Policy Number	**RX501.146**
Policy Effective Date	**5/7/2026**

Vutrisiran (Amvuttra®) and Patisiran (Onpattro®)

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility of consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (small, mid-market, large groups, municipalities/counties/schools, state employees, fully-insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association, New England Journal of Medicine, and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Initial Treatment - Hereditary Transthyretin-Mediated Amyloidosis Polyneuropathy
Patisiran and vutrisiran **may be considered medically necessary** for individuals if they meet criteria 1 through 5:

1. 18 years of age or older.
2. Confirmatory diagnosis of hereditary transthyretin amyloidosis by a genetic test or tissue biopsy showing amyloid deposition.
3. Presence of clinical signs and symptoms of polyneuropathy characterized by any one of the following:
   - Baseline polyneuropathy disability IIIb or lower (see Table 1 in Description section);
   - Baseline familial amyloid polyneuropathy Stage 1 or 2 (see Table 1 in Description section).
4. Does not have ANY of the following:
   - New York Heart Association class III or IV heart failure;
   - Sensorimotor or autonomic neuropathy not related to hATTR amyloidosis (monoclonal gammopathy, autoimmune disease, etc.).

Continuation of Treatment - Hereditary Transthyretin-Mediated Amyloidosis Polyneuropathy
Incremental reauthorization of patisiran and vutrisiran **may be considered medically necessary** for individuals if they meet criteria 1 through 2:

1. Continues to meet the initial treatment criteria cited above; and
2. Documentation of stabilization or improvement via use of objective measurements, such as 10-MWT, COMPASS-31, PND Score or 5 EQ-5D.

Cardiomyopathy of Wild-Type or Hereditary Transthyretin-Mediated Amyloidosis
Vutrisiran **may be considered medically necessary** for individuals with cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits when meeting ALL of the follow criteria:
1. 18 years of age or older; and
2. Confirmatory diagnosis of hATTR by a genetic test or tissue biopsy showing amyloid deposition; and
3. Evidence of cardiomyopathy due to transthyretin-mediated amyloidosis by any of the below:
    - Evidence of amyloid deposits in the heart by cardiovascular magnetic resonance, nuclear imaging, or tissue biopsy and
4. New York Heart Association Class I or II heart failure or Class III heart failure that is not considered high risk (i.e., excludes patients with NYHA high risk Class III disease and Class IV disease).

Patisiran and vutrisiran **are considered experimental, investigational and/or unproven** for all other non-FDA indications or when the above criteria are not met.

Policy Guidelines

Patisiran Only
- It is given as intravenous infusion based on body weight.
    - For individuals less than 100 kg: 0.3 mg/kg once every 3 weeks.
    - For individuals weighing 100 kg or more: 30 mg once every 3 weeks.
- Treatment requires premedication with intravenous corticosteroid, oral acetaminophen, intravenous histamine (H1) blocker, and intravenous H2 blocker prior to its administration to reduce the risk of infusion-related reactions. For premedications not available or not tolerated intravenously, equivalents may be administered orally.

Vutrisiran Only
- It is given as subcutaneous injection.
    - 25 mg once every 3 months (quarterly).
    - Injection should be administered by a health care professional.

Patisiran and Vutrisiran
Treatment leads to a decrease in serum vitamin A levels and therefore vitamin A supplementation at the recommended daily allowance is advised. Individuals should be

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

Description

Hereditary Transthyretin-Mediated Amyloidosis
Hereditary transthyretin-mediated amyloidosis is a rare, progressive, and fatal autosomal dominant genetic disease with variable penetrance. Transthyretin is a transporter protein that carries thyroxine and retinol (vitamin A) and is primarily synthesized in the liver (95%) but also choroid plexus. The gene for transthyretin is located on chromosome 18. Variance in the transthyretin gene results in the production of misfolded transthyretin protein. More than 120 variants have been described, including single variants, compound heterozygotes, and deletions. The valine-to-methionine substitution at position 30 (V30M) is the most common variant observed worldwide, while valine-to-isoleucine substitution at position 122 (V122I) is the most common variant in the U.S. The misfolded protein generated because of a variant in the transthyretin gene is insoluble and accumulates as amyloid fibrils (i.e., amyloidosis) in multiple organs of the body, such as the liver, nerves, heart, and kidneys causing disruption of organ tissue structure and function.

Historically, hATTR was classified into 2 distinct syndromes—amyloidosis with polyneuropathy (previously known as familial amyloid polyneuropathy or FAP) and amyloidosis with cardiomyopathy (previously known as familial amyloid cardiomyopathy). (3) While hATTR patients may show predominance of polyneuropathy or cardiomyopathy, it is now recognized that most patients manifest signs and symptoms of both syndromes over the course of their disease and, therefore, the current clinical approach treats FAP and familial amyloid cardiomyopathy as 1 hereditary disease with a spectrum of clinical manifestations. (4) The first symptoms of hATTR amyloidosis typically appear between the mid-20s and the mid-60s, involving multiple tissues and organs and often seem unrelated. Neurologic symptoms include severe sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and autonomic dysfunction resulting in orthostatic hypotension, diarrhea, impotence, and bladder disturbances. (5) While the neurologic symptoms of hATTR are among the most physically disabling, cardiac manifestations are the most predictive of early death. Cardiac manifestations include arrhythmias, conduction disorders, cardiomegaly, and heart failure. If the disease is untreated, the median survival for patients with predominantly neuropathic symptoms is 5 to 15 years, while patients with predominantly cardiomyopathic symptoms have a median survival of 2.5 to 6 years. (6,7)

The FAP stage system and the polyneuropathy disability score are the two most used clinical staging systems and are summarized in Table 1. Higher scores on each of the staging systems are indicative of greater disease severity.

Table 1. Clinical Staging in Hereditary Transthyretin-Mediated Amyloidosis

FAP Stage	**Clinical Description**
Stage 0	No Symptoms
Stage 1	Unimpaired ambulation
Stage 2	Assistance with ambulation required
Stage 3	Wheelchair-bound or bedridden
PND Score	
Stage 0	No symptoms
Stage I	Sensory disturbances but preserved walking capability
Stage II	Impaired walking capacity but ability to walk without a stick or crutches
Stage IIIA	Walking with the help of 1 stick or crutch
Stage IIIB	Walking with the help of 2 sticks or crutches
Stage IV	Confined to a wheelchair or bedridden

Adapted from Ando et al. (2013) (5)
FAP: familial amyloid polyneuropathy; PND: polyneuropathy disability.

Diagnosis

The diagnosis of hATTR based on clinical signs and symptoms is difficult because of heterogeneity in clinical manifestations and the nonspecific nature of signs and symptoms that may mimic other conditions. Furthermore, the age of onset and rate of progression are highly variable from patient to patient. (4) As a result, many patients are misdiagnosed or their diagnosis is delayed, and patients often see physicians across multiple specialties before receiving an accurate diagnosis. (4)

To confirm the diagnosis, proven amyloid deposition in biopsy specimens and identification of a pathogenic variant in the transthyretin gene are necessary. (8) Amyloid deposition in the biopsied tissues can be confirmed by using Congo red staining and, ideally, immunohistochemical study as well as laser capture tandem mass spectrometry. However, mass spectrometry can only demonstrate a mass difference between wild-type and transthyretin protein variants in serum. It does not specify the site and kind of amino acid substitution in a number of disease-related transthyretin variants; thus, DNA sequencing is usually required. Sequence analysis of the transthyretin gene, the only gene in which mutation is known to cause hATTR, detects more than 99% of pathogenic variants. (8)

There are currently 2 genetic test programs that offer no-cost, confidential genetic testing and genetic counseling services sponsored by the manufacturer of patisiran. It is summarized in Table 2.

Table 2. Characteristics of Genetic Testing Program Offered by Manufacturers in the United States.

Program	Program Eligibility	Tests Offered	Detail
AlnylamAct™	Patients 18 years and older with a suspected diagnosis or a confirmed family history of hATTR amyloidosis.	Invitae Cardiomyopathy Comprehensive Panel	Testing for ~50 genes associated with inherited cardiomyopathy conditions, including hATTR amyloidosis
		Invitae Comprehensive Neuropathies Panel	Testing for ~70 genes that cause dominant, recessive, and X-linked hereditary neuropathies, including hATTR amyloidosis
		Invitae Transthyretin Amyloidosis Test	Single-gene genetic testing for the TTR gene, which is associated with hATTR amyloidosis

Adapted from AlnylamAct™ Program (9)
hATTR: hereditary transthyretin-mediated amyloidosis; TTR: transthyretin

Epidemiology

It is estimated that the neuropathy-predominant form of hATTR affects at least 10,000 people worldwide, (10) and roughly 3,000-3,500 people in the United States (U.S.). (11) Due to under-diagnosis and a lack of population-based data, these numbers may underestimate the actual prevalence. (12) According to unpublished data from Alnylam, there may be 10,000 to 15,000 individuals with the neuropathy-predominant form of hATTR (AMCP dossier).

The prevalence of the cardiomyopathy form of hATTR is also problematic to estimate. About 50,000 people worldwide may have hATTR amyloidosis. (10, 11) In the U.S. general population, the prevalence of V122I variant (which is the most common variant seen in the U.S.) is 3.4%. (13) However, phenotypic penetrance resulting in overt clinical cardiac disease depends on age and varies widely from 7% to 80%. (14) Higher estimates of clinical prevalence were reported in studies with very small samples of carriers. Characteristics of hATTR in the U.S. by different variants are summarized in Table 3.

Table 3. Characteristics of Hereditary Transthyretin Amyloidosis in the United States by Variants

Variant	Median Age at Symptoms Onset (Yr)	Median Age at Diagnosis (Yr)	Median age at Death (Year)
T60A	60.2	64.5	67.6
V30M	64.3	67.8	74.7
V122I	63.7	69.3	72.9
S77Y	55.8	60.1	65.8
Other	53.1	56.7	62.1

Adapted from Swiecicki et al. 2015 (15)

Treatment

Prior to the approval of patisiran and inotersen in 2018, there was no U.S. Food and Drug Administration approved treatment available in the U.S. for the treatment of hATTR. As of Sept. 27, 2024, inotersen (Tegsedi) was discontinued in the United States due to low utilization. (16)

As transthyretin is primarily formed in the liver, orthotopic liver transplantation has been the disease-modifying treatment available to most patients with hATTR. This procedure can remove approximately 95% of the production of variant transthyretin. However, limited organ availability, exclusion of older patients and those with advanced disease, the high costs of transplantation, the risks of lifelong immunosuppression, and reports of disease progression following liver transplantation limits it use. Furthermore, orthotopic liver transplantation is not recommended for patients with cardiac involvement due to the observed post-transplant progression of cardiac; making a considerable proportion of patients in the U.S. who will develop cardiomyopathy ineligible for transplantation. (17) As such the procedure is not commonly performed in the U.S.

Mechanism of Action

The function of small interfering ribonucleic acid is to regulate gene expression, or how much protein will be made from a particular gene. Patisiran and vutrisiran are small interfering ribonucleic acid that are designed to selectively target variant and wild-type transthyretin messenger RNA through RNA interference, which results in a reduction of serum transthyretin and transthyretin deposits in tissues.

Wild-Type Transthyretin-Mediated Amyloidosis

In ATTRwt, the natural transthuretin protein becomes unstable with age, making it prone to misfold and form amyloid deposits mainly in the heart, causing cardiomyopathy. (18) ATTRwt is most commonly reported in men over the age of 60, and is not inherited, unlike other types of transthyretin-mediated amyloidosis.

Symptoms usually start after the age of 60 and are mostly associated with cardiomyopathy. Amyloid deposits in the heart make the heart wall stiffen and work inefficiently. Eventually this leads to congestive heart failure with symptoms such as shortness of breath, leg swelling, fatigue, nausea and an irregular heartbeat or palpitations. Other symptoms unrelated to the heart may also exist and in some cases often are present 8-10 years before heart-related symptoms, the most commonly reported is carpal tunnel syndrome.

Diagnosis

If transthyretin-mediated amyloidosis is suspected, a number of tests are carried out including an abdominal fat pad biopsy to confirm the presence of amyloid deposits. Tests are also done to determine the effect of the amyloid deposits on the heart, nerves and other organs. These tests include blood, nerve and muscle tests, echocardiogram, magnetic resonance imaging (MRI) and other types of scans. In some cases, organ biopsies may also be completed to determine organ involvement. Some scans can help identify the type of amyloidosis and distinguish transthyretin-mediated amyloidosis from amyloid light-chain (AL) amyloidosis in the heart. Other tests, called immunohistochemistry and mass spectrometry, are used to differentiate between transthyretin-mediated amyloidosis and AL amyloidosis. To distinguish between wild-type and hereditary transthyretin-mediated amyloidosis, a blood test to screen for genetic mutations causing hATTR is necessary. The absence of these genetic mutations will confirm a diagnosis of ATTRwt.

Treatment

In transthyretin-mediated amyloidosis there are several different therapeutic approaches, which aim to do one of the following:

- Stabilizing the TTR protein,
- Stopping the production of TTR protein, or
- Removing the amyloid deposits.

The approach in stopping production of TTR proteins is through 'gene silencing.' Novel treatments known as "gene silencers" have shown promising results in clinical studies. They prevent TTR protein production by blocking the TTR gene. The gene silencing drug Vutrisiran (Amvuttra) has been approved for use for transthyretin-mediated amyloidosis cardiomyopathy. Amvuttra works by decreasing the amount of TTR protein made in the liver, which leads to the formation of fewer harmful amyloid fibrils depositing in the heart and causing cardiomyopathy. It acts as a gene silencer to lower the amount of TTR protein circulating in the body, and lessening disease progression.

Regulatory Status

In August 2018, patisiran (Onpattro, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (2)

In June 2022, vutrisiran (Amvuttra, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

In March 2025, vutrisiran (Amvuttra, Alnylam Pharmaceuticals, Inc.) was approved by the FDA for "treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits." (1)

Rationale

This policy is based on the U.S. Food and Drug Administration labeled indications for vutrisiran (Amvuttra) and patisiran (Onpattro) and a review of relevant professional guidelines and position statements.

Vutrisiran (Amvuttra) (1)
Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis
The efficacy of Amvuttra was evaluated in a randomized, open-label clinical trial in adult patients with hATTR-PN (HELIOS-A; 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 HELIOS-A 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 HELIOS-A 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 4, 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.

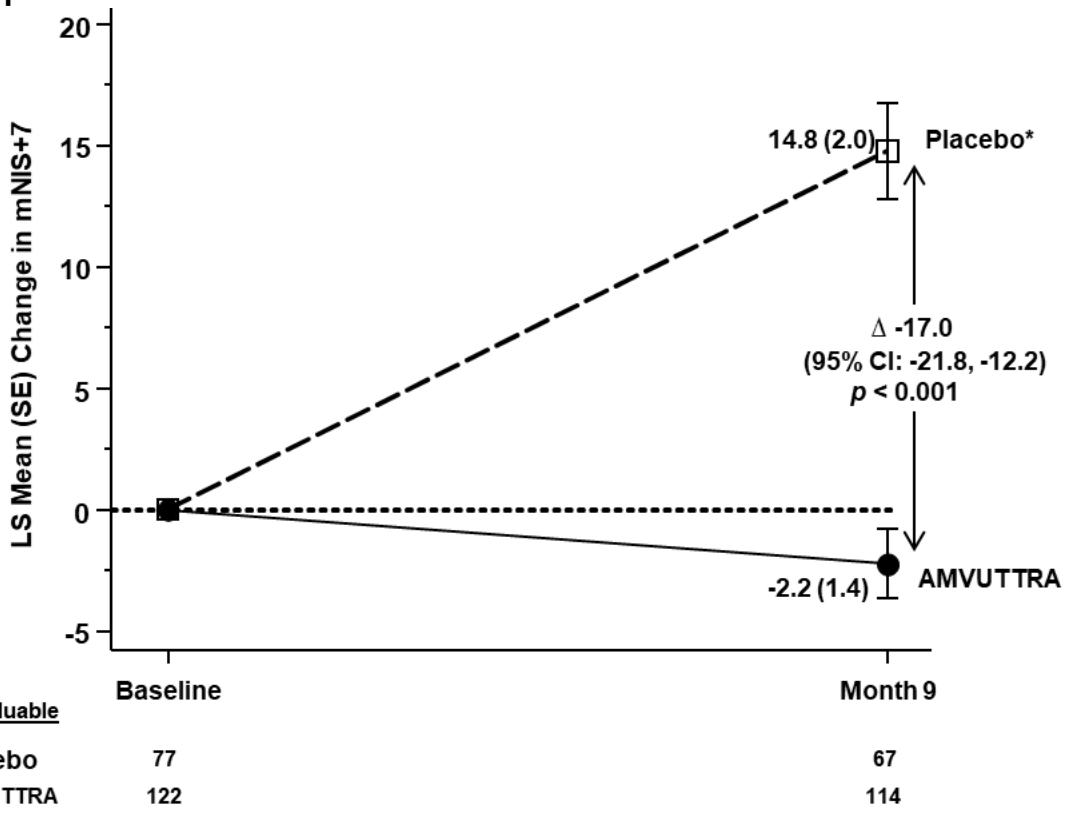
The change from baseline to Month 9 in modified body mass index nominally favored Amvuttra [Table 4].

Table 4. Clinical Efficacy Results (Comparison of Amvuttra Treatment in HELIOS-A to an External Placebo Control[a]

Endpoint[b]	Baseline, Mean (SD)		Change from Baseline to Month 9, LS Mean (SEM)		Amvuttra-Placebo[a] Treatment Difference, LS Mean (95% CI)	p-value
	Amvuttra N=122 (HELIOS-A)	Placebo[a] N=77 (NCT01960348)	Amvuttra (HELIOS-A)	Placebo[a] (NCT01960348)		
mNIS+7[c]	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[c]	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)[d]	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[e]	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.
[a] External placebo group from another randomized controlled trial (NCT01960348).
[b] All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method.
[c] A lower number indicates less impairment/fewer symptoms.
[d] A higher number indicates less disability/less impairment.
[e] mBMI: nominal p-value; body mass index (BMI: kg/m^2) multiplied by serum albumin (g/L).

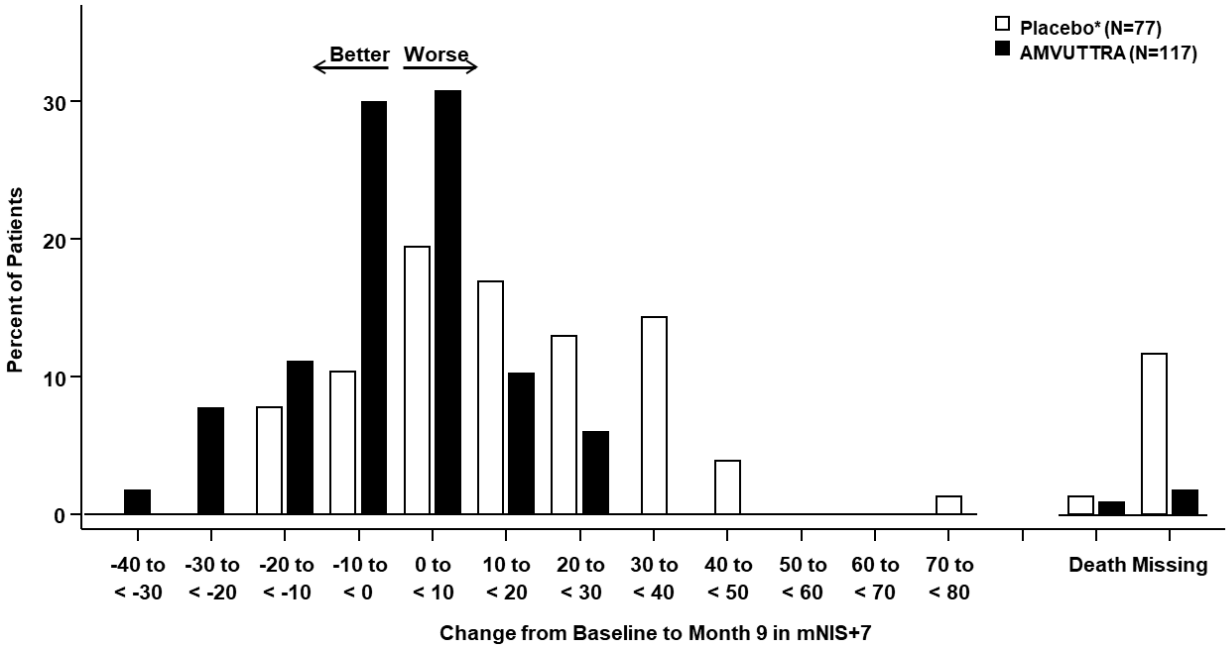
Figure 1: Change from Baseline in mNIS+7
(Comparison of Amvuttra Treatment in HELIOS-A to an External Placebo Control*)



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).

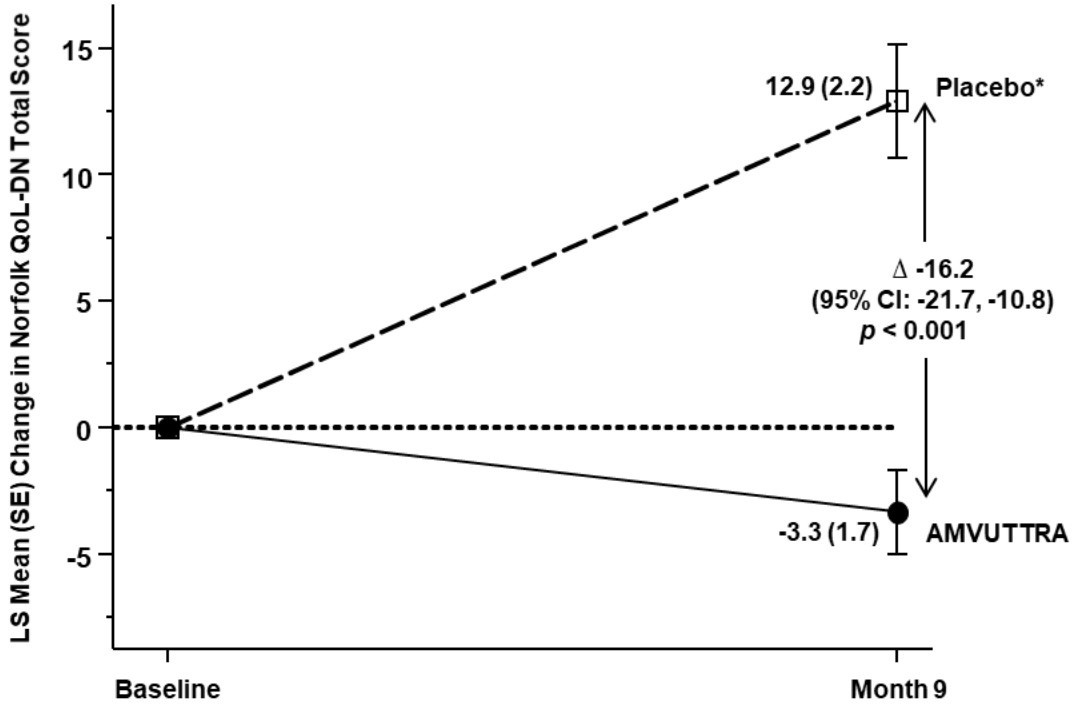
Figure 2: Histogram of mNIS+7 Change from Baseline at Month 9 (Comparison of Amvuttra Treatment in HELIOS-A to an External Placebo Control*)



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).

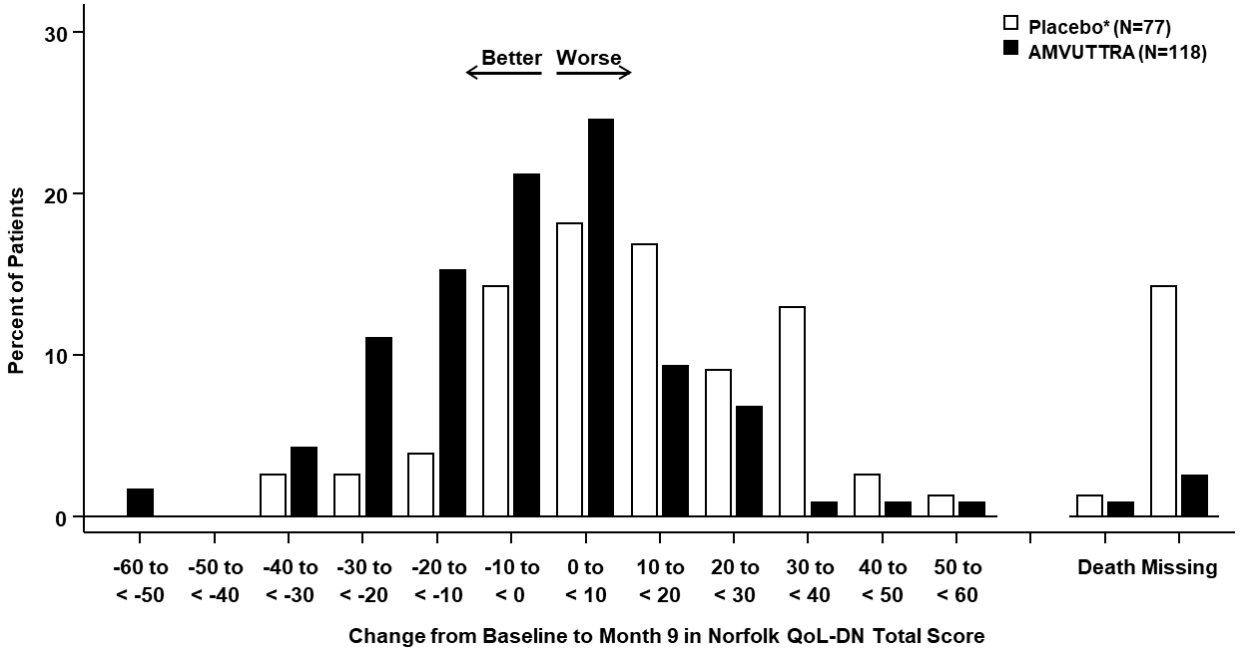
Figure 3: Change from Baseline in Norfolk QoL-DN Total Score (Comparison of Amvuttra Treatment in HELIOS-A to an External Placebo Control*)



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 4: Histogram of Norfolk QoL-DN Total Score Change from Baseline at Month 9 (Comparison of Amvuttra Treatment in HELIOS-A 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 HELIOS-A 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.

Cardiomyopathy of Wild-type or Hereditary Transthyretin-mediated Amyloidosis

The efficacy of Amvuttra was evaluated in a multicenter, international, randomized, double-blind, placebo-controlled trial (HELIOS-B, NCT04153149) in 654 adult patients with wild-type or hereditary ATTR-CM. Patients were randomized 1:1 to receive 25 mg of Amvuttra (n=326) subcutaneously once every 3 months, or matching placebo (n=328).

Treatment assignment was stratified by baseline tafamidis use (yes versus no), ATTR disease type (wtATTR or hATTR amyloidosis), and by baseline New York Heart Association (NYHA) Class I or II and age <75 years versus all other. At baseline, 40% of patients were on tafamidis. The mean age of study participants was 75 years, 93% were male, 84% were White, 7% were Black or African American, 6% were Asian, 2% did not report race and 1% were race other, 88% had wildtype ATTR, 13% were NYHA Class I, 78% were NYHA Class II, and 9% NYHA Class III. No significant imbalance in baseline characteristics was observed between the two treatment groups.

Participants were permitted to initiate open-label tafamidis during the study. A total of 85 participants initiated tafamidis: 44 (22%) in the Amvuttra arm and 41 (21%) in the placebo arm. The median time to initiation of tafamidis for these 85 participants was 18 months.

The primary efficacy endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) during the double-blind treatment period of up to 36 months, evaluated in the overall population and in the monotherapy population (defined as patients not receiving tafamidis at study baseline).

Amvuttra led to significant reduction in the risk of all-cause mortality and recurrent CV events compared to placebo in the overall and monotherapy population of 28% and 33%, respectively (Table 5). The majority of the deaths (77%) were CV-related. A Kaplan-Meier curve illustrating time to first CV event or all-cause mortality is presented in Figure 5.

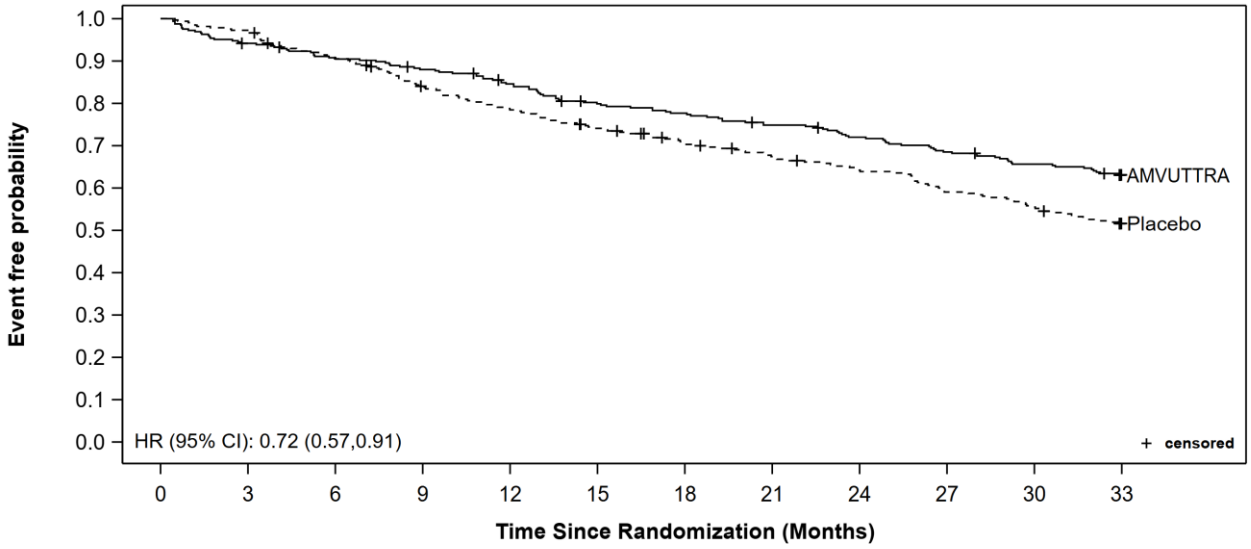
Both components of the primary composite endpoint individually contributed to the treatment effect in the overall and monotherapy population (Table 5).

Table 5. Primary Composite Endpoint and its Individual Component in HELIOS-B

Endpoint		**Overall Population**		**Monotherapy Population**	
		Amvuttra (N=326)	**Placebo (N=328)**	**Amvuttra (N=196)**	**Placebo (N=199)**
Primary composite endpoint[a]	Hazard ratio (95% CI)[b] p-value[b]	0.72 (0.55, 0.93) 0.01		0.67 (0.49, 0.93) 0.02	
Components of the Primary Composite Endpoint					
All-cause mortality	Hazard Ratio (95% CI)[c]	0.69 (0.49, 0.98)		0.71 (0.4 7, 1.06)	
CV hospitalizations and UHF visits	Hazard Ratio (95% CI)[b]	0.73 (0.5 5, 0.96)		0.67 (0.4 7, 0.96)	

CI: confidence interval; CV: cardiovascular; UHF: urgent heart failure.
Heart transplantation and left ventricular assist device placement are treated as death. Deaths after study discontinuation are included in the all-cause mortality component analysis.
[a] Primary composite endpoint defined as: composite outcome of all-cause mortality and recurrent CV events. Primary analysis included at least 33 months (and up to 36 months) follow-up on all patients.
[b] Hazard ratio (95% CI) and p-value are based on a modified Andersen-Gill method.
[c] Hazard ratio (95% CI) is based on a Cox proportional hazard model.

Figure 5: Time to All-Cause Mortality or First CV Event (Overall population)



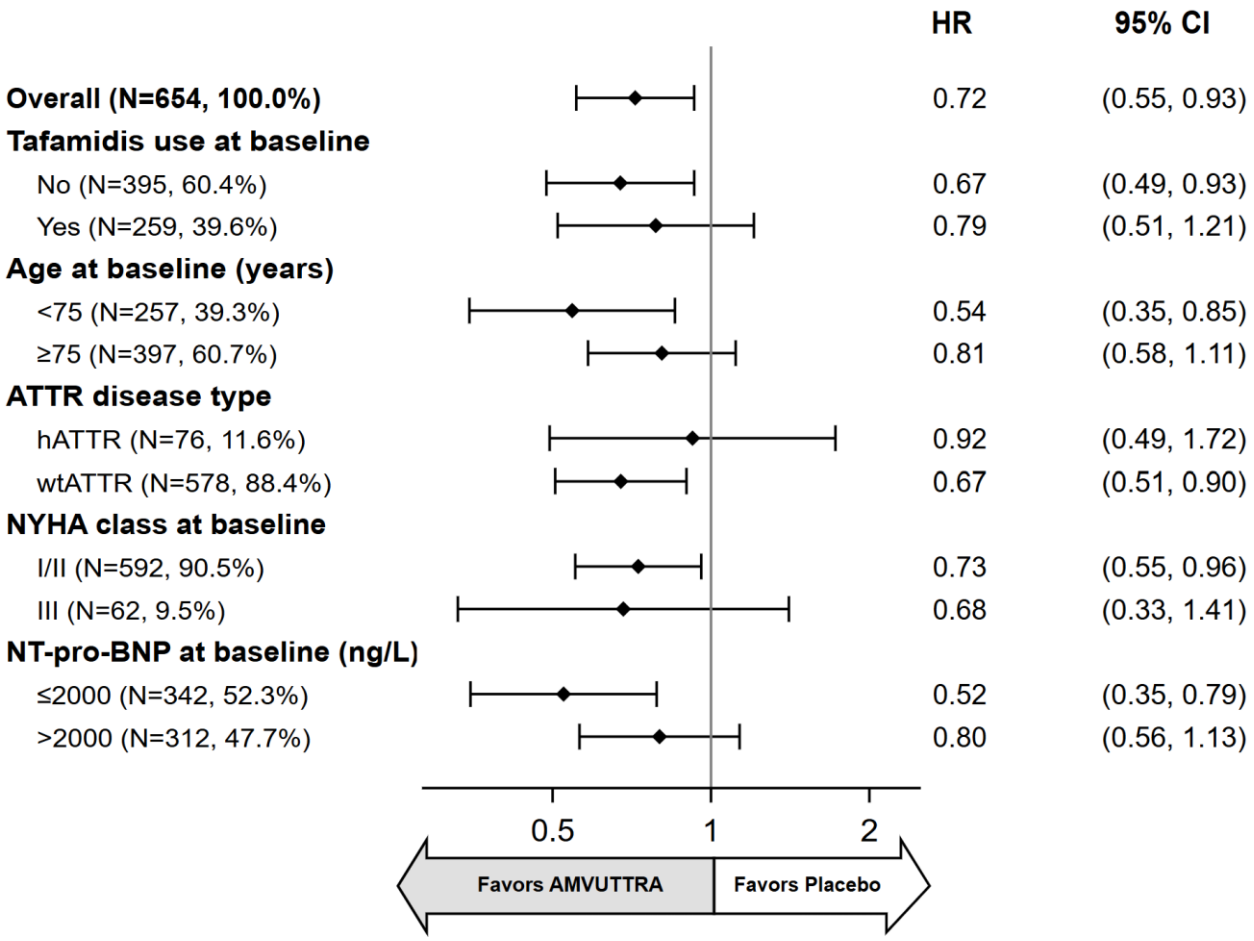
No. at Risk (Cumulative No. of Events)

AMVUTTRA	326(0)	306(19)	294(30)	284(39)	271(50)	254(65)	247(72)	237(81)	227(90)	216(101)	206(110)	185(118)
Placebo	328(0)	317(11)	295(31)	270(53)	253(70)	237(84)	221(96)	210(105)	199(115)	183(131)	172(142)	155(154)

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
Heart transplantation and left ventricular assist device placement are treated as death. HR and 95% CI are based on a Cox proportional hazard model. First CV event = First CV hospitalization or urgent heart failure visit after randomization.

Results from the subgroup analysis for the primary composite endpoint were consistent across prespecified subgroups in the overall population (Figure 6) and monotherapy population.

Figure 6: Subgroup Analyses of the Primary Composite Endpoint (Overall Population)



ATTR: transthyretin amyloidosis; CI: confidence interval; hATTR: hereditary transthyretin amyloidosis; HR: hazard ratio; NT-pro-BNP:N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association; wtATTR: wild-type transthyretin amyloidosis. HR and 95% CI are based on modified Andersen-Gill model analyses.

The treatment effect of Amvuttra on functional capacity and health status were assessed by the change from baseline to Month 30 in distance walked on 6-Minute Walk Test, and the Kansas City Cardiomyopathy Questionnaire-Overall Summary score, respectively.

At Month 30, the LS mean difference in change from baseline in distance walked on 6-MWT was 22 (95% CI: 8, 35; p=0.002) meters and 25 (95% CI: 7, 44; p=0.006) meters favoring Amvuttra over placebo in the overall population and monotherapy population, respectively.

At Month 30, the LS mean difference in the change from baseline in KCCQ-OS was 6 (95% CI: 2, 9; p=0.001) and 8 (95% CI: 4, 13; p=0.0003) favoring Amvuttra over placebo in the overall population and monotherapy population respectively.

Patisiran (Onpattro) (2)

The efficacy of Onpattro was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (NCT 01960348). Patients were randomized in a 2:1 ratio to receive Onpattro 0.3 mg/kg (N=148) or placebo (N=77), respectively, via intravenous infusion once every 3 weeks for 18 months. All patients received premedication with a corticosteroid, acetaminophen, and H1 and H2 blockers. Ninety-three percent of Onpattro-treated patients and 62% of placebo-treated patients completed 18 months of the assigned treatment.

The primary efficacy endpoint was the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7). The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified +7 (+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 clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Month 18 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 version of the Norfolk QoL-DN that was used in the trial had a total score range from -4 to 136, with higher scores representing greater impairment.

The changes from baseline to Month 18 on both the mNIS+7 and the Norfolk QoL-DN significantly favored Onpattro (Table 6, Figure 7 and Figure 9). The distributions of changes in mNIS+7 and Norfolk QoL-DN scores from baseline to Month 18 by percent of patients are shown in Figure 8 and Figure 10, respectively.

The changes from baseline to Month 18 in modified body mass index and gait speed (10-meter walk test) significantly favored Onpattro (Table 6).

Table 6. Clinical Efficacy Results from the Placebo-Controlled Study

Endpoint[a]	**Baseline, Mean (SD)**		**Change from Baseline to Month 18, LS Mean (SEM)**		**Onpattro-Placebo Treatment Difference, LS Mean (95% CI)**	**p-value**
	Onpattro N=148	**Placebo N=77**	**Onpattro**	**Placebo**		
Primary						
mNIS+7[b]	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0	p<0.001

					(-39.9, -28.1)	
Secondary						
Norfolk QoL-DN[b]	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	p<0.001
10-meter walk test (m/sec)[c]	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	p<0.001
mBMI[d]	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	p<0.001

CI: confidence interval; LS: least squares; 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.

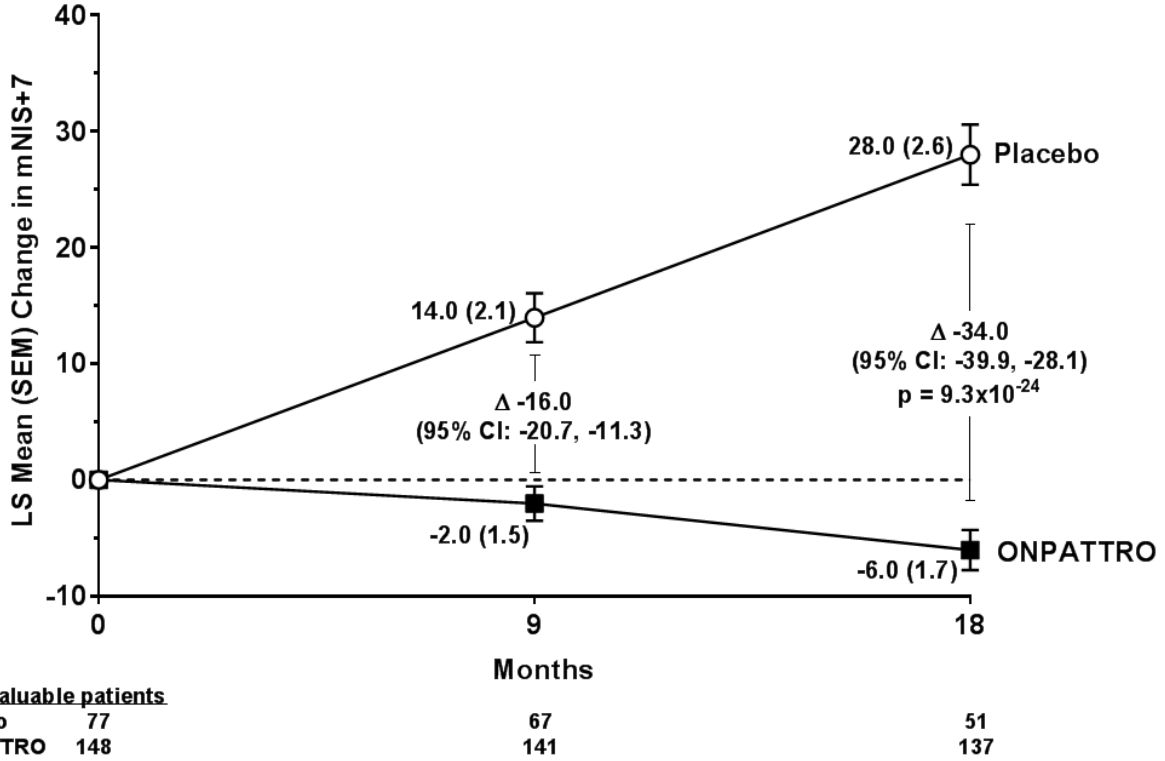
[a] All endpoints analyzed using the mixed-effective model repeated measures method.

[b] A lower value indicates less impairment/fewer symptoms.

[c] A higher number indicates less disability/less impairment.

[d] mBMI: body mass index (BMI: kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

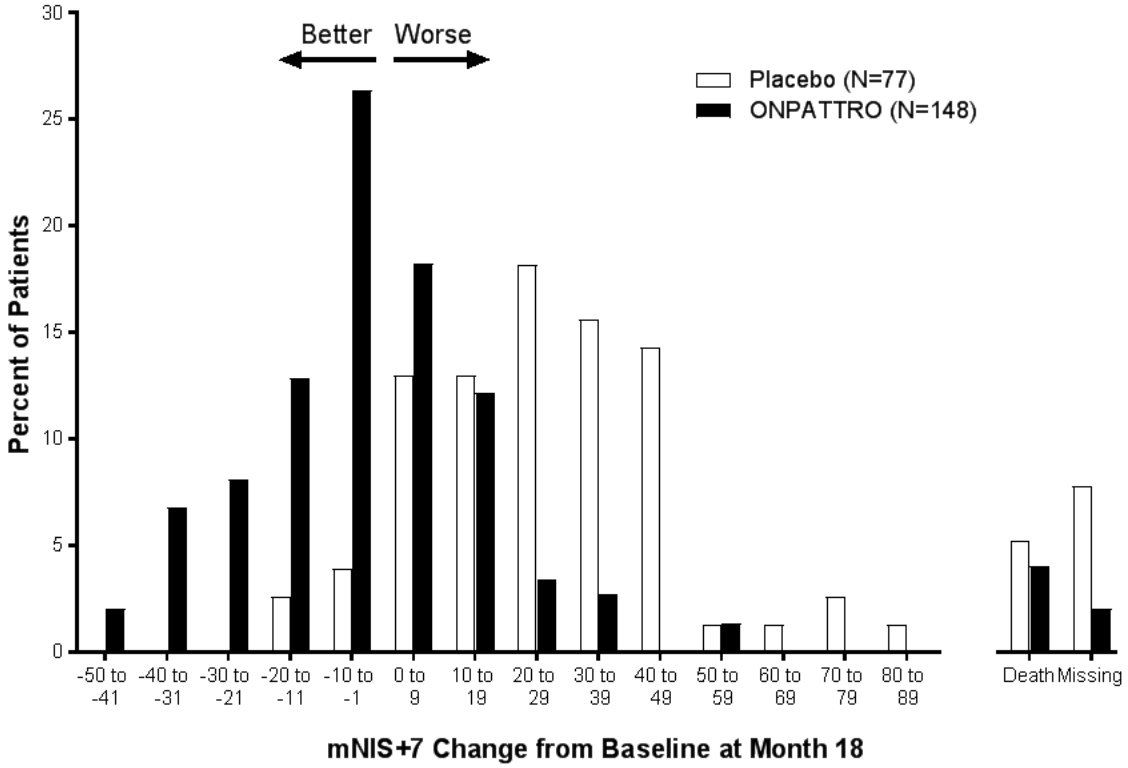
Figure 7: Change from Baseline in mNIS+7



A decrease in mNIS+7 indicates improvement.

Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for Onpattro – placebo.

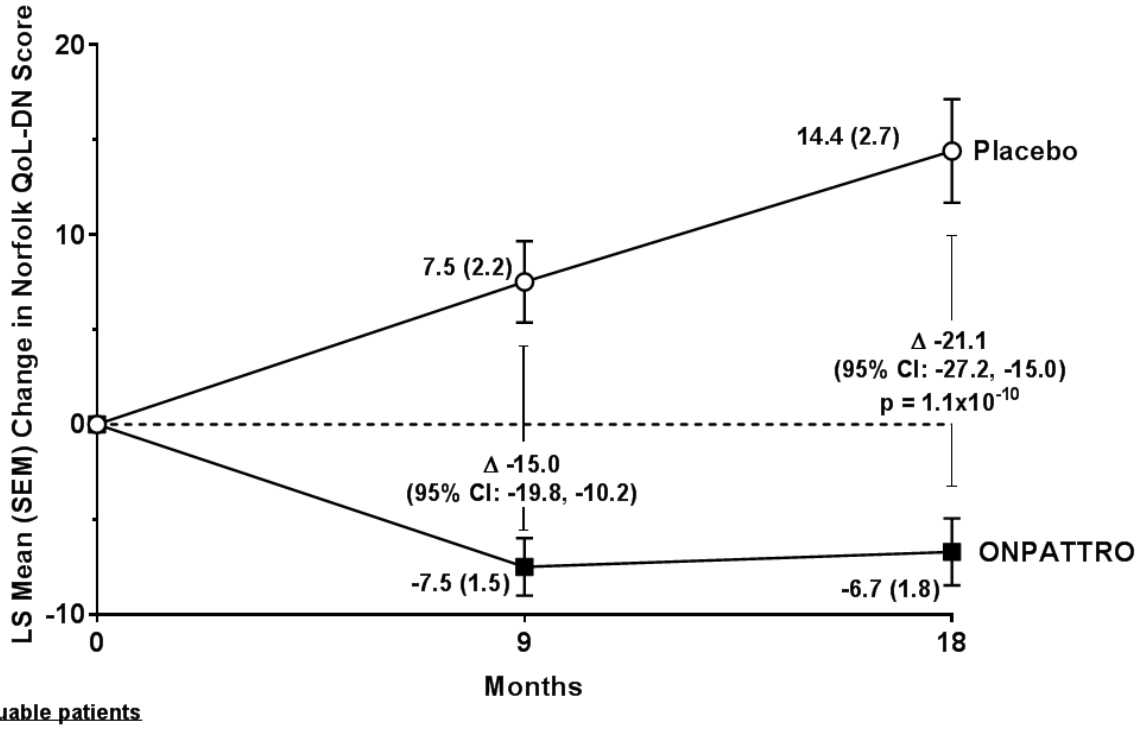
Figure 8: Histogram of mNIS+7 Change from Baseline at Month 18



mNIS+7 change scores are rounded to the nearest whole number; last available post-baseline scores were used.

Categories are mutually exclusive; patients who died before 18 months are summarized in the "Death" category only.

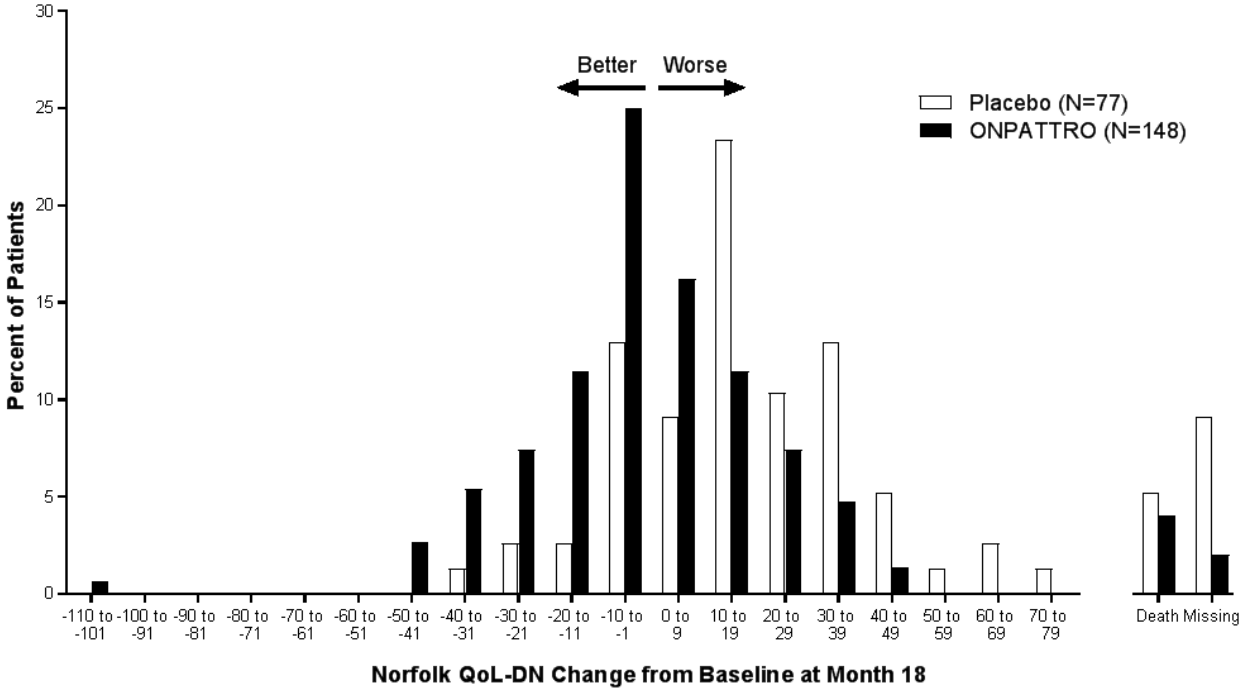
Figure 9: Change from Baseline in Norfolk QoL-DN Score



N of evaluable patients			
Placebo	76	65	48
ONPATTRO	148	141	136

A decrease in Norfolk QoL-DN score indicates improvement.
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for Onpattro – placebo.

Figure 10: Histogram of Norfolk QoL-DN Change from Baseline at Month 18



Norfolk QoL-DN change scores are rounded to the nearest whole number; last available post-baseline scores were used.
Categories are mutually exclusive; patients who died before 18 months are summarized in the "Death" category only.

Patients receiving Onpattro experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage.

Practice Guidelines and Position Statements

American Heart Association

The American Heart Association published a scientific statement in July 2020 intended to guide clinical practice and to facilitate management conformity by covering current diagnostic and treatment strategies, as well as unmet needs and areas of active investigation in ATTR-CM. (25)

Consensus Statements from European Network for Transthyretin-Mediated Amyloidosis-Familial Amyloid Polyneuropathy

Consensus statements from the European Network (2016) for transthyretin-mediated amyloidosis-familial amyloid polyneuropathy were published prior to the approval of patisiran and vutrisiran and, therefore, do not include any recommendation for these drugs. (26) These guidelines recommend that following a clinical suspicion, positive results from both biopsy and genetic analysis are essential to distinguish transthyretin-mediated amyloidosis-familial amyloid polyneuropathy from a large number of peripheral neuropathies.

Institute for Clinical and Economic Review (ICER)

The ICER (2018) published a Report on comparative effectiveness and value of patisiran for hereditary transthyretin-mediated amyloidosis. (10) Using criteria from the U.S. Preventive Services Task Force, the authors of the ICER rated the APOLLO trial to be of fair quality due to differential drop-out between treatment groups.

In summarizing the clinical evidence, the ICER Report observed that limitations in the clinical evidence include study populations that limit the generalizability of clinical outcomes to all hATTR patients, clinical outcome measures (mNIS+7 and Norfolk-QOL-DN) without defined thresholds for clinical significance, limited functional outcomes such as disease stage progression, and limited data on patients with cardiac involvement, especially among cardiac-dominant patients who are at a higher risk for mortality than patients with neuropathy-predominant hATTR. Further, there may be uncertainties related to the translation of neurologic outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of patisiran.

The Report concluded that for patisiran, there is moderate certainty of a substantial net health benefit with a high certainty of at least a small net health benefit compared to best supportive care, and therefore rated the clinical evidence for patisiran to be incremental or better ("B+").

National Institute for Health and Care Excellence
On August 14, 2019, the NICE issued highly specialized technologies guidance on patisiran for treating hereditary transthyretin amyloidosis. Patisiran is recommended, within its marketing authorization, as an option for treating hereditary transthyretin amyloidosis in adults with stage 1 and stage 2 polyneuropathy. It is recommended only if the company provides patisiran according to the commercial arrangement. (27)

On February 15, 2023, the NICE issued technology appraisal guidance on vutrisiran for treating hereditary transthyretin amyloidosis. Vutrisiran is recommended, within its marketing authorization, as an option for treating hereditary transthyretin-related amyloidosis in adults with stage 1 or stage 2 polyneuropathy. It is only recommended if the company provides vutrisiran according to the commercial arrangement. (28)

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 7.

Table 7. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT06465810[a]	Non-interventional Study of Patients With Transthyretin (ATTR) Amyloidosis (MaesTTRo)	1600	Dec 2031
Patisiran			
Ongoing			
NCT03997383[a]	APOLLO-B: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR Amyloidosis With Cardiomyopathy)	360	Mar 2027
NCT04561518[a]	ConTTRibute: A Global Observational Study of Patients With Transthyretin (TTR)-Mediated Amyloidosis (ATTR Amyloidosis)	1500	Sep 2030
NCT05873868	Myocardial Effects in Patients With hATTR With Polyneuropathy Treated With Patisiran or Vutrisiran (MyocardON-TTR)	20	Jul 2026
Vutrisiran			
Ongoing			

NCT04153149[a]	HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy	655	Dec 2026
NCT06679946[a]	A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy	800	Jun 2028
Unpublished			
NCT04201418[a]	A Phase 4 Multicenter Observational Study to Evaluate the Effectiveness of Patisiran in Patients With Polyneuropathy of Hereditary Transthyretin-Mediated (ATTRv) Amyloidosis With a V122I or T60A Mutation	67	May 2022 Completed no results

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0222, J0225

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	New medical document. Patisiran and Vutrisiran may be considered medically necessary for individuals with hereditary transthyretin-mediated amyloidosis polyneuropathy when criteria for initial treatment or continuation of treatment listed in Coverage are met. Vutrisiran may be considered medically necessary for individuals with cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis when criteria in coverage are met. Patisiran and vutrisiran are considered experimental, investigational and/or unproven for all other non-FDA indications or when the above criteria are not met.