CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215515Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	June 13, 2022
From	Laura Jawidzik, MD Teresa Buracchio, MD Billy Dunn, MD
Subject	Summary Memorandum
NDA/BLA # and Supplement#	NDA 215515
Applicant	Alnylam Pharmaceuticals, Inc.
Date of Submission	April 14, 2021
PDUFA Goal Date	July 14, 2022
Name	Amvuttra (vutrisiran)
Dosage Form(s)/Strength	25 mg administered subcutaneously every 3 months
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
Recommended Dosing Regimen(s) (if applicable)	25 mg administered subcutaneously every 3 months

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Vutrisiran is a small interfering ribonucleic acid (siRNA)-GalNAc conjugate targeting transthyretin (TTR) messenger RNA (mRNA). Vutrisiran causes degradation of mutant and wild-type TTR mRNA through RNA interference, resulting in reduction of serum TTR protein and TTR protein deposition. The GalNAc moiety enhances uptake by the liver. The dose of vutrisiran proposed for marketing is 25 mg administered subcutaneously (SC) every three months. At this dose, vutrisiran has been demonstrated to reduce TTR levels by an average of 85%.

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is an autosomal dominant disorder caused by mutations in the TTR gene, located on chromosome 18q. Wild-type TTR protein is primarily synthesized in the liver and exists in a tetrameric state transporting thyroxine (T4) and vitamin A (retinol) in association with retinol binding protein (RBP). More than 120 different point mutations in the TTR gene have been identified that lead to hATTR amyloidosis. A replacement of valine by methionine at position 30 (V30M) is the most common mutation causing hATTR amyloidosis. These mutations result in protein misfolding, aggregation, and deposition in the peripheral and central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. Symptom onset typically occurs between 20 and 70 years of age, with death occurring within 5 to 12 years of onset, most commonly from cardiac dysfunction, infection, or cachexia. Many patients experience a prominent neuropathy defined by the presence of peripheral neuropathy and autonomic dysfunction [referred to as hATTR-polyneuropathy (hATTR-PN)]. The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons, with the highest rates occurring in certain endemic countries such as Portugal and Sweden.

There are two FDA-approved treatments for the hATTR-PN: patisiran and inotersen. Patisiran is an siRNA that degrades mutant and wild-type TTR. It is administered intravenously every three weeks. Inotersen is an antisense oligonucleotide administered subcutaneously once weekly. Inotersen has a boxed warning for life-threatening thrombocytopenia and glomerulonephritis.

The Applicant has provided data from a single adequate and well-controlled clinical trial (HELIOS-A) as the primary basis of support of the effectiveness of vutrisiran for the treatment of hATTR-PN. HELIOS-A is an ongoing, externally-controlled trial that utilized the placebo arm from the APOLLO study as the comparator. The APOLLO study served as the primary evidence of effectiveness of patisiran for the treatment of hATTR-PN. The use of the APOLLO placebo arm as an external control was a design feature that was discussed at the end-of-phase 2 (EOP2) meeting (August 10, 2018). The Division was open to the use of the external control, with the expectation that there would need to be a large

magnitude of effect with the use of vutrisiran, comparable to the treatment effects observed with patisiran. The Division recommended inclusion of an active control as well to assess the relative efficacy and safety of vutrisiran to approved therapy. The Applicant agreed and included patisiran-treated subjects in the HELIOS-A study.

HELIOS-A is an 18-month, randomized, open-label, study of vutrisiran in adult patients with hATTR-PN using patisiran as an active control. Subjects were given vutrisiran 25 mg SC every three months or 0.3 mg/kg dose of patisiran administered intravenously (IV). An objective evaluation of polyneuropathy also used in the APOLLO study (consisting of a clinical neurological examination and tests of nerve conduction, sensation, and postural blood pressure) showed that vutrisiran-treated subjects experienced a modest degree of numerical improvement during the first 9 months of the study. Subjects from the APOLLO placebo group experienced an expected rate of worsening during the first 9 months of the APOLLO trial. The clinical meaningfulness of these results was confirmed by a similar pattern of findings on a patient-reported subjective assessment of the clinical impact of polyneuropathy. This pattern of stability and even improvement in the signs and symptoms of patients' polyneuropathy is inconsistent with the natural history of the disease. The application meets the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence. HELIOS-A is an adequate and well-controlled clinical investigation and is supported 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).

The safety database for vutrisiran was adequate for the intended population and proposed dosing regimen. Identified risks can be mitigated through product labeling. The overall benefit-risk profile is favorable as described in the benefit-risk framework below. Wild-type TTR reduction leads to reductions in vitamin A levels. Subjects in the vutrisiran development program were instructed to supplement with the recommended daily allowance of vitamin A, and no vitamin A-related ocular toxicities were observed. Vitamin A supplementation will be recommended in labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene. Wild-type TTR protein is primarily synthesized in the liver and exists in a tetrameric state transporting thyroxine (T4) and vitamin A (retinol) in association with retinol binding protein (RBP). More than 120 different point mutations in the TTR gene have been identified that lead to hATTR amyloidosis. A replacement of valine by methionine at position 30 (V30M) is the most common mutation causing hATTR amyloidosis. These	Hereditary ATTR amyloidosis is a serious disease, leading to significant disability and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mutations result in protein misfolding, aggregation, and deposition in the peripheral and central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. Symptom onset typically occurs between 20 and 70 years of age, with death occurring within 5 to 12 years of onset, most commonly because of cardiac dysfunction, infection, or cachexia. Many patients experience a prominent neuropathy defined by the presence of peripheral neuropathy and autonomic dysfunction. • The global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons, with the highest rates occurring in certain endemic countries such as Portugal and Sweden.	
Current Treatment Options	• Patisiran and inotersen are approved for treatment of hATTR. • Inotersen is available only through a restricted distribution program because of the risks of thrombocytopenia and glomerulonephritis. • Patisiran is given by intravenous infusion every 3 weeks and carries a warning for infusion-related reactions. • 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.	There remains a significant unmet clinical need for effective treatments for hATTR because not all patients are able to receive or tolerate the currently available clinical treatments.
Benefit	• Vutrisiran is a small interfering ribonucleic acid (siRNA) that directs sequence-specific degradation of TTR messenger RNA (mRNA) in the liver resulting in a reduction in both the wild-type and mutant TTR protein. • The dose of vutrisiran proposed for marketing has been demonstrated to reduce TTR levels by an average of 85% at steady state. • The Applicant has provided data from HELIOS-A; an 18-month, open-label, externally-controlled trial in adult patients with hATTR-PN. Placebo-treated patients from the APOLLO study of patisiran in hATTR served as a comparator. This trial evaluated a 25 mg dose of vutrisiran administered SC every three months. The trial's primary efficacy analysis demonstrated a highly statistically significant treatment effect ($p<0.0001$) on the modified Neuropathy Impairment Scale +7 (mNIS+7); an objective evaluation of the signs and	HELIOS-A provided reliable and statistically persuasive evidence that vustirian can help hATTR subjects achieve a clinically meaningful improvement in symptoms of their disease. Confirmatory evidence is provided by mechanistic and scientific knowledge about the effectiveness of other drugs in the same class (i.e., patisiran for the treatment of hATTR).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	symptoms of polyneuropathy. Mean mNIS+7 scores in vutrisiran-treated patients demonstrated a numerical improvement during the trial. At month 9, vutrisiran-treated patients improved by 2 points while placebo-treated patients declined by 15 points. • A similar pattern of treatment effects was observed on the Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) scale, which supports the clinical meaningfulness of the objective mNIS+7 scores. At month 9, vutrisiran-treated patients improved by 3 points while placebo-treated patients declined by 13 points from baseline. This represents a stastistically significant improvement and clinically meaningful improvement in quality of life for vutrisiran-treated subjects as compared to placebo (LS mean difference between groups of 16.2 points, p <0.0001).	
Risk and Risk Management	• 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 to vutrisiran. • The most common adverse reactions reported in at least 5% of subjects treatment with vutrisiran were arthralgias, dyspnea, and decreased vitamin A. Most subjects in the trial developed low vitamin A despite adequate supplementation. However, only a subset of them were reported as adverse reactions • Wild-type TTR reduction leads to reductions in vitamin A levels. Patients in the vutrisiran development program were instructed to supplement with the recommended daily allowance of vitamin A, and no vitamin A-related ocular toxicities were observed. • Two cases of atrioventricular block, including one case of complete AV block, occurred in vutrisiran-treated patients. This will be noted in product labeling similarly to labeling for patisiran.	The safety database was adequate in terms of size and duration given that hATTR is a rare disease. The risks associated with the treatment of vutrisiran are acceptable for the indicated population. Risk will be managed through product labeling. Warnings and precautions will described the risk of vitamin A deficiency and the need for supplementation. Because the risk of adverse outcomes in pregnancy has not been characterized, and because vutrisiran will be used in women of childbearing potential, a pregnancy outcomes study will be a postmarketing requirement.

2. Background

This review discusses the data submitted by Alnylam Pharmaceuticals in support of a new drug application (NDA) for vutrisiran for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN). Vutrisiran is a new molecular entity (NME) that has not been approved for any indication and has not been the subject of a prior marketing application.

Hereditary ATTR is a life-threatening autosomal dominant disorder caused by mutations in the TTR gene. Wild-type TTR is primarily synthesized in the liver and exists in a tetramer. Mutations in the TTR gene lead to midfolding of the TTR protein, which results in protein aggregation and amyloid deposition in the peripheral nervous system, central nervous system, heart, kidneys, eyes, bone, and gastrointestinal tract. The global prevalence of hATTR-PN is estimated to be betwem 5,000 and 10,000 individuals, with the highest prevalence rates occurring certain countries such as Portugal and Sweden. Symptom onset typically begins between age 20 and 70 years of age. Death generally occurs within 5 to 12 years after onset of symptoms, often due to cardiac dysfunction, infection, or cachexia.

Vutrisiran is a small interfering ribonucleic acid (siRNA)-GalNAc conjugate targeting TTR messenger RNA (mRNA). Vutrisiran causes degradation of variant and wild-type TTR mRNA through RNA interference. This results in reduction of serum TTR protein and TTR protein deposition. The GalNAc moiety enhances uptake by the liver. Once taken up into hepatocytes, the siRNA specifically targets the TTR mRNA for destruction via the RNA-induced silencing complex pathway, resulting in reduced production of the TTR protein.

There are two other FDA-approved treatments for the polyneuropathy of hATTR in adults, both of which reduce TTR protein: patisiran and inotersen. Patisiran (marketed as Onpattro) and inotersen (marketed as Tegsedi) were both approved in 2018. Patisiran is also an siRNA that targets TTR mRNA and causes degradation of both variant and wild-type TTR. Patisiran is administered intravenously every three weeks. Inotersen is an antisense oligonucleotide (ASO) that causes degradation of mutant and wild-type TTR by binding to the TTR mRNA. Inotersen is administered subcutaneously once weekly. Inotersen is available only through a restricted distribution program called the TEGSEDI REMS Program because of the risks of thrombocytopenia and glomerulonephritis.

The Applicant has provided data from a single adequate and well-controlled clinical trial (HELIOS-A) as the primary basis of support of the effectiveness of vutrisiran for the treatment of hATTR-PN. HELIOS-A was an externally controlled trial that utilized the placebo arm from the APOLLO study as the comparator. The APOLLO study served as the primary evidence of effectiveness of patisiran for the treatment of hATTR-PN. The use of the APOLLO placebo arm as an external control was a design feature that was discussed at the end-of-phase 2 (EOP2) meeting (August 10, 2018). The Division was open to the use of the external control, with the expectation that there would need to be a large magnitude of effect with the use of vutrisiran, comparable to the treatment effects observed with patisiran. The

Division recommended inclusion of an active control as well. The Applicant agreed and included patisiran-treated subjects in the HELIOS-A study.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team recommends approval. From a quality perspective, the review team finds that the application provides for adequate assurance that the product will be suitable for use by the intended patient population. From a quality perspective, the application meets all applicable standards to support identity, strength, quality, and purity of the product.

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ integrated review lists the entire OPQ team that was involved with the review of this application. The quality review team included consultative device reviewers from the Center for Devices and Radiological Health (CDRH). Please refer to the integrated OPQ review for details of the product quality assessment.

Drug Substance
According to the OPQ review, the drug substance is produced with adequate quality for use in the intended patient population. No deficiencies were identified by the drug substance reviewers.

Drug Product
The drug product is a 50 mg/ml sterile solution of vutrisiran. The commercial container closure system is a prefilled syringe with a 1 mL glass barrel and rubber stopper plunger, filled with 0.5 mL of drug product. The prefilled syringe was used in clincal studies.

Stability data for the registration batches was provided up to 18 months, with 24 months of supportive data provided as well. However, only nine of months of long-term leachable stability data was provided. Extractable and leachable studies have demonstrated a low risk of leachables from the container closure system and the Applicant has committed to submitting additional data as it becomes available up to 36 months. Given the available data, the Applicant's commitment to continue leachable studies, and the low risk of leachables, OPQ agreed to an expiration dating period of 24 months for product stored at 2°C to 30°C.

Manufacturing
OPQ determined the proposed commercial manufacturing process and inprocess controls are adequate to ensure product quality and patient safety. All facilities that will be used for commercial manufacture and testing of vutrisiran were evaluated and deemed acceptable.

It was noted that the target fill volume for the syringe is (b) (4) mL with limits of (b) (4) to (b) (4) mL. The clinical team was asked to evaluate the potential impact of this overfill on safety and found no potential impact on safety.

Facilities
On March 25, 2022, the Applicant submitted a CMC-related amendment to the application. The amendment removed the (b) (4) secondary packaging site from the application and added (b) (4) as the secondary packaging and labeling site to the application. This submission was considered a major amenedment which extended the review time by three months. The original PDUFA date of April 14, 2022, was amended to July 14, 2022. The new facility was found to be adequate and no outstanding facilities issues were identifed.

Consult to CDRH
The device aspects of the product including syringe and needle shield were reviewed by Porshe Bennett (CDRH). Her review recommends approval from a device perspective. The CDRH review noted variability in the deliverable volume device performance but did not determine this finding to be an approvability issue and deferred the the acceptability of the variability to CDER. OPQ reviewed the results provided for deliverable volume and found that it was unlikely that any variability detected would adversely impact product quality.

There were no outstanding issues identified in the integrated OPQ review.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for the application was Dr. David Hawver and Dr. Lois Freed performed the secondary review. The Division of Pharmacology-Toxicology for Neuroscience (DPT-N) concludes that the nonclinical data support approval of vutrisiran.

The following are the key findings from the nonclinical review:

- Because of species differences in the targeted TTR mRNA sequence, vutrisiran is pharmacologically active in human and cynomolgus monkey but not in rodent or rabbit.
- Because TTR acts as a carrier for thyroxine and vitamin A in the circulation, serum levels of these molecules were substantially reduced in monkeys administered vutrisiran as expected. These changes were not associated with adverse effects on the thyroid, pituitary, eye, ophthalmic examinations, or electroretinography evaluations that included visual evoked potentials.
- In the pivotal general toxicology studies of SC vutrisiran in rat (13- and 26-week) and cynomolgus monkey (13- and 40-week), non-adverse findings were observed in the liver (both species), kidneys (rat), and lymph nodes (monkey). Plasma exposures (AUC) at the NOAELs were ~600 and ~4400 times, respectively, those expected in humans at the proposed clinical dose of 25 mg once every 3 months, after adjusting for the 3-fold difference in dosing frequency.
- Administraton of vutrisiran to rats and cynomolgus monkeys results in excretion primarily in the urine rather than feces.
- In vitro drug-drug interaction studies demonstrated that vutrisiran was neither a substrate nor an inhibitor of human P450 CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.
- A standard battery of reproductive and development studies of SC vutrisiran were conducted in rat and rabbit. Adverse effects were limited to the rat embryofetal

development study, in which administration of vutrisiran resulted in reductions in maternal and fetal body weights, and vacuolation/ degeneration and individual cell necrosis in liver in dams at the mid-dose and high-dose (HD); and increases in premature delivery, early and late resorptions, post-implantation losses, and the number of dead fetuses at the HD. The low-dose was the NOAEL for maternal and developmental toxicity.

- There are no novel excipients in the drug product. No impurities or degradants of concern have been identified.
- Vutrisiran was negative in a standard battery of genetic toxicology studies (in vitro bacterial reverse mutation and human lymphocyte chromosome aberration, and in vivo rat bone marrow micronucleus assays) that were adequately conducted.
- Per prior agreement, 2-year carcinogenicity studies of vutrisiran in rat and mouse are to be conducted as postmarketing requirements.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was conducted by Yifei Zhang, Ph.D. (primary reviewer), Vishnu Sharma, Ph.D., Hobart Rogers, Pharm.D., Ph.D., Atul Bhattaram, Ph.D., Christian Grimstein, Ph.D., and Bilal AbuAsal, Ph.D. (team lead). The signatory for the OCP review was Mehul Mehta, Ph.D. OCP recommends approval of this application.

Table 1 summarizes the conclusion of the OCP review with respect to the pharmacologic and clinical pharmacokinetic properties of vutrisiran.

Table 1: Summary of OCP Findings

Mechanism of Action	Vutrisiran is a double-stranded siRNA-GalNAc conjugate that causes degradation of variant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.
General pharmacokinetics (PK)	Following a single subcutaneous administration, vutrisiran Cmax increased proportionally with dose while AUC was slightly more than dose proportional over the dosage range of 5 to 300 mg (0.2 to 12 times of the recommended dosage). No accumulation of vutrisiran was observed in plasma after repeated every 3 months dosing.
Absorption	In humans, vutrisiran was rapidly absorbed from the SC injection site into plasma. The median (range) Tmax of vutrisiran is 4 (0.17, 12.0) hours.
Distribution	Human plasma binding of vutrisiran was concentration-dependent, ranging from 77.9% at 0.5 μg/mL to 19.0% at 50 μg/mL. Plasma protein binding of vutrisiran is expected to be approximately 80% at therapeutic dose, based on mean Cmax of approximately 0.1 μg/mL. Vutrisiran distributes primarily to the liver after subcutaneous administration. The population estimate for the apparent central compartment volume of distribution of vutrisiran in humans was 10.1 L.

Metabolism	Vutrisiran is metabolized by endo- and exo- nucleases to short nucleotide fragments of varying sizes within the liver. Metabolite profiling in human plasma samples indicates that there are no detectable circulating metabolites of vutrisiran.
Excretion	Following administration of vutrisiran at a single dose of 25 mg, the median (range) apparent clearance is 21.4 (19.8, 30) L/hour, and the median (range) elimination half-life of vutrisiran is 5.2 (2.2, 6.4) hours. The mean fraction of unchanged vutrisiran eliminated in urine was approximately 19.4 %, and the mean renal clearance ranged from 4.5 to 5.7 L/hour.
QT prolongation	The QT prolongation effect of vutrisiran was evaluated in Study ALNTTRSC02-001 using exposure-response analysis. At 9-times the recommended dose of 25 mg once every three months, vutrisiran does not prolong the QT interval to any clinically relevant extent. A dedicated thorough QT study has not been conducted with vutrisiran.
Drug-drug interactions	Transporter substrate/inhibition studies have not been performed with vutrisiran. In vitro DDI data from similar GalNAc-siRNA conjugate molecules suggest a low potential for DDI with transporters. In vitro studies suggest that vutrisiran is not a substrate of major CYP enzymes, and not an inhibitor of major CYP enzymes at concentrations up to 612 μM (10,000 μg/mL). Vutrisiran was not tested as an inducer of CYP enzymes in vitro. In vitro DDI data from similar GalNAc-siRNA conjugate molecules suggest a low potential of DDI to induce CYP enzymes.
Intrinsic/Extrinsic	No therapeutic individualization is required for vutrisiran based on intrinsic or extrinsic factors. No dedicated clinical studies were conducted in subjects with renal or hepatic impairment. According to population-pharmacokinetic (pop-PK) modeling, mild/moderate renal impairment or mild hepatic impairment did not significantly impact the PK of vutrisiran. Therefore, no dose adjustment is warranted in patients with mild/moderate renal impairment or mild hepatic impairment. The effect of severe renal impairment and moderate/severe hepatic impairment on the PK and PD of vutrisiran has not been studied.
Immunogenicity	A total of 4 (2.2%) vutrisiran-treated subjects developed treatment-emergent anti-drug antibodies (ADA). No clinically significant differences in the safety, efficacy, PK, or pharmacodynamic (PD) profiles of vutrisiran were observed in subjects who tested positive for ADA.
Food effects	Vutrisiran is administered by SC route; food is not expected to affect the exposure.

Source: Adapted from the integrated clinical pharmacology review

OCP agrees with the recommended dose of 25 mg SC administered every three months. With a single dose of vutrisiran maximum TTR reduction was reached at 6 weeks after administration and maintained for 90 days after the dose. At week 6, TTR reduction of 74.2%

was reached. The median steady-state trough reduction of TTR was 84.8%. TTR is a carrier of vitamin A. Vutrisiran showed a dose-dependent reduction in serum vitamin A levels in parallel with TTR reduction.

The vial with syringe presentation was used in the Phase 1 clinical study and pivotal efficacy study. The "to-be-marketed" presentation (pre-filled syringe) was introduced into the Phase 3 trial to replace the "vial with syringe" after the month 9 efficacy assessment. Per the review, bridging between the vial and pre-filled syringe was established by pop-PK and similar median TTR percent reductions from baseline observed with "vial with syringe" and the pre-filled syringe. The OCP team concluded that the injection site is not expected to significantly affect the PK/PD of vutrisiran.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Raine Paine was the clinical reviewer for this application. Dr. Tristan Massie was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader.

HELIOS-A (Study 002)

The primary evidence of effectiveness for this application is based on the interim analysis of clinical efficacy endpoints at month 9 from the HELIOS-A study. HELIOS-A is an ongoing, 18-month, Phase 3, randomized, open-label, externally-controlled study of vutrisiran using the placebo treatment arm from the APOLLO study as a comparator. The APOLLO study was an 18-month, Phase 3, placebo-controlled, randomized, double-blind study of patisiran that served as the primary evidence of effectiveness for the approval of patisiran for the treatment of hATTR-polyneuropathy (hATTR-PN) in adult patients. The HELIOS-A study also included an active control arm with patisiran. The patisiran arm was not powered for formal comparisons to vutrisiran on clinical outcomes but was intended to assess the relative efficacy and safety of vutrisiran to approved therapy.

HELIOS-A was a multinational study conducted at 57 study centers in 22 countries. In HELIOS-A, a total of 164 subjects were randomized 3:1 to receive either vutrisiran 25 mg SC every three months (Q3M), or patisiran 0.3mg/kg IV once every three weeks (Q3W). Randomization was stratified by TTR genotype (Val30Met vs. all others) and baseline neuropathy impairment score (NIS) score.

Subjects were required to be between 18 and 85 years of age (inclusive) and have a diagnosis of hATTR amyloidosis with a documented mutation in the TTR gene. Subjects were also required to have a baseline NIS of 5 to 130 where higher scores indicate more severe polyneuropathy. Baseline polyneuropathy disability (PND) score was required to be $\leq$ 3b which corresponds to walking with the aid of two sticks/crutches. Karnofsky performance

score was required to be ≥60% (lower scores indicate an increasing need for reliance on others for self-care).

The primary efficacy endpoint was the change from baseline to Month 9 in the modified neuropathy impairment score +7 (mNIS+7) as compared to the placebo group from the APOLLO study at Month 9, analyzed using general ANCOVA/multiple imputation methods of the mITT population. Scores on the mNIS range from 0 to 304, with higher scores indicating more severe neuropathy.

The mNIS+7 is an objective evaluation of small and large nerve fiber function and comprises the NIS and Modified +7 composite scores. In the version of the mNIS+7 used in the trial, the NIS objectively measures deficits in cranial nerve function, muscle strength, and reflexes, and the +7 assesses postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. The maximum possible score was 304 points, with higher scores representing a greater severity of disease. The mNIS+7 is capable of detecting small changes in some of its components that may not clearly be clinically meaningful. For this reason, the Division has required additional measures to support the clinical meaningfulness of the mNIS+7. The APOLLO study and HELIOS-A study also included the Norfolk Quality of Life-Diabetic Neuropathy scale (Norfolk QoL-DN). The Norfolk QoL-DN is a 35-item patient-reported measure that evaluates a subject's perception of impairment with respect to physical functioning, activities of daily living, neuropathy symptoms, small fiber neuropathy, and autonomic dysfunction. The maximum score on the scale 136 with higher scores respresenting worse quality of life. The analysis of the Norfolk-QoL-DN was performed using ANCOVA with multiple imputation methods.

The timed 10-meter walk test was a secondary endpoint. Modified body mass index change from baseline at month 9 was an exploratory endpoint.

Results

HELIOS-A enrolled 164 subjects (122 vutrisiran-treated, and 42 patisiran-treated). There were 77 placebo-treated subjects from APOLLO for the external comparator group. The mean age of the vutrisiran-treated group was 58 (range 26 to 85). Sixty-five percent were male, 71% were white, and 17% were Asian. Twenty-six percent were from North America.

Baseline characteristics between the vutrisran-treated group and the placebo group differed (Table 2). The vutisiran-treated subjects in HELIOS-A generally entered the trial with more favorable baseline parameters compared to placebo-treated subjects in APOLLO. The vutrisiran-treated group and the active comparator (patisiran-treated subjects) had more similar baseline disease characteristics. Per Dr. Massie's review, baseline differences between groups may make comparisons to the external control unreliable.

Table 2: Notable Baseline Values

Demographic	APOLLO Placebo (N=77)	HELIOS-A Vutrisiran (N=122)	HELIOS-A Patisiran (N=42)
Age (median) (min, max)	63.0 (34, 80)	60.0 (26, 85)	60.0 (31, 81)
Sex (% male)	75.3	64.8	64.3
Race (% Asian)	32.5	17.2	19.0
Genotype (%V30M)	52	44	
Baseline mNIS+7 (mean) (min, max)	74.6 (11.0, 153.5)	60.1 (2.5, 158.0)	57.7 (7.0, 137.6)
Baseline Norfolk (min, max)	55.5 (8, 111)	47.1 (-1, 105)	47.3 (1, 125)
10-Meter Walk Test	0.8 m/s	1.1 m/s	1.0 m/s
Modified Body Mass Index	989.9 kg/m2	1057.5 kg/m2	1029.1 kg/m2

Adapted from Study 002 CSR Table 6

Of the 122 subjects in the vutrisiran-treated arm, 3 (2.5%) discontinued study drug prior to month 9. Two discontinuations were due to the death of the subject and one discontinuation was a physician's decision to discontinue a subject who did not comply with study visits. Of the 42 subjects in the patisiran-treated arm, 2 (4.8%) discontinued study drug prior to month 9 both due to death of the subject.

The results of the primary efficacy analysis at month 9 for the mNIS+7 were statisitically significant in favor of vutrisiran. At month 9, the vutrisiran-treated subjects showed an improvement in neuropathy compared to baseline while the placebo group showed a worsening of neuropathy (Table). At month 9, mNIS+7 scores improved from baseline by a least squares (LS) mean of 2 points in the vutrisran-treated subjects, whereas the mNIS+7 score worsened by a LS mean of 15 points in the placebo-treated subjects (Table 3).

Table 3: Study 002 Primary Analysis: mNIS+7 Change from Baseline at Month 9 (mITT Population)

	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
Mean baseline value (SD)	74.6 (37.0)	60.6 (36.0)
Month 9 observed mean (SD)	91.0 (41.3)	57.5 (38.0)
Change from baseline Month 9 LS mean (SE)	**14.8 (2.0)**	**-2.2 (1.4)**
95% CI	(10.8, 18.7)	(-5.0, 0.6)
LS Mean Difference (SE) (vutrisiran-placebo)		**-17.0 (2.4)**
95% CI		-21.8, -12.2
p-value		p<0.0001

Source: statistical review table 4 and table 5

A descriptive analysis of the mNIS+7 demonstrated that the change from baseline in the active control arm (patisiran-treated subjects) was comparable to the vutrisiran arm.

The results of the analysis of the Norfolk-QoL-DN were also statistically significant in favor of vutrisiran (Table 4). At month 9, Norfolk-QoL-DN scores improved in vutrisiran-treated subjects compared to baseline (LS mean change of -3.3) while placebo-treated subjects worsened (LS mean change from baseline of 12.9). This represents a stastistically significant and clinically meaningful improvement in quality of life for vutrisiran-treated subjects as compared to placebo (LS mean difference between groups of 16.2 points, p <0.0001).

Table 4 Study 002 Norfolk-QoL-DN: Change from Baseline at Month 9 (mITT Population)

	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
Mean baseline value (SD)	55.5 (24.3)	47.1 (26.3)
Month 9 observed mean (SD)	66.2 (27.6)	41.8 (26.6)
Change from baseline 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		p<0.0001

Source: statistical review table 6 and table 7

A descriptive analysis of the Norfolk-QoL-DN demonstrated that the change from baseline in the active control arm (patisiran-treated subjects) was comparable to the vutrisiran arm.

The trial was not designed to show a statistical improvement in mNIS+7 or Norfolk-QoL-DN scores from baseline. However, both the vutrisiran- and patisiran-treated groups numerically improved from baseline to month 9 on both endpoints, which is inconsistent with the natural history of the disease. Placebo-treated subjects from the APOLLO study notably declined over the same length of treatment.

The trial also evaluated the timed 10-meter walk test (10-MWT) at month 9 in the testing hierarchy (Table). Modified body mass index (mBMI) at month 9 was an exploratory endpoint in HELIOS-A. The mBMI is the product of BMI and the concentration of serum albumin. Although the mBMI measured at 9 months was an exploratory endpoint, its inclusion in product labeling was considered and ultimately accepted because of its clinical meaningfulness and large effect size. The mBMI measured at 18 months is a prespecified, hierarchically-ordered endpoint in this trial. However, 18-month data was not available at the time of this review.

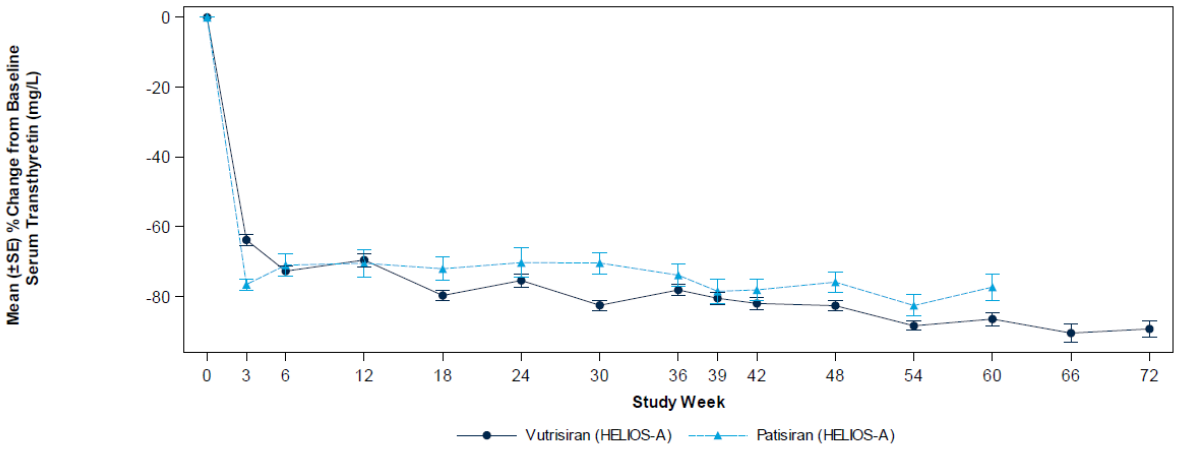
Table 5 Study 002: Additional Efficacy Endpoints

	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)
10-MWT (in m/s)		
Change from baseline Month 9 LS mean (SE)	-0.133 (0.025)	-0.001 (0.019)
LS Mean Difference (SE) (vutrisiran-placebo)		0.131 (0.031)
95% CI, p-value		(0.070, 0.193), <0.0001
mBMI		
Change from baseline Month 9 LS mean (SE)	-60.2 (10.1)	7.6 (7.9)
LS Mean Difference (SE) (vutrisiran-placebo)		67.8 (12.6)
95% CI, p-value*		(43.0, 92.6), p<0.0001

*nominal p-value
Source: clinical review table 9 and CSR table 24

The Applicant also evaluated the percent reduction in serum TTR in the vutrisiran group compared to the within-study patisrian group. A 10% noninferiority margin was prespecified by the Applicant, but no agreements were made with the Agency regarding the appropriateness of this choice of margin. Dr. Massie confirmed that TTR reduction was similar between vutrisiran and patisiran, and was non-inferior with respect to the prespecified 10% margin (Figure 1).

Figure 1 Study 002: Serum TTR Comparison between Vutrisiran and Patisiran



N evaluable															
Vutrisiran (HELIOS-A)	122	114	109	119	105	117	91	118	113	51	85	35	41	8	11
Patisiran (HELIOS-A)	42	42	41	41	37	38	39	34	37	22	27	14	12		

Abbreviations: mITT=modified intent-to-treat; SE=standard error; TTR=transthyretin.
Note: Month 9 and Month 18 nontrough TTR assessments presented at Weeks 39 and 81, respectively.
Source: statistical review figure 4

Dr. Massie concludes that the large effect patisiran displayed in the APOLLO trial compared to the APOLLO placebo group and the large effect of vutrisiran compared to the same external placebo group (and with similar treatment effect to active control patisiran in HELIOS-A) may alleviate the concerns about baseline differences. Additionally, the within-study comparison in the percentage reduction in serum TTR between patisiran and vutrisian improves the interpretability of the study.

Dr. Massie also concludes that there was a similar effect of vutrisiran on the mNIS+7 across subgroups including age, race, baseline NIS, genotype, and previous tetramer stabilizer use. There was a suggestion of a smaller effect in males than females, but still nominally significant compared to the APOLLO placebo group. There was significant variation between regions with North America having a larger treatment difference than the other two regions (i.e., Western Europe and "Rest of World").

Efficacy Conclusions
The efficacy results from HELIOS-A (Study 002) support the approval of vutrisiran for the treatment of polyneuropathy in adult patients with hATTR amyloidosis. The application meets the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence. HELIOS-A was an adequate and well-controlled clinical investigation that was robustly positive on clinically meaningful outcomes. Vutrisiran's treatment effect was statistically significant on the study's primary efficacy endpoint, and was supported by an effect on secondary endpoints that were controlled for type I error, including the Norfolk-QoL-DN and the 10-MWT. Given the size of the patient population, the study was large and multicenter. No single clinical site contributed disproportionately to the observed treatment effect. Results were generalizable across important demographic subgroups. Finally, 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)

8. Clinical/Safety

Dr. Paine conducted the safety review of this application with support from clinical data analyst, Dr. Rui Li.

Dr. Paine's review indicates that a total of 133 patients diagnosed with hATTR have been exposed to vutrisiran. In addition, 60 healthy volunteers were exposed in a Phase 1 single ascending dose study to doses up to 300 mg SC. At the initial filing, a total of 118 patients received 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. Dr. Paine concludes that the safety database is adequate and is consistent with what the Agency agreed to at the pre-NDA meeting.

The following are the main conclusions from Dr. Paine's safety review of the application:

There were three deaths (2.5%) in the vustrisiran group in the HELIOS-A study, three deaths (7%) in the patisiran active comparator group, and 6 (8%) in the APOLLO placebo group. The three deaths in the vutrisiran group were 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. None of the deaths had a clear relationship to the use of vutrisiran.

The incidence of serious adverse events (SAEs) was 24% in the vutrisiran arm, 43% in the active control (patisrian arm), and 40% in the APOLLO placebo group. Rates of cardiac SAEs in the vutrisiran arm were similar to those in the active control arm. Serious adverse reactions that occurred in at least 1% of subjects treated with vutrisiran were cardiac arrhythmia (2.5%) (including ventricular tachycardia, tachycardia paroxysmal, and atrial fibrillation, pyelonephritis (1.6%), and atrioventricular (AV) block (1.6%).

Table 1, reproduced from Dr. Paine's review, summarized the most common treatment-emergent adverse events that occurred in HELIOS-A.

Table 1 Adverse Reactions from HELIOS-A that Occurred in at Least 5% of Vutrisiran-Treated Subjects

	Vutrisiran N=122 n (%)
Arthralgia*	11
Dyspnea	7
Vitamin A decreased**	7

*comprises similar terms
**reflects only those reported as an adverse reaction
Source: clinical review

There were no clinically significant differences between vutrisiran-treated and placebo-treated subjects on hematological parameters, blood chemistry, renal function, liver function tests (LFTs), thyroid function, and coagulation parameters. There were no cases of Hy's Law.

Reductions in serum vitamin A levels were observed in vutrisiran-treated subjects as expected from the mechanism of action. Decreases in vitamin A are a known secondary pharmacodynamic effect from the reduction in serum TTR protein. Despite vitamin A supplementation, almost all subjects were noted to develop low vitamin A levels.

Per Dr. Paine's review, there were no clinically significant changes in mean values for vital signs including blood pressure, heart rate, respiratory rate, and temperature.

In the vutrisiran-treated subjects, the incidence of anti-drug antibodies (ADA) was 4.1%. No association between adverse events and ADAs were noted in Dr. Paine's review. However, the number of antibody-positive subjects was too small to draw definitive conclusions on the relationship between ADAs and safety.

Dr. Paine noted that 4.1% of vutrisirian-treated subjects reported injection site reactions. Vutrisiran was initially supplied in the HELIOS-A study in a vial and then the presentation was later changed to a pre-filled syringe. Dr. Paine notes that there is no difference in the safety profile of vutrisiran before and after the introduction of the pre-filled syringe. The Applicant has not conducted any human factors studies to demonstrate that patients can administer the product safely at home. The product labeling will reflect this and state that vutrisiran should be administered by a healthcare professional.

The safety review was limited in the ability to make direct comparisons to the external control group from the APOLLO trial. HELIOS-A was conducted during the COVID-19 pandemic, but the APOLLO trial was completed prior to the pandemic. Patisiran (and the placebo from the APOLLO trial) were given IV every three weeks while vutrisiran was given SC once every three months. The placebo arm from APOLLO and the active control arm from HELIOS-A were utilized to inform the review and make relative safety comparisons. However, because of the limitations in making direct comparisons to the placebo arm in the APOLLO trial, the final labeling includes only descriptive safety information from HELIOS-A vutrisiran arm without description of the placebo arm from the APOLLO trial.

Overall, the risks associated with vutrisiran are acceptable and do not preclude approval. As in the patisiran labeling, there will be a warning for reduced vitamin A and the need for supplementation.

9. Advisory Committee Meeting

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

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Financial disclosures
Dr. Paine concluded that the Applicant has adequately disclosed financial interests and arrangements with clinical investigators.

Good Clinical Practice (GCP) issues
No GCP issues were noted during the review.

Office of Scientific Investigations (OSI) audits
OSI investigated three clinical investigator sites and concluded that the data generated by these sites appears acceptable in support of the indication.

Controlled Substance Staff
At the preNDA meeting, CSS determined that their involvement was not needed for the review of this application.

12. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for the safe use of vutrisiran.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following will be postmarketing requirements:

a. A two-year carcinogenicity study of vutrisiran in rat.
b. A two-year carcinogenicity study of vutrisiran in mouse.

c. 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.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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