amvuttra® (vutrisiran) injection 25 mg/0.5 mL

AMVUTTRA® (vutrisiran) Access and Reimbursement Guide

Alnylam ASSIST®

8AM–6PM, Monday–Friday **1-833-256-2748** **1-833-256-2747**

To learn more, visit **www.AlnylamAssist.com/hcp/amvuttra**

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After determining that AMVUTTRA is clinically appropriate for a patient, starting treatment without delay is critical to managing their disease. This guide covers the access and reimbursement process for AMVUTTRA and can help get patients started.

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How to use this guide:

This guide provides information on the access and reimbursement process for AMVUTTRA.
Use the table of contents and the tabs above throughout to move through this guide.
Resources that are referenced within this guide are linked and available at www.amvuttrahcp.com.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Conduct benefit verification and choose the patient's site of care

Confirming the patient's benefits is an important step in assessing the best approach to acquiring AMVUTTRA for the patient's treatment.

Benefit verification

Coverage and site of care options for AMVUTTRA will vary by insurance plan and on practice or health system preferences. Alnylam Assist® can help.

- An Alnylam Case Manager can provide support by conducting a benefit verification and sending a summary within 2 business days of submitting a Start Form. More information about Alnylam Assist® support services can be found on the **next page**
- The practice or health system can confirm the patient's benefits with their insurance plan and move forward with the preferred acquisition method

More information about the benefit verification process can be found on **page 7**.

Determine site of care

AMVUTTRA offers flexibility for where patients can receive treatment.[a]

In office/within the health system

AMVUTTRA can be acquired through the buy-and-bill process to be administered in office or at a site of care within the health system

Alternate site of care

The HCP may refer the patient to receive AMVUTTRA at a local clinic or infusion center. The alternate site of care acquires AMVUTTRA for administration

Patient's home

Home administration may be an option for some patients if covered by their insurance plan

[a]Some insurance plans may have a site of care policy that requires patients to be treated in a particular setting.

HCP=healthcare professional.

Support services through Alnylam Assist®

Alnylam Assist® offers support services to patients and healthcare professionals, including:

- AMVUTTRA coverage, prior authorization, coding, reimbursement education, and patient-specific benefit verification
- Low or no-cost programs for eligible patients,[a] including copay support, a Patient Assistance Program, and a Quick Start Program
- One-on-one support for healthcare professionals and their patients throughout their treatment journey

How to get started with Alnylam Assist®

- Submit a Start Form to access all Alnylam Assist® services for the patient
- If you choose not to submit a Start Form, you may still access some Alnylam Assist® services individually

To learn more, contact your local Alnylam representative, or scan or click to visit www.AlnylamAssist.com/hcp/amvuttra

Alnylam ASSIST®

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To learn more, visit **www.AlnylamAssist.com/hcp/amvuttra**

[a]Patients must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the program at any time.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Flexible acquisition options for AMVUTTRA

AMVUTTRA can be obtained through a specialty distributor or a specialty pharmacy (SP).

	Confirm insurance coverage and select an acquisition method	
Step 1: Conduct benefit verification Verify benefits based on the patient's insurance plan and complete a PA if required	**AMVUTTRA is predominantly covered under the medical benefit**	In some cases, AMVUTTRA may be covered under the pharmacy benefit
Step 2: Order AMVUTTRA Order AMVUTTRA through the preferred acquisition process or based on the patient's insurance requirements	**The HCP office, health system, or alternate site of care acquires AMVUTTRA through the buy-and-bill process by ordering via a specialty distributor**	The SP handles the acquisition process and delivers AMVUTTRA to the site of care or the patient's home for administration
Step 3: Administer AMVUTTRA Review OOP costs and confirm appointment for administration with the patient	**AMVUTTRA is administered to the patient**	AMVUTTRA is administered to the patient
Step 4: Submit claim Submit a reimbursement claim to the patient's insurance plan	**The HCP office, health system, or alternate site of care submits the claim to the insurance plan for product reimbursement**	No action for HCP
Step 5: Receive reimbursement Track reimbursement	**The HCP office, health system, or alternate site of care receives reimbursement from the patient's insurance plan**	The SP manages product reimbursement

HCP=healthcare professional; OOP=out-of-pocket; PA=prior authorization.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

AMVUTTRA buy-and-bill process overview

Use this checklist to help navigate the buy-and-bill fulfillment pathway.

VERIFY BENEFITS

- ❑ Alnylam Assist® can help verify the patient's benefits or the office can choose to verify benefits directly with the patient's insurance plan. See page 7 for more information
- ❑ Review coverage with the patient, including any utilization requirements, such as PA criteria, payer site of care requirements, and OOP costs

ORDER AMVUTTRA

- ❑ Purchase AMVUTTRA through the specialty distributor. See contact information on page 10

ADMINISTER AMVUTTRA

- ❑ Collect the patient's copay or coinsurance according to the office's billing practices at time of visit
- ❑ Administer AMVUTTRA as described in section 2.2 of the Prescribing Information. See page 12 for more information
- ❑ Schedule the patient's next appointment

SUBMIT CLAIM

- ❑ Fill out a CMS-1500 form for billing prescribed medications administered in an **HCP's office**. See page 14 for more information

OR

- ❑ Fill out a CMS-1450 (UB-04) form for billing prescribed medications administered in a **hospital outpatient setting**. See page 15 for more information

MANAGE REIMBURSEMENT

- ❑ Process payment claims for **product reimbursement and administration** as applicable
- ❑ Review the remittance advice (also referred to as an explanation of benefits) to ensure appropriate payment has been received
- ❑ File an appeal, if the claim is rejected or denied
  - An Alnylam Field Reimbursement Team member at Alnylam Assist® can offer education on the appeals process

CMS=Centers for Medicare & Medicaid Services; HCP=healthcare professional; OOP=out-of-pocket; PA=prior authorization.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Navigating insurance requirements for AMVUTTRA

Benefit verification

A benefit verification should be conducted for the patient after they are prescribed AMVUTTRA. Alnylam Assist® can help verify the patient's benefits and/or the HCP office/health system can choose to verify benefits directly with the patient's insurance plan.

Benefit verification completed by Alnylam Assist®

- An Alnylam Case Manager can provide support by conducting a benefit verification and sending a summary within 2 business days of submitting a Start Form
- Alnylam Case Managers can also explain the requirements and processes for prior authorizations, claims, and appeals
- Alnylam Assist® can provide information about patient financial assistance programs for eligible patients,[a] if necessary

Benefit verification completed by the HCP office or health system

- Contact the patient's insurance plan to confirm their benefits
- Review coverage with the patient, including any utilization requirements, such as PA criteria, payer site of care requirements, and OOP costs

If a patient's insurance or site of care changes, a new benefit investigation must be completed

[a]Patients must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the program at any time.

HCP=healthcare professional; PA=prior authorization; OOP=out-of-pocket.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Navigating insurance requirements for AMVUTTRA (cont.)

Prior authorization (PA)

Payers may require documentation of medical necessity criteria, drug information, and other information to support a PA and coverage decision making for AMVUTTRA. The level of information may vary based on payer requirements. To receive the most up-to-date information about payer requirements, please visit the health plan's website.

For questions related to PA, please reach out to your local Alnylam Field Reimbursement Team contact. To get in contact, please call Alnylam Assist® at 1-833-256-2748

Get educational resources for navigating insurance requirements

- Sample Letters of Medical Necessity for supplementing a coverage request
- AMVUTTRA Coverage and Prior Authorization Checklists for information on general payer requirements

Visit www.AlnylamAssist.com/hcp/amvuttra to access these resources

This document is provided for informational purposes only. It is the sole responsibility of the healthcare professional to ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient. Coverage and reimbursement may vary significantly by payer, plan, patient, and setting of care. Healthcare professionals should always check with payers to confirm coverage requirements.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Understanding coverage for patients

AMVUTTRA is accessible and affordable for most patients, regardless of insurance type

- AMVUTTRA is predominantly covered under the medical benefit
- Most patients receive coverage through Medicare[1]
- Access to AMVUTTRA usually does not require prior authorization for Medicare Fee-for-Service (FFS) Part B
- Prior authorization may be required for Medicare Advantage patients or patients with commercial insurance

Most patients treated with AMVUTTRA pay $0 out-of-pocket[2]

Low or no-cost financial assistance programs are available for eligible patients,[a] including copay support, a Patient Assistance Program, and a Quick Start Program

To learn more about financial assistance programs, scan or click to visit **www.AlnylamAssist.com/hcp/amvuttra**

[a]Patients must meet specified eligibility criteria to qualify for assistance. Alnylam reserves the right to make eligibility determinations and to modify or discontinue the program at any time.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Specialty distributors and specialty pharmacies for AMVUTTRA

AMVUTTRA can be acquired directly from the specialty distributor or through a specialty pharmacy and should be administered by an HCP.[3] Please contact the following authorized specialty distributors or specialty pharmacies.

Specialty distributors

McKesson Plasma and Biologics

Phone: 1-877-625-2566

(E.g., independent physicians/clinics)

McKesson Medical-Surgical

Phone: 1-855-571-2100

(E.g., ordering contact information: McKesson Medical-Surgical Customer Service)

McKesson Specialty Health (for multi-specialty customers)

Phone: 1-855-477-9800

(E.g., hospitals, VA/government, hospital outpatient/340B, specialty pharmacies, retail accounts)

Specialty pharmacies

Accredo Health Group Inc.

Phone: 1-866-581-5248

CVS Specialty

Phone: 1-866-526-4984

Orsini

Phone: 1-800-372-9581

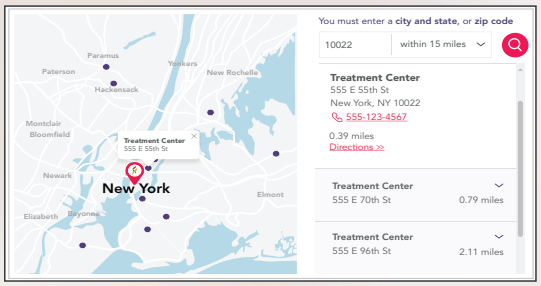
PANTHERx

Phone: 1-833-789-3419

HCP=healthcare professional; VA=US Department of Veterans Affairs.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Locate a treatment center near the patient



You can refer patients to an alternate site of care which will purchase and administer AMVUTTRA. The **AMVUTTRA Treatment Center Directory** can help locate the treatment center closest to the patient.

Locate an alternate site of care

- ❑ Visit the **AMVUTTRA Treatment Center Directory** to locate a treatment center for the patient
- ❑ Contact a member of the Alnylam Field Reimbursement Team who can provide education on how to select a treatment site

Refer the patient to the alternate site of care

- ❑ Call the alternate site of care to confirm that the site can administer AMVUTTRA and collect information about the process for referring patients to their site for administration
- ❑ Send required information to the alternate site of care

Follow-up after administration

- ❑ Ensure the patient has received AMVUTTRA and has scheduled their next appointment

The AMVUTTRA Treatment Center Directory is for informational purposes only. No fees or other remuneration have been or will be exchanged for a treatment center's inclusion in this database. Inclusion of centers in this database will be based on opt-in approval by authorized personnel for those sites listed. Inclusion in this database does not represent an endorsement of, recommendation for, or referral to the treatment centers listed in this database by Alnylam Pharmaceuticals. Likewise, participating treatment centers do not necessarily administer or endorse any Alnylam products.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Administering AMVUTTRA

Consider the following during the patient's visit for AMVUTTRA administration

Review the patient's OOP costs before AMVUTTRA is administered

Collect the copay or coinsurance according to the office's billing practices

Administer AMVUTTRA as described in section 2.2 of the Prescribing Information

- Reference the **AMVUTTRA Administration Guide** for step-by-step instructions

Schedule the patient's next appointment

- The next dose of AMVUTTRA should be administered after 3 months[3]

OOP=out-of-pocket.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Relevant codes for AMVUTTRA claims

The following codes can be used to support appropriate claims submissions for AMVUTTRA.[a]

Code Type	Code	Code Description
ICD-10-CM[4]	E85.1	Neuropathic heredofamilial amyloidosis (includes transthyretin-related (ATTR) familial amyloid polyneuropathy)
	E85.82	Wild-type transthyretin-related (ATTR) amyloidosis
	E85.4	Organ-limited amyloidosis (includes transthyretin-related (ATTR) familial amyloid cardiomyopathy)
CPT©[b]	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	J0225	Injection, vutrisiran, 1 mg
NDC[3]	10-digit: 71336-1003-1 11-digit: 71336-1003-01	25 mg/0.5 mL single-dose prefilled syringe

[a]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.

[b]CPT © 2025 American Medical Association. All rights reserved. CPT® 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.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Sample CMS-1500 claim form for AMVUTTRA

AMVUTTRA and the associated services provided in a **physician office** are billed on the CMS-1500 claim form or its electronic equivalent. A sample CMS-1500 claim form for billing AMVUTTRA is provided below.

Locator 21

Enter the appropriate primary diagnosis code from the patient's medical record in Locator 21A.

Locator 21ICD-IND

Enter "0" to indicate use of ICD-10-CM diagnosis coding system.

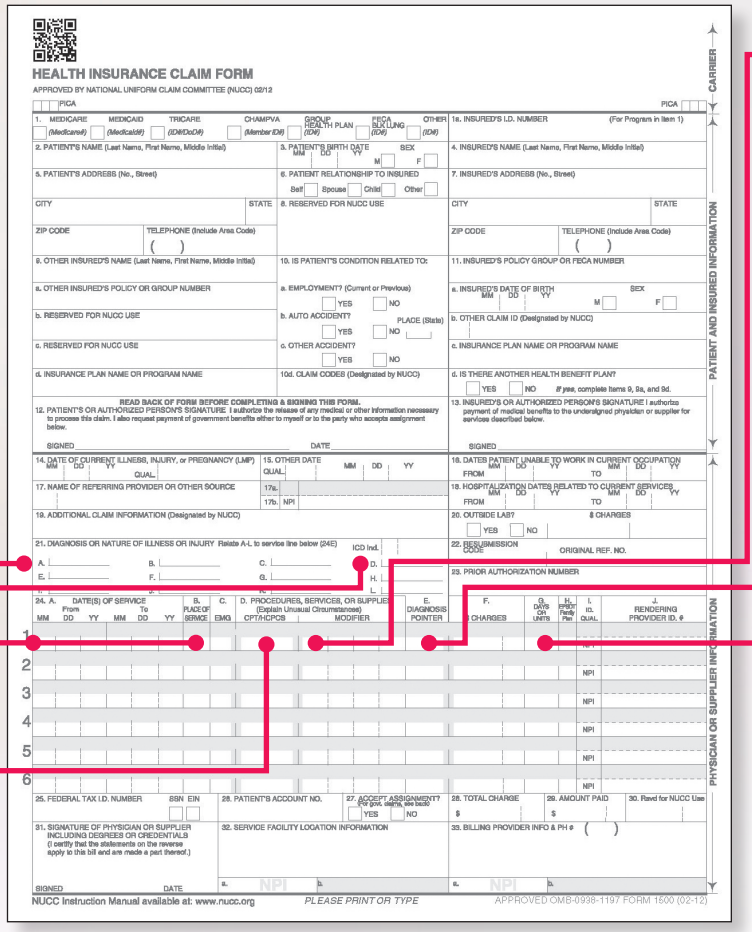
Locator 24A-B

Enter the date of service and the appropriate place of service code.

Locator 24

Enter the HCPCS code J0225 first, followed by the CPT code 96372 for the drug administration after the J0225 entries.

- 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


HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) | MEDICAID (Medicaid#) | TRICARE (ID#/DoD#) | CHAMPVA (Member ID#) | GROUP HEALTH PLAN (ID#) | FECA BLK LUNG (ID#) | OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY | SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self | Spouse | Child | Other

7. INSURED'S ADDRESS (No., Street)

CITY | STATE

8. RESERVED FOR NUCC USE

CITY | STATE

ZIP CODE | TELEPHONE (Include Area Code) ( )

ZIP CODE | TELEPHONE (Include Area Code) ( )

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY | SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? YES NO PLACE (State)

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO If yes, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.

15. OTHER DATE MM DD YY QUAL.

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM TO

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE

17a.

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM TO

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. B. C. D. E. F. G. H. I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY	To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H. EPSDT Family Plan	I. ID. QUAL.	J. RENDERING PROVIDER ID. #
1											NPI
2											NPI
3											NPI
4											NPI
5											NPI
6											NPI

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For gov. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

Locator 24D

Enter HCPCS code J0225 – Injection, vutrisiran, 1 mg.

In shaded area of Locator 24D, enter the NDC (when applicable): N471336100301 ML1.

Locator 24E

Specify the diagnosis, from Locator 21, that relates to the product of procedure listed in Locator 24D.

Locator 24G

Enter the number of service units for each line item.

Please note, the sample CMS-1500 claim form 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.

CMS=Centers for Medicare & Medicaid Services; CPT=Current Procedural Terminology; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; NDC=National Drug Code.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Sample UB-04 claim form for AMVUTTRA

AMVUTTRA and the associated services provided in a **hospital outpatient setting** are billed on the UB-04 (CMS-1450) claim form or its electronic equivalent. A sample UB-04 claim form for billing AMVUTTRA is provided below.

Locator 42

List the appropriate revenue code for the service provided.

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

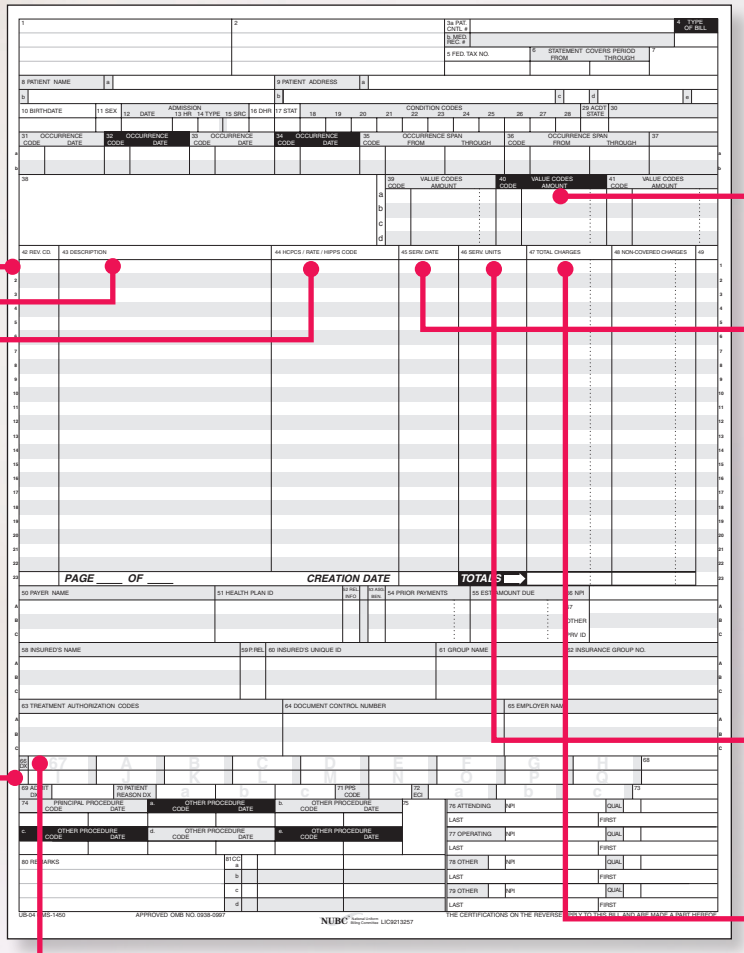
For payers other than Medicare, the revenue code for AMVUTTRA may vary, although some **commercial payers and Medicaid** accept revenue code 0250—General pharmacy.

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.



Locator 40

Enter HCPCS code J0225 on the first line.

- 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

Locator 45

Enter the service date.

Locator 46

Enter the number of service units for each line item.

Locator 47

Enter the total charge for each line item.

Locator 66

Enter "0" to indicate use of the ICD-10-CM diagnosis coding system.

Locator 67

Enter the primary diagnosis code.

Please note, the sample UB-04 claim form 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.

CMS=Centers for Medicare & Medicaid Services; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; NDC=National Drug Code.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

Manage reimbursement

Consider the following to manage reimbursement claims for AMVUTTRA

Understand the reimbursement rate based on the plan contract and published fee schedules prior to administering AMVUTTRA. Periodically review these rates and fee schedules for updates. Reimbursement rates vary based on individual insurance plans

If a patient is enrolled in the **Alnylam Assist® Copay Program**, refer to the **Copay Claim Submission Guide** for additional information on how to submit a claim for AMVUTTRA

Allocate an experienced staff member to track billing and scheduling

Audit claims on a regular basis

If a claim is denied, an **appeal can be filed** by the HCP office or health system. If a claim is denied at an alternate site of care, the prescribing HCP may need to complete the information required for an appeal

Alnylam ASSIST®

For questions, please reach out to your local Alnylam Field Reimbursement Team contact. To get in contact, please call Alnylam Assist® at 1-833-256-2748

HCP=healthcare professional.

Please see Indications and Important Safety Information on page 17 and full Prescribing Information.

TO LEARN MORE ABOUT AMVUTTRA

Scan or click to visit
www.amvuttrahcp.com

Indications and Important Safety Information

Indications

AMVUTTRA® (vutrisiran) is indicated for the treatment of the:

- cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits.
- polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) 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

In a study of patients with hATTR-PN, 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%).

In a study of patients with ATTR-CM, no new safety issues were identified.

For additional information about AMVUTTRA, please see the full Prescribing Information.

References: 1. Chen H, Chandrashekar P, Fischer K, et al. Navigating the complex web of prescribing amyloidosis therapeutics: a primer. *J Am Heart Assoc*. 2022;11(7):e023895. **2.** Data on file. Alnylam Pharmaceuticals, Inc. **3.** AMVUTTRA Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc. **4.** Centers for Medicare & Medicaid Services. ICD-10. Accessed March 20, 2025. https://www.cms.gov/medicare/coding-billing/icd-10-codes

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amvuttra (vutrisiran) injection 25 mg/0.5 mL

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

----------RECENT MAJOR CHANGES----------
Indication and Usage (1) 3/2025

----------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 (1.1)
- the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits (1.2)

----------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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis

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

1.2 Cardiomyopathy of Wild-type or Hereditary Transthyretin-mediated Amyloidosis

AMVUTTRA is indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits.

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

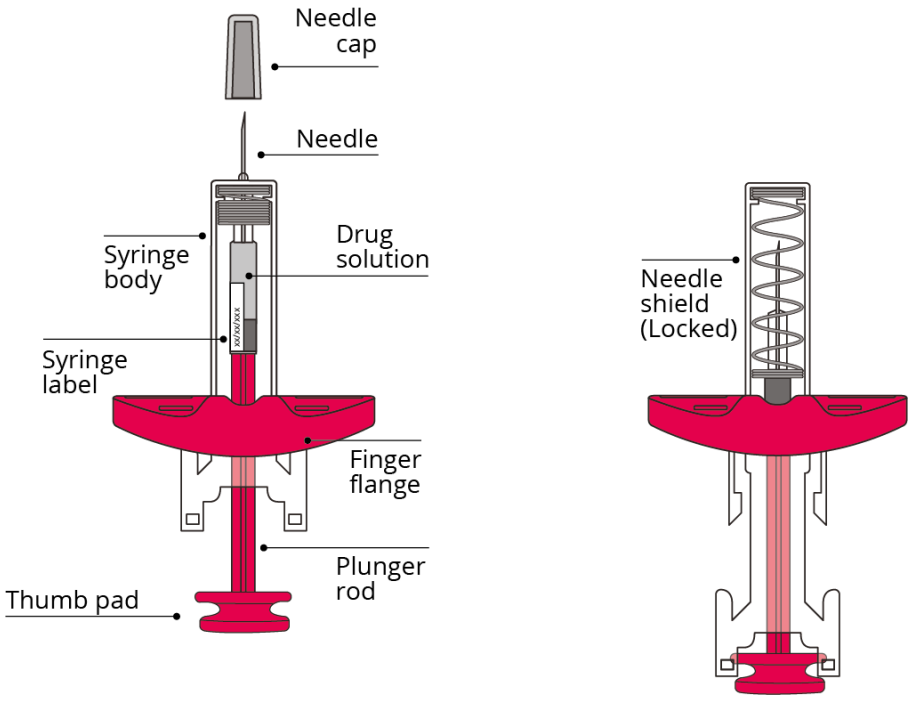
If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

2.2 Administration Instructions

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

Syringe Appearance Before and After Use

Before Use **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.

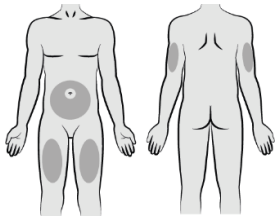
   Check the following:

   - 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.

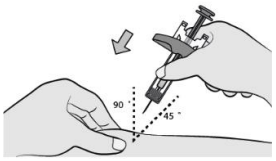
   Do not recap the syringe.

   Do not use the syringe if it is dropped.

4. *Perform the injection*

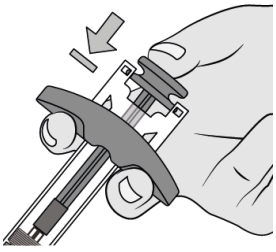
   Pinch the cleaned skin.

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

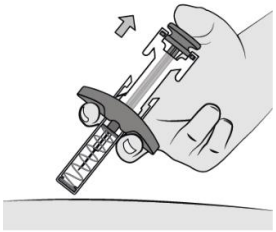
   Inject all of the medication.

   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.

Two Phase 3 randomized, multi-center studies evaluated the safety of AMVUTTRA in 448 transthyretin-mediated amyloidosis (ATTR) patients, including 122 patients with hATTR-PN (HELIOS-A) and 326 patients with ATTR-CM (HELIOS-B) *[see Clinical Studies (14)]*. In both studies, patients were instructed to take the recommended daily allowance of vitamin A *[see Warnings and Precautions (5.1)]*.

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis

In HELIOS-A, 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)*.

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 in HELIOS-A

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

In HELIOS-A, 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.

Cardiomyopathy of Wild-type or Hereditary Transthyretin-mediated Amyloidosis

In HELIOS-B, safety was evaluated in 654 patients with ATTR-CM, which included 257 patients treated with AMVUTTRA for ≥30 months, and 77 patients treated with AMVUTTRA for ≥36 months *[see Clinical Studies (14)]*. No new safety issues were identified. Eighty-two percent of patients treated with AMVUTTRA had normal vitamin A levels at baseline, and 80% of those with a normal baseline developed low vitamin A levels.

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 ≥65 years of age *[see Clinical Pharmacology (12.3)]*. In HELIOS-A, a total of 46 (38%) patients ≥65 years of age, including 7 (6%) patients ≥75 years of age, received AMVUTTRA In HELIOS-B, a total of 299 (92%) patients ≥65 years old, including 203 (62%) ≥75 years old, received AMVUTTRA. No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Renal Impairment

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

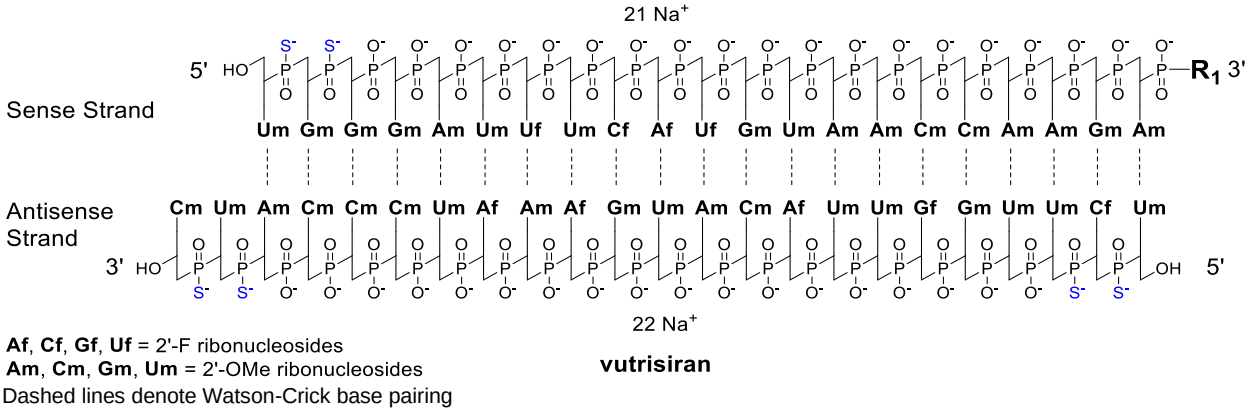
8.7 Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) or moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*. AMVUTTRA has not been studied in patients with severe hepatic impairment.

11 DESCRIPTION

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.

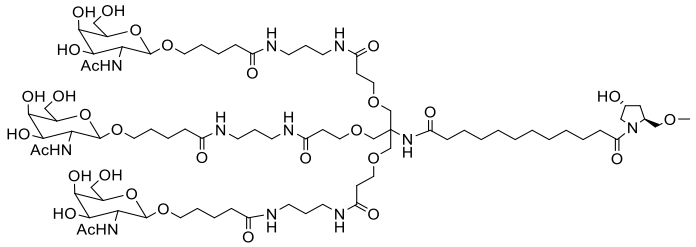
The structural formula of vutrisiran sodium is presented below.



Af, **Cf**, **Gf**, **Uf** = 2'-F ribonucleosides
Am, **Cm**, **Gm**, **Um** = 2'-OMe ribonucleosides
Dashed lines denote Watson-Crick base pairing

vutrisiran

R_1 =



The molecular formula of vutrisiran sodium is $C_{530}H_{672}F_9N_{171}Na_{43}O_{323}P_{43}S_6$ with a molecular weight of 17,290 Da. The molecular formula of the free acid is $C_{530}H_{715}F_9N_{171}O_{323}P_{43}S_6$ with a molecular weight of 16,345 Da.

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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.

12.2 Pharmacodynamics

The pharmacodynamic effects of AMVUTTRA were evaluated in patients with hATTR-PN and ATTR-CM, treated with 25 mg AMVUTTRA administered by subcutaneous injection once every 3 months.

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis

In HELIOS-A *[see Clinical Studies (14)]*, 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.

Vutrisiran also reduced the mean steady state serum vitamin A by 62% over 9 months *[see Warnings and Precautions (5.1)]*.

Cardiomyopathy of Wild-type (wt) or Hereditary Transthyretin-mediated Amyloidosis (hATTR)

In HELIOS-B, the mean serum TTR reduction profile was similar with that observed in HELIOS-A, and consistent across the subgroups studied (age, sex, race, body weight, anti-drug antibody [ADA] status, ATTR disease type (wtATTR versus hATTR), NYHA class, and baseline tafamidis use).

Vutrisiran reduced the mean steady state serum vitamin A by 65% over 36 months. *[see Warnings and Precautions (5.1)]*.

Cardiac Biomarkers

Biomarkers associated with heart failure (NT-proBNP and Troponin I) favored AMVUTTRA over placebo.

Cardiac Electrophysiology

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
General Information	
Dose Proportionality	Vutrisiran C_{max} showed dose proportional increase while AUC_{last} and AUC_{inf} 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)
Accumulation	No accumulation of vutrisiran was observed in plasma after repeated every 3 months dosage*
Absorption	
T_{max} [Median (Range)]	4 (0.17, 12.0) hours†
Distribution	
Estimated Vd/F (%RSE)	10.1 (5.8) L‡
Protein Binding	80%§
Organ Distribution	Vutrisiran distributes primarily to the liver after subcutaneous dosing
Elimination	
Half-Life [Median (Range)]	5.2 (2.2, 6.4) hours†
Apparent Clearance [Median (Range)]	21.4 (19.8, 30) L/hour†
Metabolism	
Primary Pathway	Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver
Excretion	
Primary Pathway	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¶

AUC_{inf} = area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC_{last} = area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max} = maximum plasma concentration; CV = coefficient of variation; RSE = relative standard error; T_{max} = time to maximum concentration; Vd/F = apparent volume of distribution

*After 25 mg every 3 months dosage in hATTR amyloidosis patients
†After 25 mg single dose in healthy subjects
‡Based on population PK model estimation
§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)
¶After single subcutaneous vutrisiran dose from 5 to 300 mg (i.e., 0.2 to 12 times the recommended dose) in healthy subjects

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^2), or mild (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) and moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. Vutrisiran has not been studied in patients with severe renal impairment, end-stage renal disease, 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.

12.6 Immunogenicity

The observed incidence of anti-drug antibody (ADA, including neutralizing antibody) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in the other studies, including those of AMVUTTRA or of other siRNA products.

In HELIOS-A and HELIOS-B studies, 3 (2.5%) and 1 (0.3%) patient treated with AMVUTTRA, respectively, developed transient, low titer anti-drug antibodies. The available data are limited to make definitive conclusions regarding the effect of anti-drug antibodies on pharmacokinetics or pharmacodynamics of AMVUTTRA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Subcutaneous administration of vutrisiran to male mice (0, 2, 6, or 13 mg/kg once every 4 weeks) for 100 weeks and to female mice (0, 3, 9, or 18 mg/kg once every 4 weeks) for 98 weeks resulted in no increase in tumors.

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

14.1 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 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].

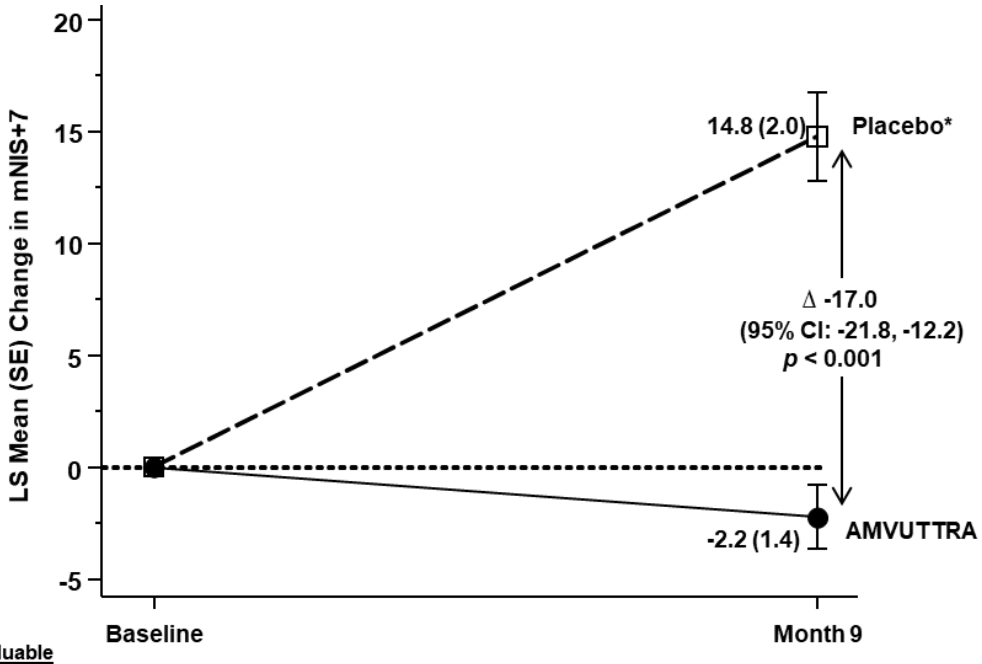
Table 3: Clinical Efficacy Results (Comparison of AMVUTTRA Treatment in HELIOS-A to an External Placebo Control*)

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 (**HELIOS-A**)	**Placebo* N=77** (NCT01960348)	**AMVUTTRA** (**HELIOS-A**)	**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).

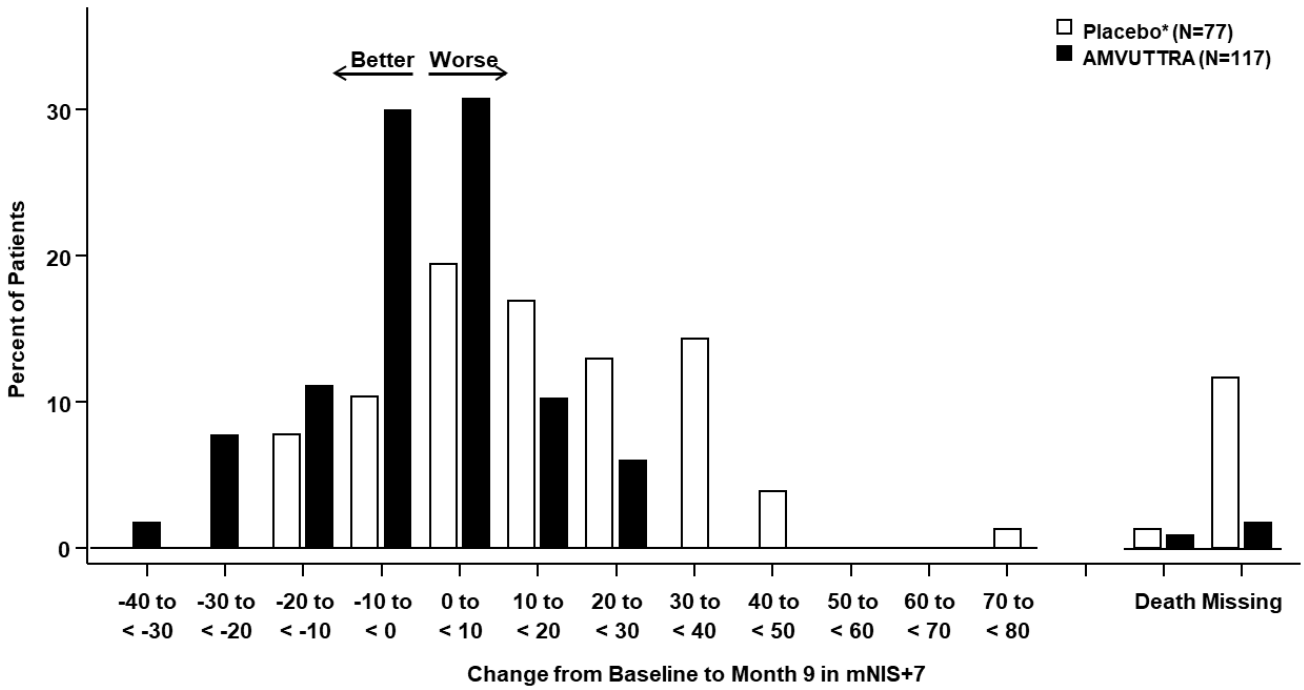
Figure 1: Change from Baseline in mNIS+7
(Comparison of AMVUTTRA Treatment in HELIOS-A to an External Placebo Control*)



N evaluable		
Placebo	77	67
AMVUTTRA	122	114

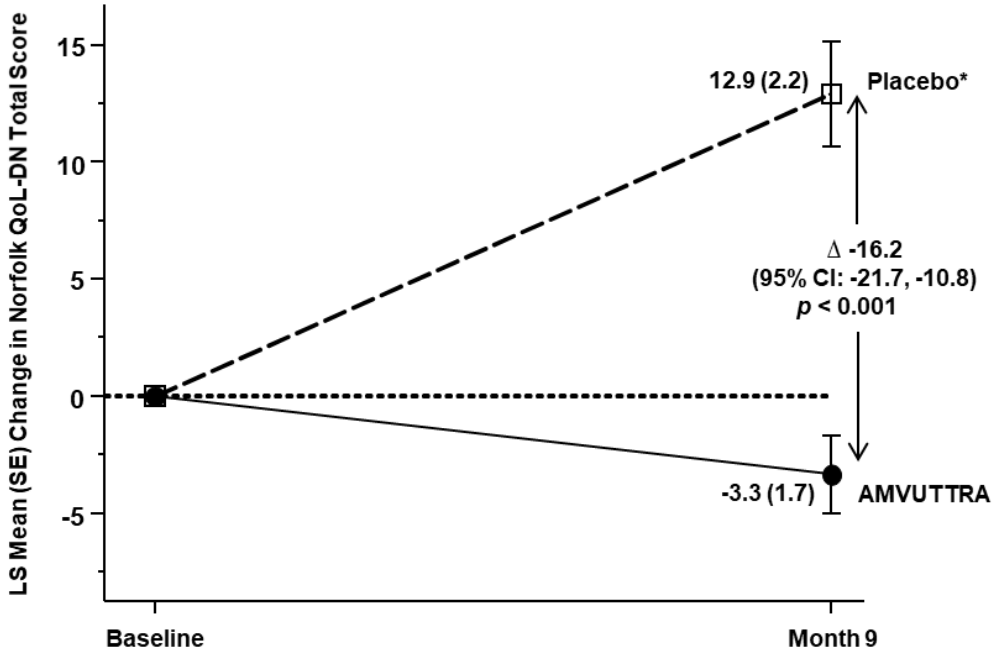
A decrease in mNIS+7 indicates improvement
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA – placebo
*External placebo group from another randomized controlled trial (NCT01960348)

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*)



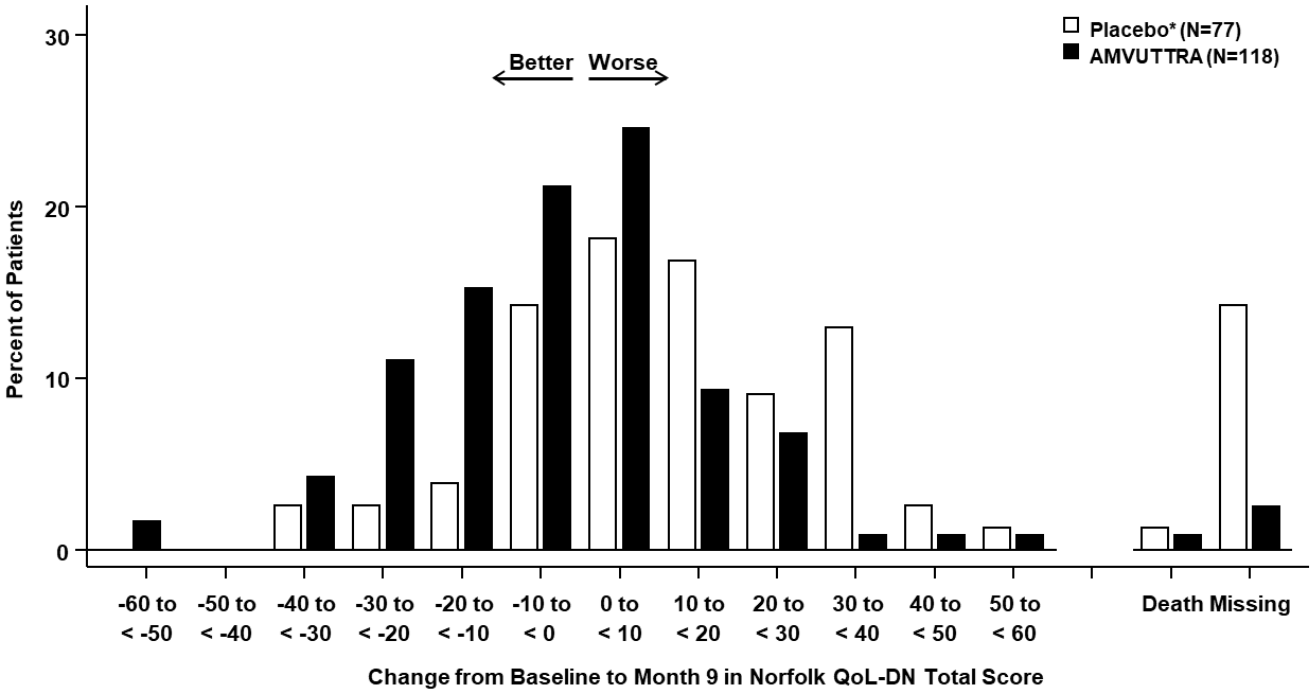
N evaluable		
Placebo	76	65
AMVUTTRA	121	114

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.

14.2 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 wild-type 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 [UHF] 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 4). 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.

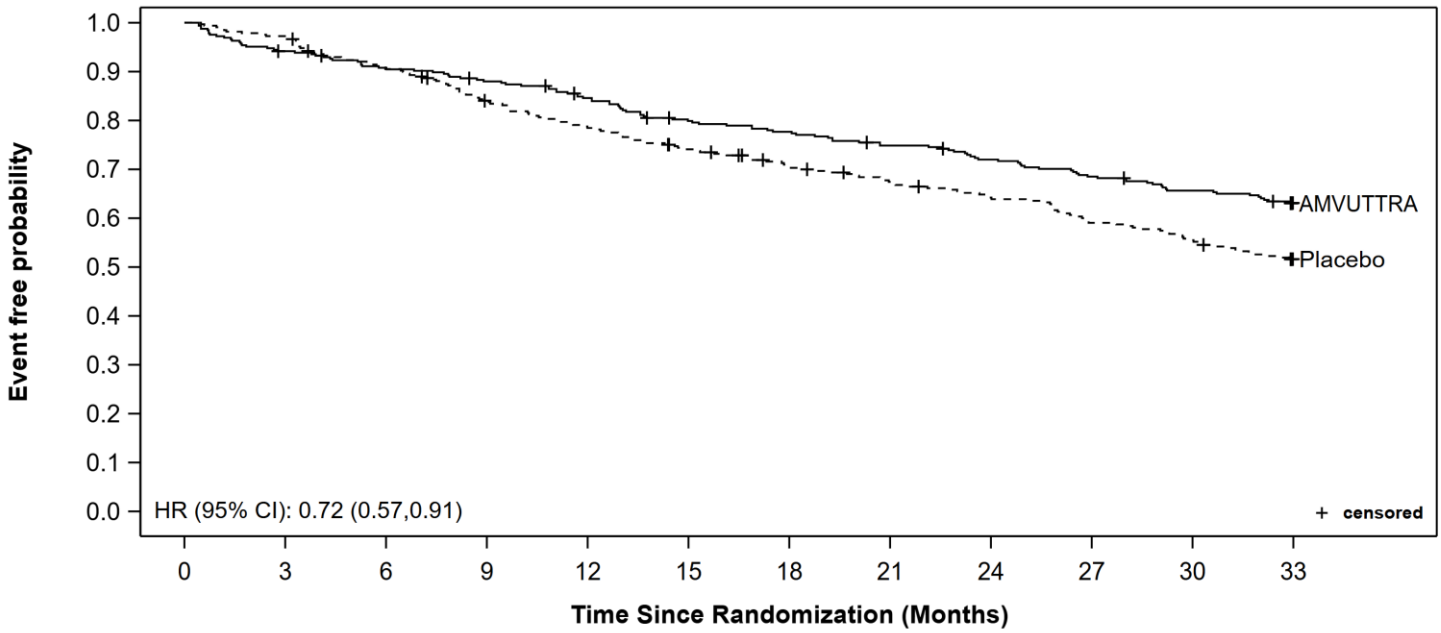
Both components of the primary composite endpoint individually contributed to the treatment effect in the overall and monotherapy population (Table 4).

Table 4: Primary Composite Endpoint and its Individual Components in HELIOS-B

Endpoint		Overall population		Monotherapy population	
		AMVUTTRA (N=326)	**Placebo (N=328)**	**AMVUTTRA (N=196)**	**Placebo (N=199)**
Primary composite endpoint*	Hazard Ratio (95% CI)†	0.72 (0.55, 0.93)		0.67 (0.49, 0.93)	
	p-value†	0.01		0.02	
Components of the Primary Composite Endpoint					
All-cause mortality	Hazard Ratio (95% CI)‡	0.69 (0.49, 0.98)		0.71 (0.47, 1.06)	
CV hospitalizations and UHF visits	Hazard Ratio (95% CI)†	0.73 (0.55, 0.96)		0.67 (0.47, 0.96)	

Abbreviations: 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.
* 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.
† Hazard Ratio (95% CI) and *p*-value are based on a modified Andersen-Gill model.
‡ 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)

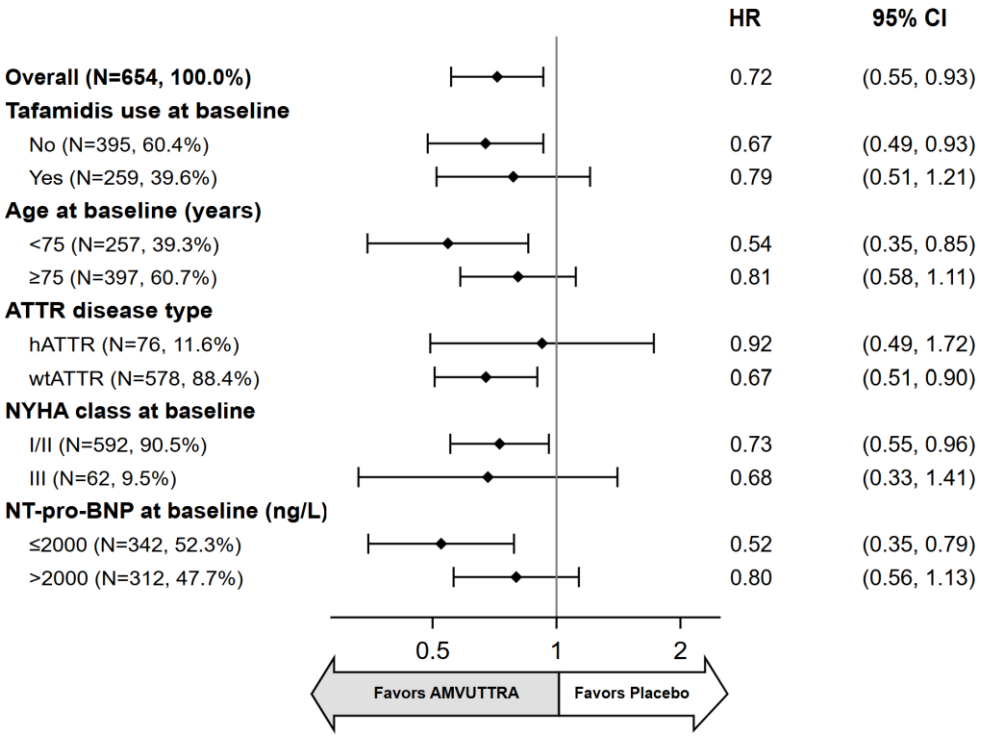
AMVUTTRA	326(0)	306(19)	294(30)	284(39)	271(50)	254(65)	247(72)	237(81)	227(90)	216(101)	206(110)	185(118)
Placebo	328(0)	317(11)	295(31)	270(53)	253(70)	237(84)	221(96)	210(105)	199(115)	183(131)	172(142)	155(154)

Abbreviations: 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)



Abbreviations: 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 (6-MWT), and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) 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.

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

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