

# Billing and Coding Guide

FOR

# AMVUTTRA<sup>®</sup> (vutrisiran)

**Hospital Outpatient  
Department**

February 2024

# Coverage, coding, and payment in the hospital outpatient department<sup>a</sup>

AMVUTTRA<sup>®</sup> (vutrisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.

## Coverage

- **For Medicare patients** receiving AMVUTTRA under Medicare Part B, the Medicare Administrative Contractors (MACs) may require additional chart documentation to determine the medical necessity of AMVUTTRA, although prior authorization is not required<sup>a,b</sup>
- **For patients enrolled in a Medicaid or commercial health plan**, AMVUTTRA coverage will vary by payer

## Payment

Payer Type	Payment Methodology
Medicare Fee-for-Service	Average Sales Price (ASP) + 6% <sup>c</sup>
Medicare Advantage, Medicaid, and commercial payers	Payment rates will vary by payer and provider contract

<sup>a</sup>It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact third-party payers for specific information on their coding, coverage, and payment policies.

<sup>b</sup>Medicare Advantage plans may require prior authorization for AMVUTTRA.

<sup>c</sup>Does not account for any required payment reductions if sequestration is in effect.

**Alnylam Field Reimbursement Directors** are available to meet with you and your staff to answer coverage, coding, and payment questions about AMVUTTRA. Contact Alnylam Assist<sup>®</sup> at 1-833-256-2748.

## Coding<sup>a</sup>

Please refer to the table below to support appropriate claims submission for AMVUTTRA<sup>®</sup> (vutrisiran).

Code Type	Code	Code Description
ICD-10-CM	E85.1	Neuropathic heredofamilial amyloidosis
CPT <sup>®b</sup>	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	J0225	Injection, vutrisiran, 1 mg (for dates of service on or after January 1, 2023)
Revenue	0250	General pharmacy
	0940	Other therapeutic services
	0636	Drugs requiring detailed coding
NDC	10-digit: 71336-1003-1 11-digit: 71336-1003-01	25 mg/0.5 mL single-dose prefilled syringe

<sup>a</sup>It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for products and services rendered. Providers should contact payers for specific information on their coding, coverage, and payment policies.

<sup>a</sup>CPT © 2019 American Medical Association. All rights reserved. CPT<sup>®</sup> is a registered trademark of the American Medical Association.

Applicable FARS/DFARS restrictions apply to government use.

Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

AMA=American Medical Association; CPT=Current Procedural Terminology; DFARS=Defense Federal Acquisition Regulation System; FARS=Federal Acquisition Regulation System; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; NDC=National Drug Code.

**Providers should consult the ICD-10-CM code book and use their own clinical judgment to confirm coding.**

# Hospital outpatient: sample UB-04 claim form

AMVUTTRA® (vutrisiran) and the associated services provided in a hospital outpatient setting are billed on the UB-04 claim form or its electronic equivalent. A sample UB-04 claim form for billing AMVUTTRA is provided on the next page.

- The sample UB-04 claim form for AMVUTTRA is for illustrative purposes
- It is the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for the products and services rendered
- Providers should contact payers for specific information on their coding, coverage, and payment policies
- Medicare claims require the use of the JW modifier (drug amount discarded/not administered to any patient) when applicable
  - Medicare requires the use of the new JZ modifier on any claims for single-use vials when there are no drug discarded amounts for dates of service on or after July 1, 2023
  - Wastage-reporting policies for payers other than Medicare may vary. Providers should check with their specific plans about policies related to billing for discarded drug and use of the JW and JZ modifiers
- Providers should contact their billing software vendors to ensure that they are utilizing the recommended loops and segments
- Payers may limit the charges on a single claim, rejecting claims over the specified limit. Providers should contact payers for information on claim charge limits and claims submission guidance

## Sample UB-04 Claim Form for AMVUTTRA® (vutrisiran)<sup>a</sup>

### Locator 42

List the appropriate revenue code for the service provided.

**For Medicare**, use the revenue code 0636—Drugs requiring detailed coding.

For payers other than Medicare, the revenue code for AMVUTTRA may vary, although some **commercial payers and Medicaid** accept revenue code 0250—General pharmacy.

### Locator 43

Enter the corresponding description for the revenue code listed in Locator 42  
OR enter the NDC (where applicable): N471336100301 ML1.

### Locator 44

Enter the appropriate HCPCS code:  
J0225—Injection, vutrisiran, 1 mg

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# Clean claim filing checklist

- ✓ **Select the appropriate primary diagnosis**
- ✓ **Confirm appropriate clinical documentation to support diagnosis**
- ✓ **Understand any payer-specific requirements (prior authorization, coding details, etc.)**
- ✓ **Utilize all appropriate ICD-10, CPT®, HCPCS, and Revenue codes**
  - For all claims in the hospital outpatient department setting, use HCPCS J0225 (Injection, vutrisiran, 1 mg)<sup>a</sup>
    - Remember: Billing unit = 1 mg
  - Remember to use the sample claim form on page 5 as a guide
- ✓ **Anticipate requests from payers for additional clinical information prior to claims being processed for payment**

It is always the provider's responsibility to determine the appropriate healthcare setting and to submit true and correct claims for those products and services rendered. Contact third-party payers for specific information on their coding and payment policies.

<sup>a</sup>HCPCS codes for AMVUTTRA® (vutrisiran) may vary for dates of service prior to January 1, 2023.

# Indication and Important Safety Information

## Indication

AMVUTTRA® (vutrisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

## Important Safety Information

### Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

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

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

### Adverse Reactions

The most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

For additional information about AMVUTTRA, please see the full [Prescribing Information](#).



8AM-6PM, Monday-Friday

📞: 1-833-256-2748 | 🖨️: 1-833-256-2747

**To learn more about AMVUTTRA<sup>®</sup>,  
visit [www.amvuttrahcp.com](http://www.amvuttrahcp.com)**



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMVUTTRA™ safely and effectively. See full prescribing information for AMVUTTRA.

**AMVUTTRA (vutrisiran) injection, for subcutaneous use**  
**Initial U.S. Approval: 2022**

### INDICATIONS AND USAGE

AMVUTTRA is a transthyretin-directed small interfering RNA indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

### DOSAGE AND ADMINISTRATION

- The recommended dosage of AMVUTTRA is 25 mg administered by subcutaneous injection once every 3 months. (2.1)
- AMVUTTRA is for subcutaneous use only and should be administered by a healthcare professional. (2.2)

### DOSAGE FORMS AND STRENGTHS

Injection: 25 mg/0.5 mL in a single-dose prefilled syringe. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND 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. (5.1)

### ADVERSE REACTIONS

The most common adverse reactions (≥5%) were pain in extremity, arthralgia, dyspnea, and vitamin A decreased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2023

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

AMVUTTRA is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dosage of AMVUTTRA is 25 mg administered by subcutaneous injection once every 3 months [see [Dosage and Administration \(2.2\)](#)].

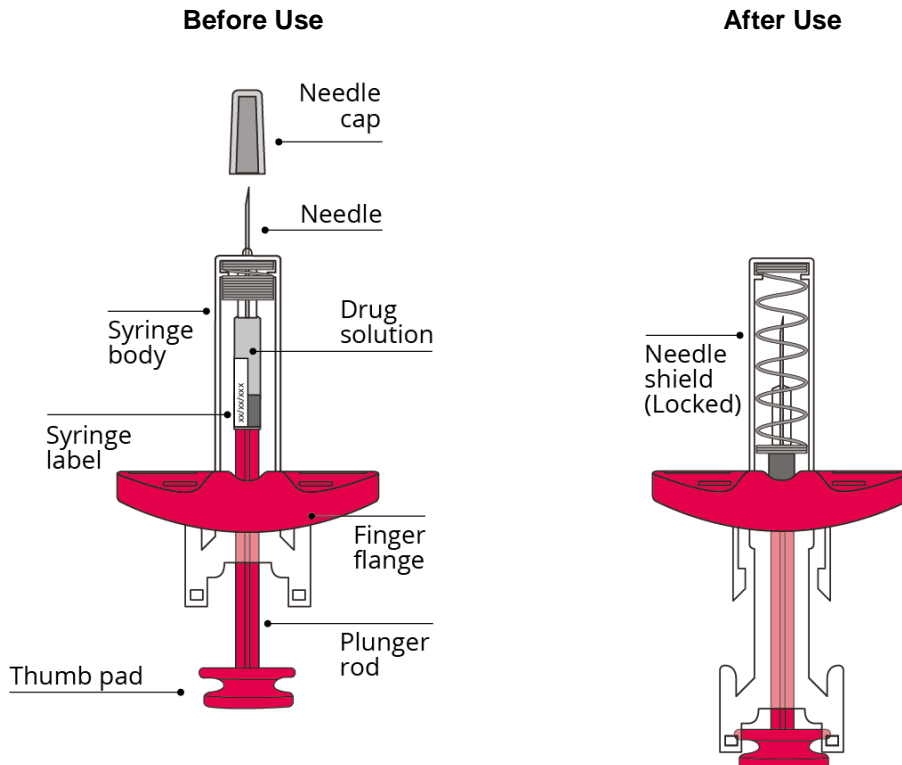
#### Missed Dose

If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

#### 2.2 Administration Instructions

AMVUTTRA is for subcutaneous use only and should be administered by a healthcare professional.

#### Syringe Appearance Before and After Use



#### Preparation and Administration

##### 1. Prepare the syringe

If stored cold, allow the syringe to warm to room temperature for 30 minutes prior to use.

Remove the syringe from the packaging by gripping the syringe body.

**Do not** touch the plunger rod until ready to inject.

Visually inspect the drug solution for discoloration and particulate matter prior to administration. AMVUTTRA is a sterile, preservative-free, clear, colorless-to-yellow solution. **Do not** use if it contains particulate matter or if it is cloudy or discolored.

Check the following:

- Syringe is not damaged, such as cracked or leaking
- Needle cap is attached to the syringe
- Expiration date on syringe label

**Do not** use the syringe if any issues are found while checking the syringe.

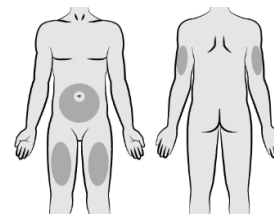
## 2. *Choose and prepare the injection site*

Choose an injection site from the following areas: the abdomen, thighs, or upper arms.

Avoid the following:

- 5-cm area around the navel
- Scar tissue or areas that are reddened, inflamed, or swollen

Clean the chosen injection site.



## 3. *Prepare the syringe for injection*

Hold the syringe body with one hand. Pull the needle cap straight off with other hand and dispose of needle cap immediately. It is normal to see a drop of liquid at the tip of the needle.

**Do not** touch the needle or let it touch any surface.

**Do not** recap the syringe.

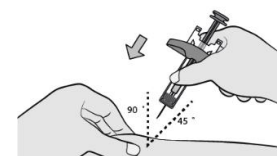
**Do not** use the syringe if it is dropped.



## 4. *Perform the injection*

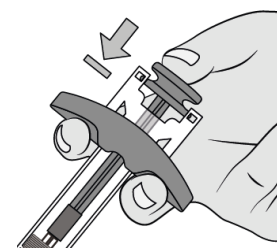
Pinch the cleaned skin.

Fully insert the needle into the pinched skin at a 45°-90° angle.



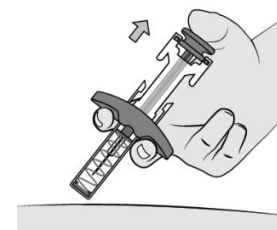
Inject all of the medication.

**Push the plunger rod as far as it will go** to administer the dose and activate the needle shield.



Release the plunger rod to allow the needle shield to cover the needle.

**Do not** block plunger rod movement.



## 5. *Dispose of the syringe*

**Immediately dispose** of the used syringe into a sharps container.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 25 mg/0.5 mL of vutrisiran as a clear, colorless-to-yellow solution in a single-dose prefilled syringe.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels [see [Adverse Reactions \(6.1\)](#) and [Clinical Pharmacology \(12.2\)](#)].

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

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

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Reduced Serum Vitamin A Levels and Recommended Supplementation [see [Warnings and Precautions \(5.1\)](#)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AMVUTTRA cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Study 1 [see [Clinical Studies \(14\)](#)], a total of 122 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received AMVUTTRA. Of these, 118 patients received at least 18 months of treatment. The mean duration of treatment was 18.8 months (range: 1.7 to 19.4 months). The median patient age at baseline was 60 years and 65% of the patients were male. Seventy percent of AMVUTTRA-treated patients were Caucasian, 17% were Asian, 3% were Black, and 9% were reported as Other. Forty-four percent of patients had the Val30Met mutation in the transthyretin gene; the remaining patients had one of 21 other mutations. At baseline, 70% of patients were in Stage 1 of the disease and 30% were in Stage 2.

The most common adverse reactions (at least 5%) were pain in extremity, arthralgia, dyspnea, and vitamin A decreased (see [Table 1](#)).

In Study 1, patients were instructed to take the recommended daily allowance of vitamin A [see [Warnings and Precautions \(5.1\)](#)]. Seventy-four percent of patients treated with AMVUTTRA had normal vitamin A levels at baseline, and 98% of those with a normal baseline developed low vitamin A levels. In some cases, the decreased vitamin A level was reported as an adverse reaction (see [Table 1](#)).

**Table 1: Adverse Reactions Reported in at least 5% of Patients Treated with AMVUTTRA (Study 1)**

Adverse Reaction	AMVUTTRA
	N=122 %
Pain in extremity*	15
Arthralgia*	11
Dyspnea*	7
Vitamin A decreased†	7
*Comprised of several similar terms	
†Percentage only reflects those reported as an adverse reaction	

Two serious adverse reactions of atrioventricular (AV) heart block (1.6%) occurred in patients treated with AMVUTTRA, including one case of complete AV block.

Injection site reactions were reported in 5 (4%) patients treated with AMVUTTRA. Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild and transient.

### 6.2 Immunogenicity

As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In Study 1, 3 (2.5%) patients treated with AMVUTTRA developed anti-drug antibodies. Although anti-drug antibody development was not found to affect the pharmacokinetics, safety, or efficacy of AMVUTTRA in these patients, the available data are too limited to make definitive conclusions.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no available data on AMVUTTRA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. AMVUTTRA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking AMVUTTRA. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by AMVUTTRA and of vitamin A supplementation are unknown [see [Warnings and Precautions \(5.1\)](#) and [Clinical Pharmacology \(12.2\)](#)].

In animal studies, subcutaneous administration of vutrisiran to pregnant rats resulted in developmental toxicity (reduced fetal body weight and embryofetal mortality) at doses associated with maternal toxicity (see [Data](#)).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

#### Data

##### *Animal Data*

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rats during the period of organogenesis resulted in embryofetal mortality at the high dose and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rabbits resulted in no adverse effects on embryofetal development.

Subcutaneous administration of vutrisiran (0, 5, 10, or 20 mg/kg) to pregnant rats every 6 days throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of vutrisiran in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMVUTTRA and any potential adverse effects on the breastfed infant from AMVUTTRA or from the underlying maternal condition.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

No dose adjustment is required in patients  $\geq 65$  years of age [see [Clinical Pharmacology \(12.3\)](#)]. A total of 46 (38%) patients  $\geq 65$  years of age, including 7 (6%) patients  $\geq 75$  years of age, received AMVUTTRA in Study 1. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

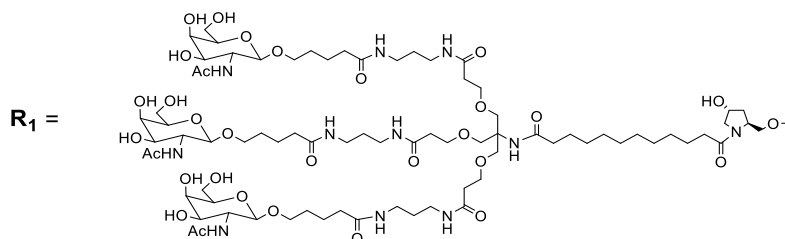
### **8.6 Renal Impairment**

No dose adjustment is recommended in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR]  $\geq 30$  to  $< 90$  mL/min/1.73 m<sup>2</sup>) [see [Clinical Pharmacology \(12.3\)](#)]. AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin  $\leq 1 \times$  ULN and AST  $>1 \times$  ULN, or total bilirubin  $>1.0$  to  $1.5 \times$  ULN and any AST) [see [Clinical Pharmacology \(12.3\)](#)]. AMVUTTRA has not been studied in patients with moderate or severe hepatic impairment.

AMVUTTRA contains vutrisiran, a chemically modified double-stranded small interfering ribonucleic acid (siRNA) that targets mutant and wild-type transthyretin (TTR) messenger RNA (mRNA) and is covalently linked to a ligand containing three *N*-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

**AF, CF, GF, UF** = 2'-F ribonucleosides  
**AM, CM, GM, UM** = 2'-OMe ribonucleosides  
 Dashed lines denote Watson-Crick base pairing



AMVUTTRA is supplied as a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous injection. Each 0.5 mL of solution contains 25 mg of vutrisiran (equivalent to 26.5 mg vutrisiran sodium), 0.2 mg sodium phosphate monobasic dihydrate, 0.7 mg sodium phosphate dibasic dihydrate, 3.2 mg sodium chloride, water for injection, and sodium hydroxide and/or phosphoric acid to adjust the pH to ~7.

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.

In Study 1 [see [Clinical Studies \(14\)](#)], following administration of the recommended AMVUTTRA dosage every 3 months to patients with hATTR amyloidosis, vutrisiran reduced mean serum TTR at steady state by 83%. Similar TTR reductions were observed regardless of Val30Met genotype status, weight, sex, age, or race.

At a dose 12 times the recommended dosage of 25 mg once every three months, AMVUTTRA does not prolong the QT interval to any clinically relevant extent.

### 12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of AMVUTTRA were evaluated following a single dose in healthy subjects and multiple doses in patients with hATTR amyloidosis, as summarized in [Table 2](#).

**Table 2: Pharmacokinetic Parameters of Vutrisiran**

	Vutrisiran
<b>General Information</b>	
<b>Dose Proportionality</b>	Vutrisiran C <sub>max</sub> showed dose proportional increase while AUC <sub>last</sub> and AUC <sub>inf</sub> were slightly more than dose proportional following single subcutaneous doses ranging from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose)
<b>Accumulation</b>	No accumulation of vutrisiran was observed in plasma after repeated every 3 months dosage*
<b>Absorption</b>	
<b>T<sub>max</sub> [Median (Range)]</b>	4 (0.17, 12.0) hours <sup>†</sup>
<b>Distribution</b>	
<b>Estimated Vd/F (%RSE)</b>	10.1 (5.8) L <sup>‡</sup>
<b>Protein Binding</b>	80% <sup>§</sup>
<b>Organ Distribution</b>	Vutrisiran distributes primarily to the liver after subcutaneous dosing
<b>Elimination</b>	
<b>Half-Life [Median (Range)]</b>	5.2 (2.2, 6.4) hours <sup>†</sup>
<b>Apparent Clearance [Median (Range)]</b>	21.4 (19.8, 30) L/hour <sup>†</sup>
<b>Metabolism</b>	
<b>Primary Pathway</b>	Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver
<b>Excretion</b>	
<b>Primary Pathway</b>	The mean fraction of unchanged vutrisiran eliminated in urine was approximately 19.4% at the recommended dose of 25 mg. The mean renal clearance of vutrisiran ranged from 4.5 to 5.7 L/hour <sup>¶</sup>
<p>AUC<sub>inf</sub> = area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC<sub>last</sub> = area under the concentration-time curve from the time of dosing to the last measurable concentration; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; RSE = relative standard error; T<sub>max</sub> = time to maximum concentration; Vd/F = apparent volume of distribution</p> <p>*After 25 mg every 3 months dosage in hATTR amyloidosis patients</p> <p><sup>†</sup>After 25 mg single dose in healthy subjects</p> <p><sup>‡</sup>Based on population PK model estimation</p> <p><sup>§</sup>Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 mcg/mL to 19% at 50 mcg/mL)</p> <p><sup>¶</sup>After single subcutaneous vutrisiran dose from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose) in healthy subjects</p>	

#### Specific Populations

No clinically significant differences in the pharmacokinetics of vutrisiran were observed based on age, sex, race, mild and moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m<sup>2</sup>), or mild hepatic impairment (total bilirubin ≤ 1 x ULN and AST > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST). Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, moderate or severe hepatic impairment, or in patients with prior liver transplant.



### Drug Interaction Studies

No clinical drug-drug interaction studies have been performed with vutrisiran. In vitro studies suggest that vutrisiran is not a substrate or inhibitor of cytochrome P450 enzymes. Vutrisiran is not expected to cause drug-drug interactions by inducing CYP enzymes or modulating the activities of drug transporters.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Subcutaneous administration of vutrisiran to male rats (0, 4, 7.5, or 15 mg/kg once every 4 weeks or 15 mg/kg once every 12 weeks) for 99 weeks and to female rats (0, 6, 12.5, or 25 mg/kg once every 4 weeks or 25 mg/kg once every 12 weeks) for 86-87 weeks resulted in no increase in tumors.

#### Mutagenesis

Vutrisiran was negative for mutagenicity in in vitro (bacterial mutagenicity, chromosomal aberration in human blood peripheral lymphocytes) and in vivo (rat bone marrow micronucleus) assays.

#### Impairment of Fertility

Subcutaneous administration of vutrisiran (0, 15, 30, or 70 mg/kg/week) to male and female rats prior to and during mating and continuing in females to gestation day 6 resulted in no adverse effects on fertility or reproductive performance.

## **14 CLINICAL STUDIES**

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 3, 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 3].



**Table 3: 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)

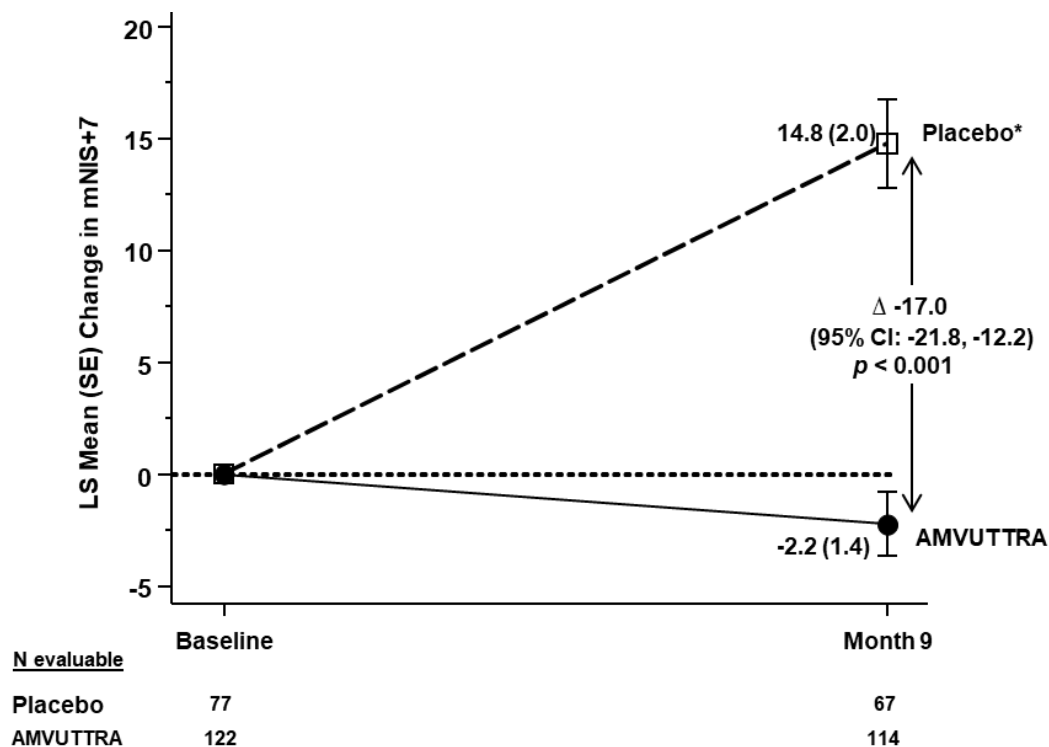
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method

‡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<sup>2</sup>) multiplied by serum albumin (g/L).

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

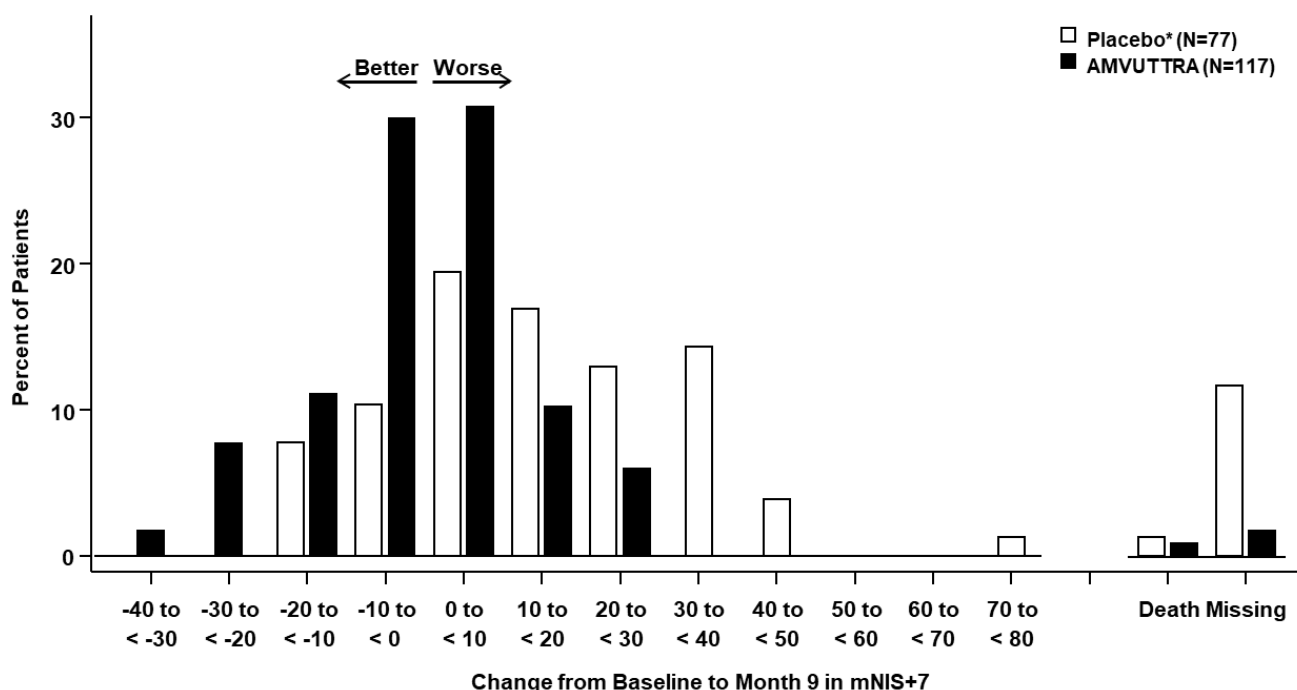


A decrease in mNIS+7 indicates improvement

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

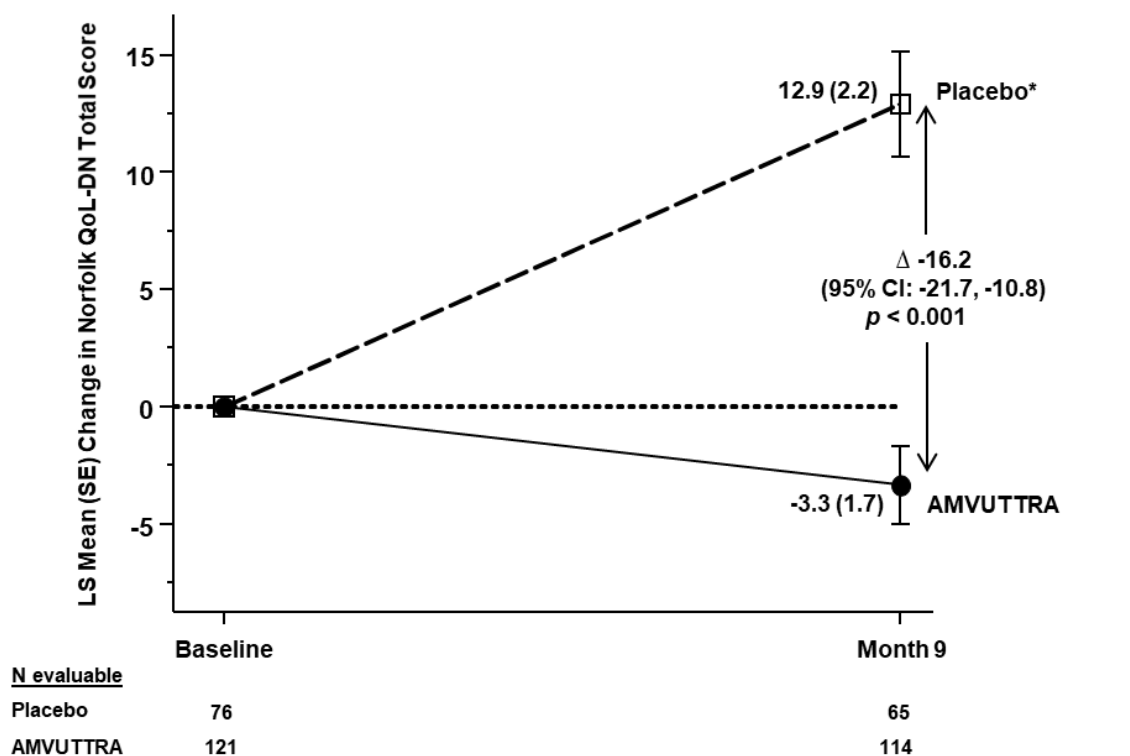
\*External placebo group from another randomized controlled trial (NCT01960348)

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



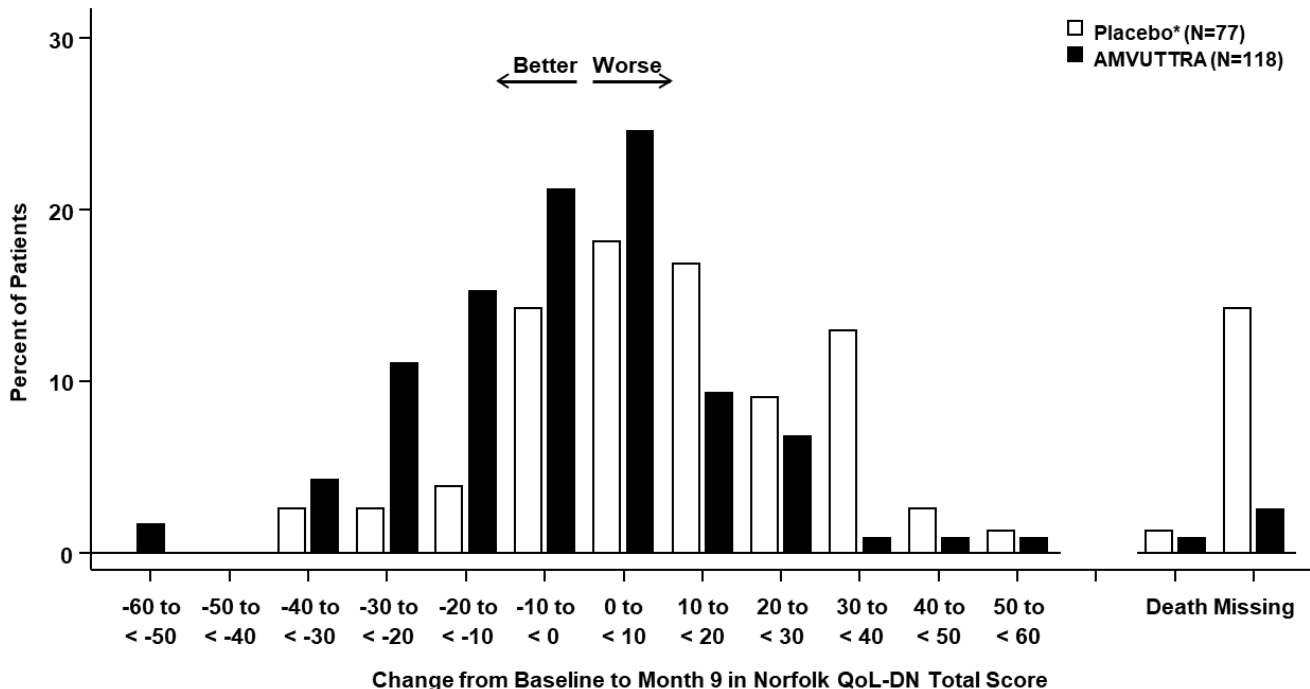
Categories are mutually exclusive; patients who died before 9 months are summarized in the "Death" category only  
 \*External placebo group from another randomized controlled trial (NCT01960348)

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



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 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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

AMVUTTRA is a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous injection. AMVUTTRA is supplied as 25 mg/0.5 mL solution in a single-dose 1-mL prefilled syringe made from Type I glass with stainless steel 29-gauge needle with a needle shield. The prefilled syringe components are not made with natural rubber latex.

AMVUTTRA is available in cartons containing one single-dose prefilled syringe each.

The NDC is: 71336-1003-1.

### 16.2 Storage and Handling

Store at 2°C to 30°C (36°F to 86°F) in the original carton, until ready for use. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

### Recommended Vitamin A Supplementation

Inform patients that AMVUTTRA treatment leads to a decrease in serum vitamin A levels. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) and refer them to an ophthalmologist if they develop these symptoms [see [Warnings and Precautions \(5.1\)](#)].

### Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking AMVUTTRA they should inform their healthcare provider. Inform patients of the potential risk to the fetus, including that AMVUTTRA treatment leads to a decrease in serum vitamin A levels [see [Use in Specific Populations \(8.1\)](#) and [Clinical Pharmacology \(12.2\)](#)].

Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142

AMVUTTRA is a pending trademark of Alnylam Pharmaceuticals, Inc.