10^9/L$	0 (0.0%)	1 (1.6%)	1 (1.6%)

Subjects had baseline and at least one postline lab test results.

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Table 25: Post-baseline shift table of Hemoglobin in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	$>10 \text{ g/L}$
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Treatment	Baseline	>10 g/L
Vutrisiran (N = 122)	>10 g/L	120 (100%)
Patisiran (N = 42)	>10 g/L	41 (100%)
APOLLO (Placebo) (N = 77)	>10 g/L	63 (100%)

Subjects had baseline and at least one postline lab test results.
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Table 26: Post-baseline shift table of Leukocytes in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	>3.0*10 ⁹ /L	>1.5-3*10 ⁹ /L
Vutrisiran (N = 122)	>3.0*10 ⁹ /L	114 (95.0%)	3 (2.5%)
	>1.5-3*10 ⁹ /L	0 (0.0%)	3 (2.5%)
Patisiran (N = 42)	>3.0*10 ⁹ /L	38 (92.7%)	2 (4.9%)
	>1.5-3*10 ⁹ /L	0 (0.0%)	1 (2.4%)
APOLLO (Placebo) (N = 77)	>3.0*10 ⁹ /L	61 (96.8%)	2 (3.2%)
	>1.5-3*10 ⁹ /L	0 (0.0%)	0 (0.0%)

Subjects had baseline and at least one postline lab test results.
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Table 27: Post-baseline shift table of Lymphocytes in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	>1.0*10 ⁹ /L	>0.5-1.0*10 ⁹ /L	<=0.5*10 ⁹ /L
Vutrisiran (N = 122)	>1.0*10 ⁹ /L	99 (82.5%)	10 (8.3%)	0 (0.0%)
	>0.5-1.0*10 ⁹ /L	2 (1.7%)	9 (7.5%)	0 (0.0%)
Patisiran (N = 42)	>1.0*10 ⁹ /L	29 (70.7%)	6 (14.6%)	0 (0.0%)
	>0.5-1.0*10 ⁹ /L	1 (2.4%)	3 (7.3%)	2 (4.9%)
APOLLO (Placebo) (N = 77)	>1.0*10 ⁹ /L	25 (39.7%)	27 (42.9%)	5 (7.9%)
	>0.5-1.0*10 ⁹ /L	2 (3.2%)	2 (3.2%)	2 (3.2%)

Subjects had baseline and at least one postline lab test results.
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Chemistry:

In the externally controlled trial database, there were no notable changes in sodium, potassium,

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random glucose, total protein, albumin, prolactin, or high-density lipoproteins.

In the vutrisiran group two subjects had Grade 3 abnormalities in chemistry parameters (1 subject with low sodium related to renal failure and 1 subject with low potassium related to furosemide use).

Renal Parameters:

No subject in the vutrisiran group met the criteria of laboratory abnormalities corresponding to CTCAE v5.0 Grade 3 creatinine increased (creatinine $>3.0 \times$ baseline or $>3.0-6.0 \times$ upper limit of normal (ULN)) or Grade 3 acute kidney injury (creatinine $>3.0 \times$ ULN or >4.0 mg/dL).

One subject in the vutrisiran group met the criterion of Grade 3 chronic kidney disease (eGFR <30 ml/min/1.73m²) during the Treatment Period. On Day 559, the subject had an SAE of acute kidney injury with moderate severity. There was evidence of urinary obstruction with bilateral hydronephrosis. The subject was treated with a urinary catheter and diuretics and the event resolved.

Post-baseline shift tables of renal laboratory parameters are shown below, based on FDA analysis of the submitted data.

Table 28: Post-baseline shift table of Creatinine in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	<130 umol/L	≥ 130 umol/L
Vutrisiran (N = 122)	<130 umol/L	111 (92.5%)	3 (2.5%)
	≥ 130 umol/L	3 (2.5%)	3 (2.5%)
Patisiran (N = 42)	<130 umol/L	35 (85.4%)	2 (4.9%)
	≥ 130 umol/L	0 (0.0%)	4 (9.8%)
APOLLO (Placebo) (N = 77)	<130 umol/L	68 (91.9%)	4 (5.4%)
	≥ 130 umol/L	0 (0.0%)	2 (2.7%)

Subjects had baseline and at least one postline lab test results.
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Table 29: Post-baseline shift table of Urea Nitrogen in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	<7 mmol/L	≥ 7 mmol/L
Vutrisiran (N = 122)	<7 mmol/L	73 (60.8%)	21 (17.5%)
	≥ 7 mmol/L	2 (1.7%)	24 (20.0%)
Patisiran (N = 42)	<7 mmol/L	19 (46.3%)	7 (17.1%)
	≥ 7 mmol/L	0 (0.0%)	15 (36.6%)

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Treatment	Baseline	<7 mmol/L	>=7 mmol/L
APOLLO (Placebo) (N = 77)	<7 mmol/L	37 (50.0%)	9 (12.2%)
	>= 7 mmol/L	4 (5.4%)	24 (32.4%)

Subjects had baseline and at least one postline lab test results.

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Note that renal impairment is a known complication of hATTR amyloidosis.

Liver: Transaminases, Bilirubin, and Alkaline Phosphatase

There were no cases of liver enzyme elevation that were consistent with Hy's Law (ALT or AST $\geq$ 3X ULN and bilirubin > 2X ULN) among subjects who received vutrisiran in the HELIOS-A and open-label extension studies.

During hospitalization for an SAE of acute kidney infection, subject (b) (6) had an AST elevation (5.5×ULN) and an ALT elevation (1.9×ULN) on study day 439. The ALT and AST elevations were not associated with an elevation of total bilirubin >2×ULN. After the data cutoff date, ALT and AST levels were within normal limits when next tested on Day 505.

Post-baseline shift tables of hepatic laboratory parameters are shown below, based on FDA analysis of the submitted data.

Table 30: Post-baseline shift table of Alanine Aminotransferase (IU/L) in the HELIOS-A study.
Source: FDA analysis

Treatment	Baseline	<3ULN
Vutrisiran (N = 122)	<3ULN	121 (100%)
Patisiran (N = 42)	<3ULN	42 (100%)
APOLLO (Placebo) (N = 77)	<3ULN	74 (100%)

Subjects had baseline and at least one postline lab test results.
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Table 31: Post-baseline shift table of Aspartate Aminotransferase (IU/L) in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	<3ULN
Vutrisiran (N = 122)	<3ULN	121 (100%)
Patisiran (N = 42)	<3ULN	42 (100%)
APOLLO (Placebo) (N = 77)	<3ULN	74 (100%)

Treatment	Baseline	<3ULN
Subjects had baseline and at least one postline lab test results. [tshiftdb.rtf] [tshiftdb.sas] 24JUN2021, 12:31		

Table 32: Post-baseline shift table of Total Bilirubin (IU/L) in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	<2ULN
Vutrisiran (N = 122)	<2ULN	121 (100%)
Patisiran (N = 42)	<2ULN	42 (100%)
APOLLO (Placebo) (N = 77)	<2ULN	74 (100%)
Subjects had baseline and at least one postline lab test results. [tshiftdb.rtf] [tshiftdb.sas] 24JUN2021, 12:31		

Table 33: Post-baseline shift table of Alkaline Phosphatase (IU/L) in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	<2ULN	2-<3ULN
Vutrisiran (N = 122)	<2ULN	118 (97.5%)	2 (1.7%)
	2-<3ULN	0 (0.0%)	1 (0.8%)
Patisiran (N = 42)	<2ULN	42 (100%)	0 (0.0%)
	2-<3ULN	0 (0.0%)	0 (0.0%)
APOLLO (Placebo) (N = 77)	<2ULN	74 (100%)	0 (0.0%)
	2-<3ULN	0 (0.0%)	0 (0.0%)
Subjects had baseline and at least one postline lab test results. [tshiftdb.rtf] [tshiftdb.sas] 24JUN2021, 12:31			

In the vutrisiran group, there was no clinically significant change in mean absolute and mean change from baseline in LFT parameters, including ALT, AST, bilirubin, and alkaline phosphatase, over the course of the HELIOS-A study.

Vitamin A:

Reductions in vitamin A levels were observed with vutrisiran treatment, as expected from

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vutrisiran's mechanism of action, as shown in the following table based on analysis of the submitted data.

Table 34: Post-baseline shift table of Vitamin A (mcg/dL) in the HELIOS-A study. Source: FDA analysis

Treatment	Baseline	>=32 ug/DL	<32 ug/DL
Vutrisiran (N = 122)	>=32 ug/DL	2 (1.7%)	88 (72.7%)
	<32 ug/DL	0 (0.0%)	31 (25.6%)
Patisiran (N = 42)	>=32 ug/DL	1 (2.4%)	28 (68.3%)
	<32 ug/DL	0 (0.0%)	12 (29.3%)
APOLLO (Placebo) (N = 77)	>=32 ug/DL	27 (35.1%)	24 (31.2%)
	<32 ug/DL	0 (0.0%)	26 (33.8%)

Subjects had baseline and at least one postline lab test results.

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Table 35: Vitamin A Level Change over Time in the HELIOS-A study. Source: FDA analysis

Vitamin A (ug/DL) Helios A Pivotal Study					
Day	Parameter	Statistics	Vutrisiran (N=122)	Patisiran (N=42)	APOLLO Placebo (N=77)
Baseline	Observed Value	N	121	41	77
		Mean	42.35	45.35	36.96
Day 22	Change Value	N	112	40	72
		Mean	-22.7	-29.4	-0.92
Day 127	Change Value	N	104	36	70
		Mean	-27.4	-27.2	-0.91
Day 253	Change Value	N	118	30	61
		Mean	-27	-25.5	-1.14
Month 9	Change Value	N	112	35	66
		Mean	-27.6	-29.9	0.73

The HELIOS-A study defines the normal range for Vitamin A as 32-93 mcg/dL. There were 90 subjects who had normal Vitamin A levels at baseline. The shift table above shows that nearly

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all subjects (88 of 90, ~98%) who had normal Vitamin A levels at baseline developed low Vitamin A levels during the HELIOS-A study. Thirty-one subjects (~26%) were low at baseline and remained low during the study.

Review of the data for the 8 subjects with a TEAE of vitamin A decreased showed that 7 of 8 subjects had a lowest vitamin A level of 10 mcg/dL and 1 subject had a lowest level of 11 mcg/dL. The Applicant has explained that not all sites reported low vitamin A levels as adverse events because vitamin A reduction is a known pharmacodynamic effect of vutrisiran.

Over the course of the study, median percent reduction in vitamin A levels through Month 9 was 60.9% in the vutrisiran group and 62.6% in the patisiran group. A decrease in serum levels of vitamin A is a known secondary pharmacodynamic effect of vutrisiran's reduction of serum TTR protein. See Section 8.5.3 for a discussion of the potential effects of vitamin A level reduction. Note that the HELIOS-A study protocol specified that all subjects take the recommended daily allowance of vitamin A supplementation.

8.4.7. Vital Signs

In the vutrisiran group, there was no clinically significant change in mean values for vital signs (including diastolic and systolic blood pressure, pulse rate, respiratory rate, weight, and temperature) over the course of the HELIOS-A study.

The following table shows the mean and median changes in systolic blood pressure in the HELIOS-A study.

Table 36: Changes in Systolic Blood Pressure (mm Hg) in the HELIOS-A Study. Source: FDA Analysis

Day	Parameter	Statistics	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
Baseline	Observed Value	N	122	42	77
		Mean	122.9	124.4	124.3
		SD	17.69	18.64	20.92
		Median	122.5	120.0	128.0
		Min	84.0	90.0	90.0
		Max	170.0	173.0	163.0
Day 211	Observed Value	N	97	40	66
		Mean	120.1	123.3	125.9
		SD	17.55	19.10	21.47
		Median	120.0	123.5	125.0
		Min	84.0	83.0	90.0
		Max	170.0	157.0	178.0

Day	Parameter	Statistics	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)
	Change Value	N	97	40	66
		Mean	-3.45	-1.45	-0.06
		SD	15.15	16.84	18.85
		Median	-4.00	1.50	0.50
		Min	-42.0	-44.0	-41.0
		Max	35.0	36.0	37.0
	Change > 20 mmHg	N (%)	3 (2.5)	3 (7.1)	9 (11.7)
	Change <- 20 mmHg	N (%)	13 (10.7)	5 (11.9)	9 (11.7)

8.4.8. Electrocardiograms (ECGs)

Among subjects in the vutrisiran group with QTcF intervals <450 msec at baseline, 2 (1.6%) subjects had QTcF intervals of >500 msec and 4 (3.3%) subjects had postbaseline increases of >60 msec in QTcF interval during the HELIOS-A study. For subjects with QTcF intervals ≥450 msec at baseline, 1 (0.8%) subject had a postbaseline increase of >60 msec in QTcF interval. Note that cardiac involvement and conduction defects are associated with hATTR amyloidosis.

8.4.9. QT

The Interdisciplinary Review Team for Cardiac Safety Studies was consulted for this NDA and made the following conclusions.

No significant QTc prolongation effect of vutrisiran was detected in this QT assessment.

The effect of vutrisiran was evaluated in Study # ALN-TTRSC02-001. This was a phase 1, randomized, single ascending dose study (25 mg to 300 mg) evaluating the safety, tolerability, PK, and PD of subcutaneous doses of vutrisiran in healthy subjects. The highest dose of 300 mg covers the high exposure scenario. As the dosing regimen is once quarterly no increase beyond the therapeutic Cmax is expected and the highest dose in the study, therefore, sufficiently covers the high exposures. The data were analyzed using exposure-response analysis as the primary analysis which did not suggest that vutrisiran is associated with significant QTc prolonging effect. The findings of this analysis are further supported by the available nonclinical data and categorical analysis.

8.4.10. Immunogenicity

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In the all vutrisiran-treated population (HELIOS-A study and open-label extension study), the incidence of treatment-emergent anti-drug antibody (ADA) was 4.1% (5 of 121 subjects). Review of the AEs of these ADA-positive subjects did not suggest an association of ADA positivity with any particular AE.

8.4.11. Blinded Serious Adverse Events from the Ongoing HELIOS-B Study of hATTR-cardiomyopathy

The Applicant has submitted blinded serious adverse events reports from the separate ongoing HELIOS-B study in 655 subjects with hATTR-cardiomyopathy. The following table, based on the submitted data, summarizes the serious adverse events that have occurred in more than one subject during this ongoing blinded study.

Serious Adverse Event	Number of Events Reported
Cardiac failure	12
Acute kidney injury	4
Atrial fibrillation	2
Bundle Branch Block	2
Encephalopathy	2
Squamous cell carcinoma	2
Syncope	2

These SAEs are consistent with those observed in the HELIOS-A study of hATTR-PN, with the exception that there were notably more cardiac failure SAEs in the HELIOS-B study, which is not unexpected given that the study focused on hATTR-cardiomyopathy subjects.

8.5. Analysis of Submission-Specific Safety Issues

When synthetic siRNAs are introduced into cells, the net effect is the binding of the siRNA to its complementary mRNA sequence, the cleavage of this target mRNA, and the suppression of the target protein encoded by the mRNA. The potential for off-target protein suppression exists if target proteins are expressed in other body systems with different functions.

The following table, generated by this reviewer from the submitted listing of adverse events for the HELIOS-A Study, summarizes the key submission-specific safety issues that were identified at the filing of this NDA.

Table 37: Overview of Key Potential Submission-Specific Safety Issues. Source: Adverse Event Data for HELIOS-A Study and Applicant's Clinical Overview, Section 5.3.6.

Key Safety Issue	Vutrisiran (N = 122)	Patisiran (N = 42)	APOLLO (Placebo) (N = 77)	Reviewer Comments
• Injection Site Reactions	5 (4.1%)	0 (0.0%)	0 (0.0%)	N=5 (4.1%) in vutrisiran group
• Drug Related Hepatic Disorders	7 (5.7%)	6 (14.3%)	6 (7.8%)	Liver is the drug's main site of action. No Hy's Law cases reported.
• Cardiac Disorders	33 (27.0%)	10 (23.8%)	28 (36.4%)	Cardiac involvement common in hATTR amyloidosis
• Renal and Urinary Disorders	17 (13.9%)	7 (16.7%)	23 (29.9%)	Renal involvement in hATTR amyloidosis common. One renal SAE reported.
• Malignancies/ Tumors	5 (4.1%)	0 (0.0%)	4 (5.2%)	
• Eye Disorders	33 (27.0%)	9 (21.4%)	20 (26.0%)	TTR lowering leads to vitamin A reduction
• Depression	4 (3.3%)	0 (0.0%)	6 (7.8%)	No suicidality

Overall, the frequency of the above adverse events is similar or greater in the external placebo control group, except for injection site reactions which are higher (4.1%) than in the external control group (0%). However, the comparison of injection site reactions is not valid because the external control group did not receive subcutaneous injections but received placebo IV infusions instead.

8.5.1. Safety using Vial versus Syringe to Administer Vutrisiran

Vutrisiran was initially supplied for the HELIOS-A study (ALN-TTRSC02-002) in a vial and later in a pre-filled syringe with passive needle safety system (PFS-S), and that subjects received various combinations of vial and syringe administrations. Prior to study week 36, all but one subject received vutrisiran via vial with syringe at each visit. Starting at Week 48 (Month 12), most subjects, 74.2%, had switched to dosing with PFS-S, and from Week 60 onwards, all subjects were dosed using PFS-S.

The CMC Process and Facility reviewers found that the volume of vutrisiran administered by syringe is variable (with a range of (b) (4) mL) and that some subjects may have received up to (b) (4) mg vutrisiran instead of the 25 mg specified in the protocol. An information request was sent to the Applicant on 9/23/2021 requesting adverse and serious adverse event data as a function of administration with pre-filled syringe or vial. The Applicant submitted the requested data and responded that during the engineering study as well as from the manufacture of clinical batches of drug product the expelled volume of vutrisiran was consistently no more than 0.553 mL.

Analysis of safety in syringe compared to the vial found no meaningful difference in safety between the vial and syringe administrations. The rate of adverse events before and after Month 12 (when most subjects had switched to PFS-S: mean 61% before month 12 vs. 48% after month 12) does not suggest worsening numbers of adverse events with PFS-S use (Source: Table 14.3.1.2.7 of 120-day safety update). There was also no meaningful difference in AE rates by system organ class before or after Month 12. Further, the plasma concentration of vutrisiran at 3 hours after administration from PFS-S or vial with syringe was similar across study visits as seen in the following figures copied from the submission (Figures 9 and 10).

Figure 9: Helios-A: Vutrisiran Plasma Concentration at 3 Hours Post-dose Across Study Visits After Dosing with PFS-S or Vial with Syringe. Source: Applicant response to information request received 23 September 2021

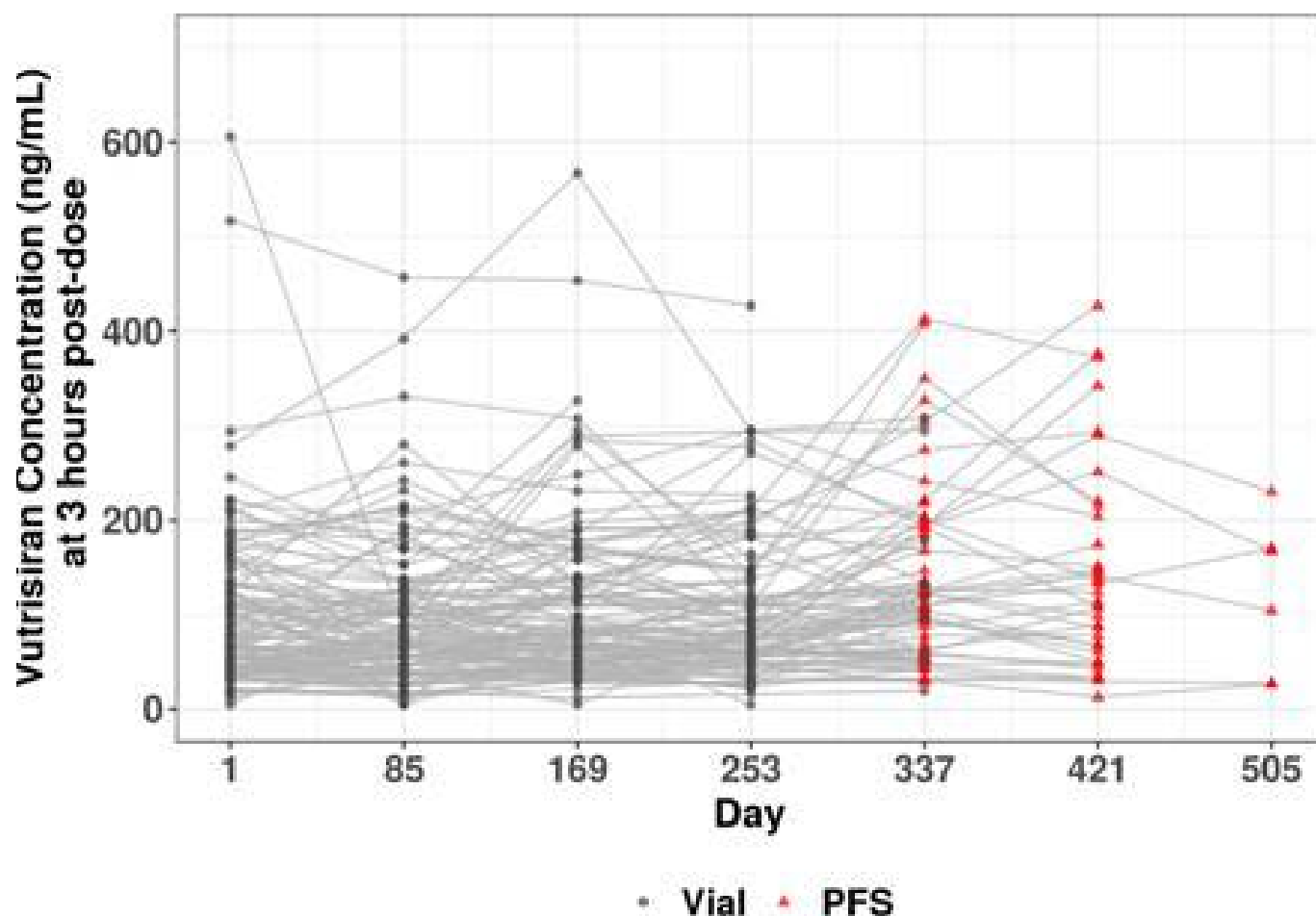
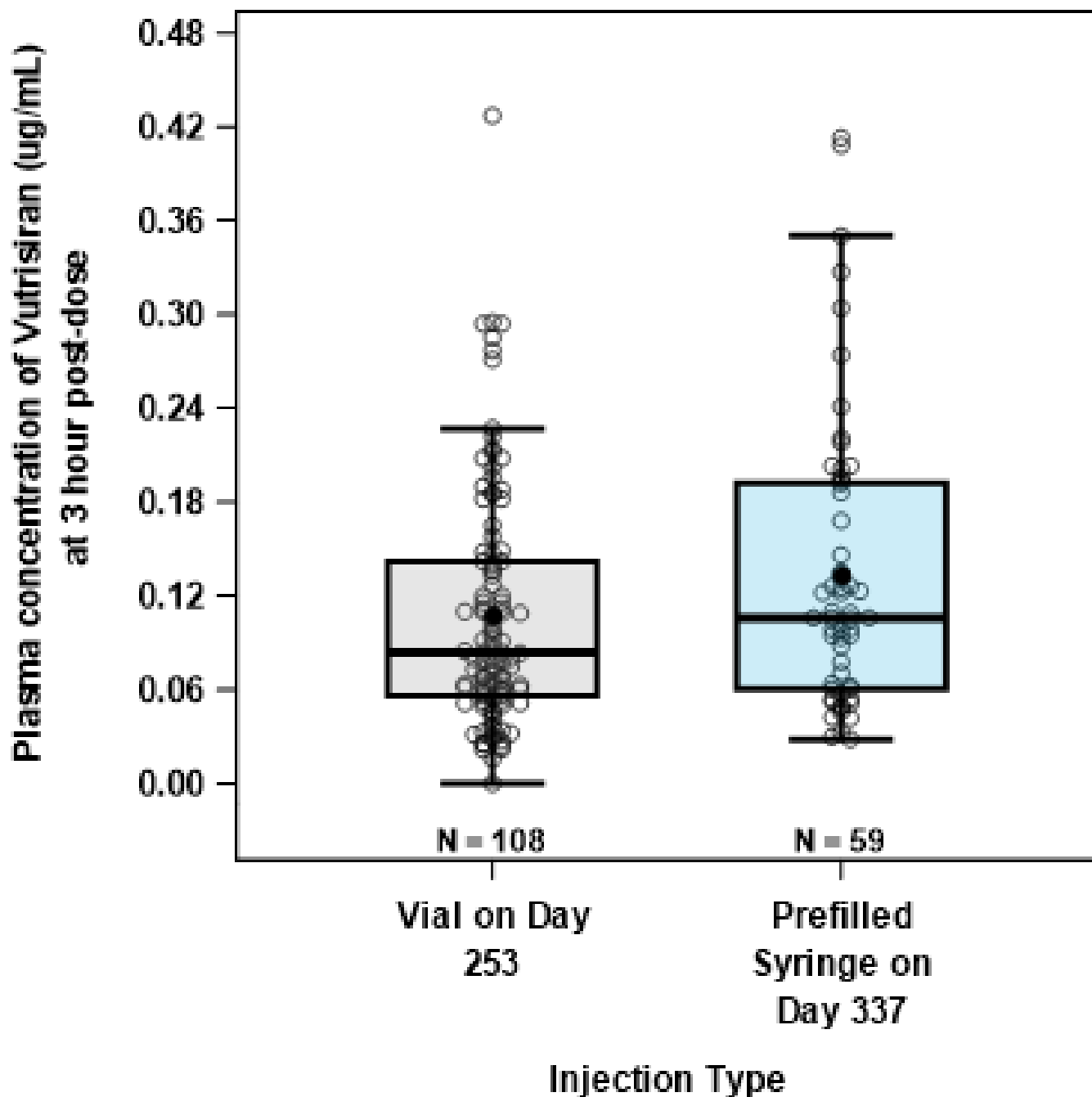


Figure 10: Comparison of Vutrisiran Plasma Concentration at 3 Hours Post dose: Dosing from Vial with Syringe on Day 253 Versus from PFS-S on Day 337. Source Applicant response to information request received 23 September 2021



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8.5.2. Cardiac Treatment Emergent Adverse Events

Evaluation of the cardiac disorders system organ class by adverse event preferred terms found a higher rate in the external placebo group (36.4%) than in the vutrisiran group (27%). However, as presented in Section 8.4.5, an analysis of treatment emergent adverse events in the externally controlled HELIOS-A study conducted using custom FDA groupings of preferred terms found an imbalance of cardiac AE groupings (acute coronary syndrome: 6.6% vutrisiran vs. 1.3% placebo; myocardial infarction FDA B: 7.4% vutrisiran vs. 3.9% placebo; myocardial ischemia FDA B: 7.4% vutrisiran vs. 3.9% placebo) that favors the external placebo group, although the vutrisiran rates were similar to those observed in the concurrent active patisiran comparator (acute coronary syndrome: 6.6% vutrisiran vs. 4.8% patisiran; myocardial infarction FDA B: 7.4% vutrisiran vs. 4.8% patisiran; myocardial ischemia FDA B: 7.4% vutrisiran vs. 4.8% patisiran).

The following table shows the preferred terms included in the FDA Acute coronary syndrome/Myocardial ischemia mapping that were positive in the vutrisiran group.

Table 38: Preferred Terms included in the FDA Acute Coronary Syndrome/Myocardial Ischemia mapping

1	Terms in FDA ACS/MI mapping	Vutrisiran	Patisiran	APOLLO (Placebo)
2		(N = 122)	(N = 42)	(N = 77)
3	ACUTE MYOCARDIAL INFARCTION	1 (0.8%)	0 (0.0%)	0 (0.0%)
4	ANGINA PECTORIS	1 (0.8%)	0 (0.0%)	0 (0.0%)
5	ARTERIOSCLEROSIS CORONARY ARTERY	0	0	0
6	CARDIAC ARREST	0 (0.0%)	0 (0.0%)	1 (1.3%)
7	CORONARY ARTERY DISEASE	0 (0.0%)	1 (2.4%)	0 (0.0%)
8	MYOCARDIAL ISCHAEMIA	1 (0.8%)	1 (2.4%)	0 (0.0%)
9	MYOCARDIAL NECROSIS MARKER INCREASED	0	0	0
10	SUDDEN CARDIAC DEATH	0	0	0
11	TROPONIN I INCREASED	1 (0.8%)	0 (0.0%)	0 (0.0%)
12	TROPONIN T INCREASED	5 (4.1%)	0 (0.0%)	0 (0.0%)
13	VENTRICULAR FIBRILLATION	0	0	0
14	VENTRICULAR TACHYCARDIA	3 (2.5%)	0 (0.0%)	2 (2.6%)

As seen in the above table, the difference in cardiac AEs in the custom FDA grouping is being driven by elevated troponin levels in 6 vutrisiran subjects compared to zero external placebo subjects. However, Troponin T was not assessed in the external placebo group so no comparison can be made. Assessment of individual subjects found that there were three vutrisiran group subjects with acute myocardial infarction, angina pectoris, and myocardial ischemia, respectively.

The narratives of five vutrisiran group subjects with cardiac SAEs were assessed and are summarized in the following table.

Table 39: Narrative Summaries of HELIOS-A study subjects with Serious Cardiac Adverse Events

Subject Number	Serious Adverse Event(s)	Relevant Current and Historical Medical Conditions
(b) (6)	dizziness	Autonomic nervous system imbalance, hypotension, congestive heart failure, congestive cardiomyopathy
	acute myocardial infarction, hypotension, pyelonephritis, and syncope	Cerebral small vessel ischemic disease, cardiac amyloidosis, Addison's disease
	cardiac failure and pneumonia, and a fatal SAE of iliac artery occlusion.	Prior deep vein thrombosis, stroke, atrial fibrillation, incomplete left bundle branch block, intraventricular conduction delay, cardiac amyloidosis, cardiac failure. Concomitant medications included Treated with apixaban. Cause of death: "cardiovascular death; presumed cardiovascular death"
	Orthostatic hypotension	autonomic neuropathy and neuropathy peripheral, orthostatic hypotension
	Myocardial ischemia	Hypercholesteremia, tobacco use, hepatic cirrhosis, pulmonary hypertension, first degree AV heart block, aortic valve stenosis, ventricular extrasystoles, coronary artery stenosis, coronary arterial stent, percutaneous coronary intervention, severely constricted right coronary artery

As seen in the above table summarizing subject narratives with cardiac SAEs, the subjects had multiple pre-existing cardiac medical conditions that are likely related to the experienced cardiac serious adverse events.

Overall, the data do not indicate a greater risk of cardiac adverse events in the vutrisiran group.

8.5.3. Ocular Effects of Vitamin A reduction

An assessment of ocular adverse events was conducted because TTR reduction in subjects treated with vutrisiran is associated with concomitant reduction in circulating serum levels of Retinol binding protein and vitamin A. Abnormal visual adaptation to darkness (night blindness) is a symptom of vitamin A deficiency. Note that subjects in the HELIOS-A study received recommended daily allowance vitamin A supplementation.

Adverse events with preferred terms in the system order class for eye disorders occurred in 27% of vutrisiran group subjects and 26% of the external placebo group. Night blindness was reported in 1 (0.8%) subject in the vutrisiran group and in 1 (1.3%) subject in the external placebo group. The vutrisiran group subject with night blindness (b) (6) had a medical history of optic ischemic neuropathy that was ongoing at the start of the study. The ophthalmologic examination conducted after the AE of night blindness did not report findings suggestive of vitamin A deficiency.

Overall, there were no ocular vitamin A related abnormalities identified in the HELIOS-A study or open-label extension study.

8.6. Safety Analyses by Demographic Subgroups

8.6.1. Age: Adverse Events Analysis

The HELIOS-A study was conducted with subjects with hATTR amyloidosis over the age of 18 years. Among subjects under the age of 65 years, the treatment emergent adverse events that occurred in at least 5% of the vutrisiran group and occurred at least 5% more frequently than in the placebo group were arthralgia, troponin T increased, thermal burn, Covid-19, dry eye, dyspnea, influenza-like illness, joint injury, and vitamin A decreased. Among subjects aged 65 years or older, the treatment emergent adverse events that occurred in at least 5% of the vutrisiran group and occurred at least 5% more frequently than in the placebo group were arthralgia, vitamin A decreased, dyspnea, eye pain, skin laceration, and pain in extremity.

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As seen in the following tables based on the submission, there were no clinically significant differences in the proportions of subjects with AEs or with SAEs between the vutrisiran and placebo groups as a function of age subgroup for the HELIOS-A study. The vutrisiran group had a lower proportion of SAEs than the placebo or patisiran groups.

Table 40: Treatment-Emergent Adverse Events by Age

Age <65 years	Placebo	Vutrisiran	Patisiran
At least 1 AE	98%	92%	94%

Age >=65 years	Placebo	Vutrisiran	Patisiran
At least 1 AE	97%	96%	100%

Table 41: Treatment-Emergent Serious Adverse Events by Age

Age <65 years	Placebo	Vutrisiran	Patisiran
At least 1 SAE	32%	12%	36%

Age >=65 years	Placebo	Vutrisiran	Patisiran
At least 1 SAE	52%	26%	55%

8.6.2. Sex: Adverse Events Analysis

As seen in the following tables based on the submission, there were no clinically significant differences in the proportions of subjects with AEs or with SAEs between the vutrisiran and placebo groups as a function of sex subgroup for the HELIOS-A study.

Table 42: Treatment-Emergent Adverse Events by Sex

Sex: Male	Placebo	Vutrisiran	Patisiran
At least 1 AE	97%	92%	93%

Sex: Female	Placebo	Vutrisiran	Patisiran
At least 1 AE	100%	95%	100%

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Table 43: Treatment-Emergent Serious Adverse Events by Sex

Sex: Male	Placebo	Vutrisiran	Patisiran
At least 1 SAE	41%	18%	33%

Sex: Female	Placebo	Vutrisiran	Patisiran
At least 1 SAE	37%	16%	53%

8.6.3. Race: Adverse Events Analysis

As seen in the following tables based on the submission, there were no clinically significant differences in the proportions of subjects with AEs or with SAEs between the vutrisiran and placebo groups as a function of race subgroup for the HELIOS-A study.

Table 44: Treatment-Emergent Adverse Events by Race

Race: White	Placebo	Vutrisiran	Patisiran
At least 1 AE	98%	93%	93%

Race: All other races	Placebo	Vutrisiran	Patisiran
At least 1 AE	96%	94%	100%

Table 45: Treatment-Emergent Serious Adverse Events by Race

Race: White	Placebo	Vutrisiran	Patisiran
At least 1 SAE	40%	19%	41%

Race: All other races	Placebo	Vutrisiran	Patisiran
At least 1 SAE	41%	14%	39%

8.7. Specific Safety Studies/Clinical Trials

No specific clinical safety studies were performed in the vutrisiran development program.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There was a higher percentage of malignancies/tumors in the external placebo group (4 subjects, 5.2%) than in the vutrisiran group (5 subjects, 4.1%). The narratives of the five vutrisiran group subjects with malignancies were reviewed. They showed no pattern and were consistent with the nature and types of malignancies reported in the general population in this age group. There does not appear to be any increased risk of cancer associated with vutrisiran treatment.

8.8.2. Human Reproduction and Pregnancy

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

As of the 09 April 2021 data cutoff date, there have been no reported pregnancies in the vutrisiran clinical development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

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

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No instances of accidental or intentional overdose of vutrisiran have been reported during the clinical development program.

A pre-NDA teleconference was held on 3/26/2021 that discussed the format and content of the future NDA submission. The Agency agreed that there was no need to include an assessment of the abuse potential of vutrisiran because the drug does not affect the CNS, it is not chemically or pharmacologically similar to other drugs with known abuse potential, and it does not produce psychoactive effects such as sedation, euphoria, and mood changes.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Vutrisiran has not been marketed in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

I expect the patterns in adverse reactions in the postmarketing data will be similar to the patterns observed in the pre-marketing data.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

The overall conclusion of this safety review is that the safety profile of vutrisiran is acceptable given the evidence of efficacy in the treatment of hATTR-PN and the poor prognosis for hATTR amyloidosis patients. The most commonly observed ($\geq 5\%$ and at least 2% more frequently in the vutrisiran group than in the external placebo group) adverse events associated with the use of vutrisiran in the 18-month external placebo-controlled study were arthralgia, vitamin A decreased, and dyspnea. Vutrisiran reduces vitamin A levels in the body. All subjects received the recommended daily amount of vitamin A as a supplement and no ocular AEs related to low vitamin A levels were observed.

Consistent with the natural history of hATTR amyloidosis, the adverse events that caused the most subjects to stop taking vutrisiran across all clinical studies were cardiac failure or cardiac death (3 subjects, 2.5%). Review of cardiac adverse events generally found no clinically significant difference in cardiac AEs and SAEs between the external placebo and vutrisiran cardiac subpopulations or total study populations.

Mortality was numerically lower in the vutrisiran group (2.5%) than in the external placebo group (8%) or concurrent comparator patisiran group (7%). However, the Phase 3 HELIOS-A clinical study was not designed to statistically evaluate an effect on survival and no conclusion regarding a potential long-term survival effect can be made.

This reviewer concludes that the safety profile of vutrisiran is acceptable, but that the label should include under Warnings and Precautions a description of the need for vitamin A supplementation to avoid possible vitamin A deficiency.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

This reviewer recommends describing the following issue in the Warnings and Precautions section of labeling: reduced serum vitamin A levels with recommended supplementation.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

None recommended.

12. Postmarketing Requirements and Commitments

If an approval action is taken, the Agency plans an FDAAA postmarketing requirement to evaluate pregnancy outcomes. The postmarketing requirement will be to conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Amvuttra (vutrisiran) 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.

13. Appendices

13.1. References

Oh, T., Lee, J., Do, S., Jeon, Y., Kim, J., Kim, K., Song, I. (2018)
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therapeutic trials.
J Neurol Sci, 44(1-2): 121-128.

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The development and validation of the Norfolk QOL-DN, a new measure of patients' perception
of the effects of diabetes and diabetic neuropathy.
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Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial
amyloid polyneuropathy.
J Peripher Nerv Syst, 19(2): 104-114.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): HELIOS-A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>9</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		

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Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>9</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Study: <u>0</u> Sponsor of covered study: <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason: 0 Investigators, <i>Not applicable</i>	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Protocol Amendments

Table 46: Listing of Major Protocol Amendments for the HELIOS-A Study. Source: HELIOS-A CSR, table 3

Amendment(s)	Primary Purpose(s)
Amendment 0.1 (France), 25 Jan 2019	To list additional requirements for study termination, in line with ICH E6 (R2) Guideline, upon request (dated 15 January 2019) from the Competent Authority in France (ANSM)
Amendment 0.2 (Japan), 14 Mar 2019	To modify female and male contraceptive language to reflect local regulations in Japan, upon request (dated 07 March 2019) from the PMDA
Amendment 0.3 (Argentina), 19 Jun 2019	To add testing for HIV at Screening in order to rule out evidence of HIV that is Exclusion Criterion No. 9 in the protocol, and to clarify that pregnancy testing in Argentina must be performed at least monthly or more frequently to coincide with the planned study visits throughout the study duration, upon request (dated 07 June 2019) from the ANMAT.
Amendment 1 (global), 10 Oct 2019 Amendment 1 (France), 10 Oct 2019 Amendment 1.1 (Japan), 10 Oct 2019 Amendment 1.2 (Argentina), 10 Oct 2019	To introduce the use of a vutrisiran in single-use, prefilled syringes after completion of a patient's Month 9 efficacy assessments. For further details, refer to ALN-TTRSC02-002 Protocol Amendment 1 Summary of Changes (Appendix 16.1.1)
Amendment 2 (global), 06 May 2020 Amendment 1.3 (France), 5 May 2020 Amendment 2.1 (Japan), 06 May 2020 Amendment 2.2 (Argentina), 06 May 2020	To incorporate changes related to USMs that were communicated to Investigators in a Dear Investigator Letter dated 31 March 2020 to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. For details on these changes, see Section 9.8.1.2 . In addition, the amendment incorporated removal of the secondary endpoint all-cause hospitalization and death events over 18 months in patients with cardiac involvement (except for Amendment 1.3). This change was implemented based on review of baseline data which suggested that a minority of patients were likely to meet pre-specified criteria for the cardiac subpopulation thus limiting the value of this analysis.

Amendment(s)	Primary Purpose(s)
	For further details, refer to ALN-TTRSC02-002 Protocol Amendment 2 Summary of Changes (Appendix 16.1.1)
Amendment 2 (France), 06 May 2020	To remove the secondary endpoint all-cause hospitalization and death events over 18 months in patients with cardiac involvement, as described above.
Amendment 3 (global), 17 Jul 2020 Amendment 3.1 (Japan), 17 Jul 2020 Amendment 3.2 (Argentina), 17 Jul 2020	To mitigate any potential impact from the COVID-19 pandemic on key efficacy assessments. Changes to endpoints at Month 9 introduced to mitigate the potential risk of these external factors confounding interpretation of the true treatment effect of vutrisiran included: • Co-primary endpoint of change from baseline in Norfolk QoL-DN total score at Month 9 was changed to the first key secondary endpoint in the hierarchical testing order. Modified NIS+7 is the sole primary endpoint at Month 9. • The secondary endpoints of mBMI and R-ODS at Month 9 were changed from secondary to exploratory endpoints. • Removed change at Month 18 compared to baseline in mNIS+7 and Norfolk QoL-DN total score in vutrisiran-treated patients. • Removed the secondary endpoint of composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo group of the APOLLO study; removed adjudication of the reasons for hospitalizations. This amendment also included analysis of efficacy endpoints at Month 18 as secondary endpoints in the statistical hierarchy to allow more complete characterization of the treatment effect of vutrisiran. The following efficacy endpoints were added to the testing hierarchy at Month 18 for change from baseline parameters compared to the placebo group (APOLLO): mNIS+7, Norfolk QoL-DN total score, timed 10-MWT, mBMI, and R-ODS. For further details, refer to ALN-TTRSC02-002 Protocol Amendment 3 Summary of Changes (Appendix 16.1.1)

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/s/

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06/13/2022 11:13:42 AM

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