NEW DRUG APPROVAL

Brand Name	Amvuttra™
Generic Name	vutrisiran
Drug Manufacturer	Alnylam Pharmaceuticals, Inc.

New Drug Approval

FDA Approval Date: June 13, 2022

Review designation: Standard; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA) 215515

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hereditary transthyretin amyloidosis (hATTR) is a severe, heterogeneous multisystem condition with prevalent peripheral (both somatic and autonomic) nervous system impairment, due to mutations in the transthyretin (TTR) gene. The condition, presenting as an adult-onset, autosomal-dominant disease with variable penetrance, is characterized by extracellular deposition of amyloid fibrils in different organs. Besides the peripheral nerves, heart, kidney and ocular vitreous may also be involved, leading to a life-threatening, multisystem disease with a great variability in clinical presentation and course, and death within 10 years on average.

hATTR has traditionally been described according to the predominant clinical features, typically either a polyneuropathy (hATTR-PN), formerly referred to as Familial Amyloid Polyneuropathy (FAP), or a cardiomyopathy (hATTR-CM), termed Familial Amyloid Cardiomyopathy (FAC), although most patients show symptoms and signs of both nerve and heart involvement. A cardiomyopathy is also characteristic of a wild-type form of the disease (ATTRwt), previously known as senile cardiac amyloidosis. To date, over 120 TTR variants have been identified as a cause of hATTR, the most common being the p. Val30Met mutation. The majority of TTR mutations cause a “neuropathic” or a “mixed” phenotype, yet some variants typically manifest with a predominant or isolated cardiomyopathy.

In the past, hATTR amyloidosis has classically been considered a rare disease with three major endemic clusters in Portugal (where it was first described), Sweden, and Japan; smaller endemic foci have been subsequently identified in Cyprus and Majorca. Within Europe, the incidence of hATTR amyloidosis is highly variable, and cases are mainly sporadic.

Familial amyloidosis caused by a transthyretin mutation occurs in approximately 1 in 100,000 Caucasians in the U.S, and more commonly in African Americans (approximately 4% in that population). This condition is prevalent in Portugal, Sweden, Japan, Ireland, Spain, France, Finland, Germany and Greece. Symptoms usually begin between 40 and 65 years of age.

Nowadays, given the increasing awareness of the disease among physicians and the current widespread availability of genetic testing, the incidence of hATTR amyloidosis is probably expected to rise, particularly in non-endemic regions. Consistently, hATTR has now been reported in at least 29 countries around the world.

Efficacy

The efficacy of Amvuttra™ was evaluated in a randomized, open-label clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT03759379). Patients were randomized 3:1 to receive

25 mg of Amvuttra™ subcutaneously once every 3 months (N=122), or 0.3 mg/kg patisiran intravenously every 3 weeks (N=42) as a reference group. Ninety-seven percent of Amvuttra™-treated patients and 93% of patisiran-treated patients completed at least 9 months of the assigned treatment. Efficacy assessments were based on a comparison of the Amvuttra™ arm of Study 1 with an external placebo group in another study (NCT01960348) composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis. The primary efficacy endpoint was the change from baseline to Month 9 in modified Neuropathy Impairment Score +7 (mNIS+7). The mNIS+7 is an objective assessment of neuropathy 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 mNIS+7 has a total score range from 0 to 304 points, with higher scores representing a greater severity of disease. The clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The Norfolk QoL-DN has a total score range from -4 to 136, with higher scores representing greater impairment. Additional endpoints were gait speed, as measured by the 10-meter walk test (10MWT), and modified body mass index (mBMI).

Treatment with Amvuttra™ in Study 1 resulted in statistically significant improvements in the mNIS+7, Norfolk QoL-DN total score, and 10-meter walk test at Month 9 compared to placebo in the external study (p<0.001) (Table 1, Figure 1 and Figure 3). The distributions of changes in mNIS+7 and Norfolk QoL-DN total scores from baseline to Month 9 by percent of patients are shown in Figure 2 and Figure 4, respectively.

The change from baseline to Month 9 in modified body mass index nominally favored Amvuttra™ (Table 1).

Table 1: Clinical Efficacy Results (Comparison of Amvuttra™ Treatment in Study 1 to an External Placebo Control*)

Endpoint†	Baseline, Mean (SD)		Change from Baseline to Month 9, LS Mean (SEM)		Amvuttra™ Placebo* Treatment Difference, LS Mean (95% CI)	p-value
	Amvuttra™ N=122 (Study 1)	Placebo* N=77 (NCT01960348	Amvuttra™ (Study 1)	Placebo* (NCT01960348)		
mNIS+7‡	60.6 (36.0)	74.6 (37.0)	-2.2 (1.4)	14.8 (2.0)	-17.0 (-21.8, -12.2)	p<0.001
Norfolk QoL-DN‡	47.1 (26.3)	55.5 (24.3)	3.3 (1.7)	12.9 (2.2)	-16.2 (-21.7, -10.8)	p<0.001
10-meter walk test (m/sec) §	1.01 (0.39)	0.79 (0.32)	0 (0.02)	-0.13 (0.03)	0.13 (0.07, 0.19)	p<0.001
mBMI¶	1058 (234)	990 (214)	7.6 (7.9)	-60.2 (10.1)	67.8 (43.0, 92.6)	p<0.001

CI = confidence interval; LS mean = least squares mean; mBMI = modified body mass index; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life-Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean

*External placebo group from another randomized controlled trial (NCT01960348)
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)
‡A lower number indicates less impairment/fewer symptoms §A higher number indicates less disability/less impairment
¶mBMI: nominal p-value; body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L).

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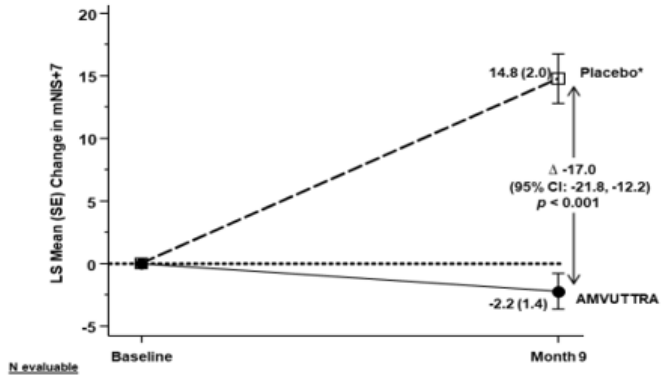
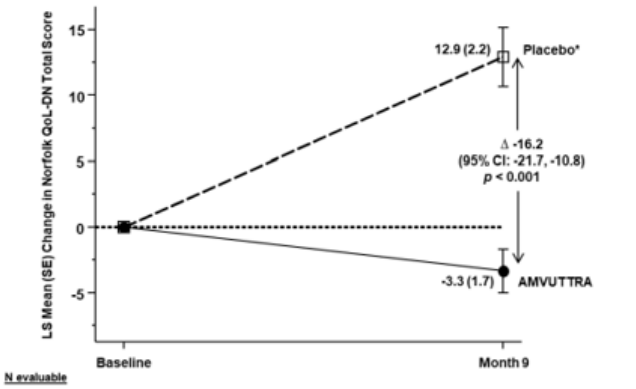
Figure 1: Change from Baseline in mNIS+7 (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



N evaluable		
Placebo	77	67
AMVUTTRA	122	114

A decrease in mNIS+7 indicates improvement
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA – placebo
*External placebo group from another randomized controlled trial (NCT01960348)

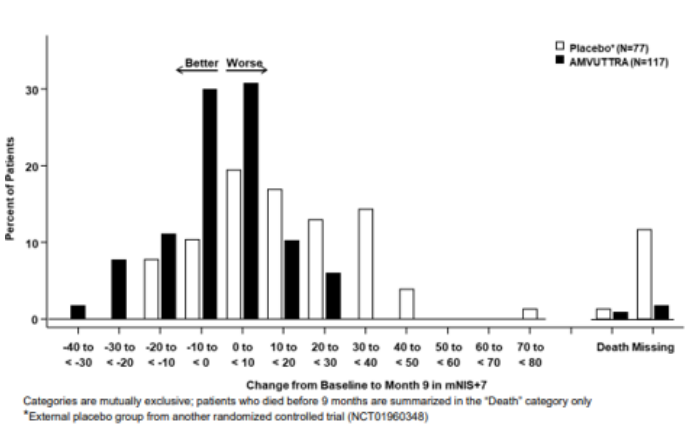
Figure 3: Change from Baseline in Norfolk QoL-DN Total Score (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



N evaluable		
Placebo	76	65
AMVUTTRA	121	114

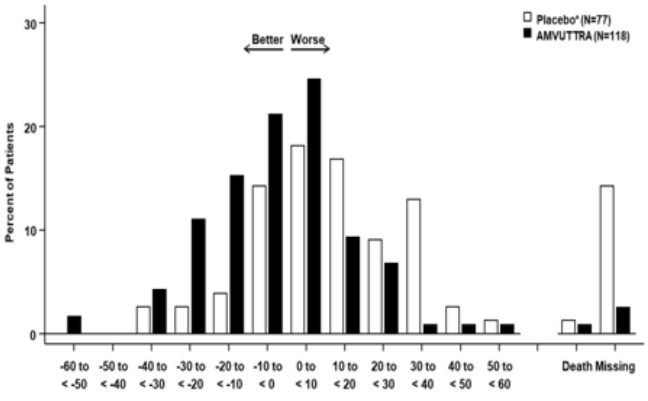
A decrease in Norfolk QoL-DN score indicates improvement
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA – placebo
*External placebo group from another randomized controlled trial (NCT01960348)

Figure 2: Histogram of mNIS+7 Change from Baseline at Month 9 (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



Categories are mutually exclusive; patients who died before 9 months are summarized in the "Death" category only
*External placebo group from another randomized controlled trial (NCT01960348)

Figure 4: Histogram of Norfolk QoL-DN Total Score Change from Baseline at Month 9 (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



Categories are mutually exclusive; patients who died before 9 months are summarized in the "Death" category only
*External placebo group from another randomized controlled trial (NCT01960348)

Patients receiving Amvuttra™ in Study 1 experienced similar improvements relative to those in the external placebo group in mNIS+7 and Norfolk QoL-DN total score across all subgroups including age, sex, race, region, NIS score, Val30Met genotype status, and disease stage.

Safety

ADVERSE EVENTS

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Adverse reactions reported in adults.

>10%: Neuromuscular & skeletal: Arthralgia (11%)

1% to 10%:

Cardiovascular: Atrioventricular block (2%; including complete atrioventricular block)

Endocrine & metabolic: Vitamin A deficiency (7%)

Immunologic: Antibody development (3%)

Local: Injection site reaction (≤4%; including bruising at injection site, erythema at injection site, injection-site pruritus, pain at injection site, warm sensation at injection site)

Respiratory: Dyspnea (7%)

WARNINGS & PRECAUTIONS

Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

CONTRAINDICATIONS

None reported

Clinical Pharmacology

MECHANISMS OF ACTION

Vutrisiran is a double-stranded siRNA-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.

Dose & Administration

ADULTS

25 mg administered by subcutaneous injection once every 3 months.

PEDIATRICS

None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

eGFR ≥30 mL/minute/1.73 m2: No dosage adjustment necessary.

eGFR <30 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

HEPATIC IMPAIRMENT

Mild impairment (total bilirubin ⩽1 times the ULN and AST >1 times ULN, or total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment necessary.

Moderate to severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 25 mg/0.5 mL in a single-dose prefilled syringe.