Alnylam ASSIST®

How to Complete the AMVUTTRA® (vutrisiran) Start Form

Please see Important Safety Information on page 7 and full Prescribing Information.

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

How to complete the AMVUTTRA® (vutrisiran) Start Form

This brochure will show you how to complete the Start Form. The notes on each page provide details to help ensure the form is filled out correctly. The Start Form serves as your patient's enrollment in Alnylam Assist® and requires the signature of both you and your patient, unless the patient is currently prescribed an Alnylam medicine and is enrolled in Alnylam Assist.

It is important to note the following before submitting the Start Form:

- Ensure highlighted key areas are correctly filled out
- Confirm that you and your patient sign where indicated
- Make sure the site of care information is provided for patients not receiving home administration, if known

Options for getting started

1. Complete and submit the **electronic Start Form** with your patient

OR

2. Complete the **paper Start Form** with your patient and fax to 1-833-256-2747

OR

3. Begin the Start Form, filling in all details required from a healthcare professional, and then have your patient complete the form via **DocuSign**

All 3 options to get started can be found at **www.AlnylamAssist.com/hcp**.

Please see Important Safety Information on page 7 and full Prescribing Information.

Alnylam ASSIST®

For patients

Already Enrolled?

Patients currently prescribed an Alnylam medicine who are enrolled in Alnylam Assist® through previous submission of a Start Form do not need to complete Sections 1 – 4.

Preferred Phone Number & Voicemail Checkbox

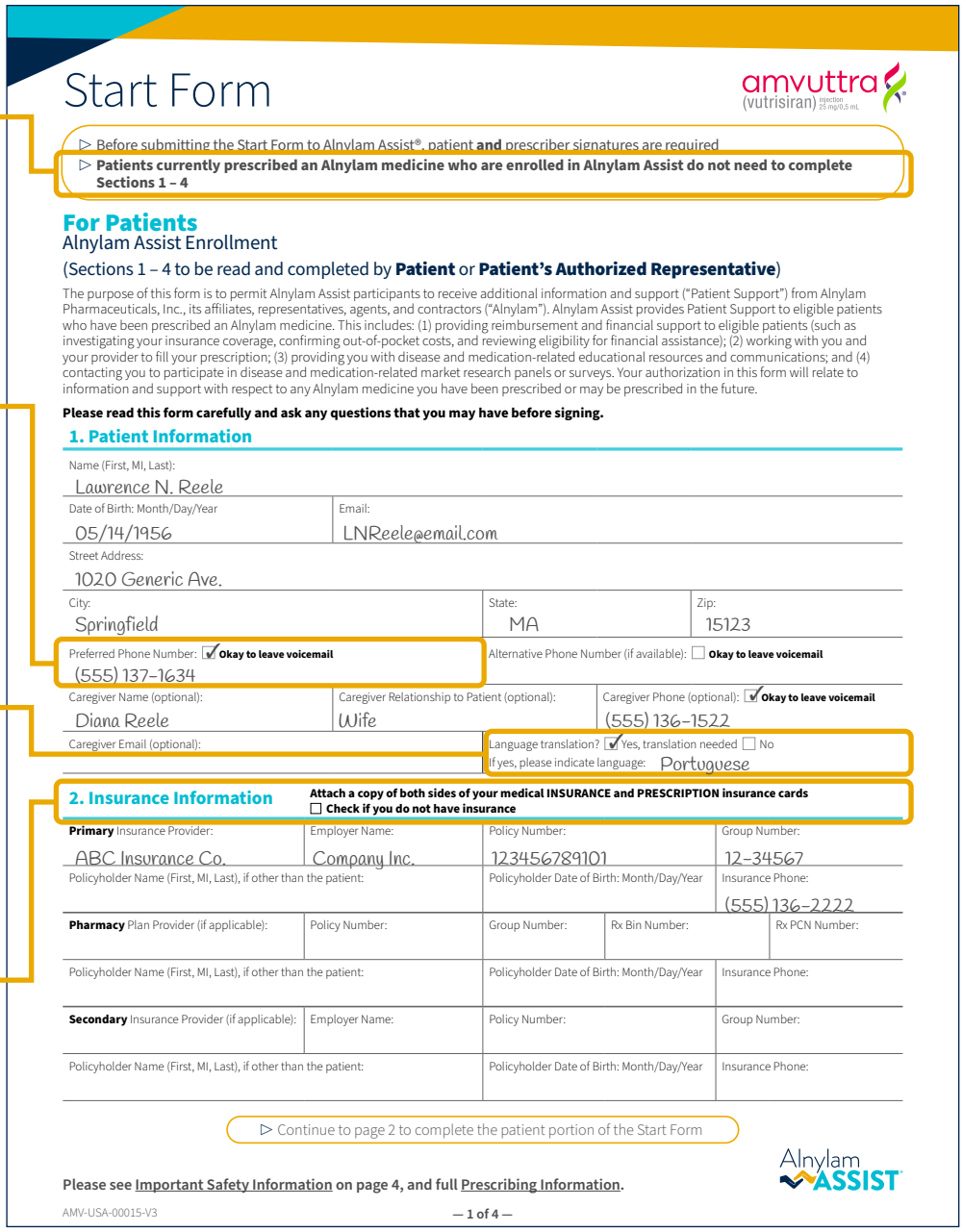
By allowing Alnylam Assist to leave voicemails, delays in benefit verification and other communications can be avoided.

Language Translation?

Alnylam Assist offers translation services for non–English-speaking patients.

Insurance Information

Patients (or their authorized representatives) can fill in the provided fields or attach copies of both sides of their insurance and pharmacy benefits cards.



Start Form

amvuttra (vutrisiran) injection 25 mg/0.5 mL

▷ Before submitting the Start Form to Alnylam Assist®, patient **and** prescriber signatures are required

▷ **Patients currently prescribed an Alnylam medicine who are enrolled in Alnylam Assist do not need to complete Sections 1 – 4**

For Patients

Alnylam Assist Enrollment

(Sections 1 – 4 to be read and completed by **Patient** or **Patient's Authorized Representative**)

The purpose of this form is to permit Alnylam Assist participants to receive additional information and support ("Patient Support") from Alnylam Pharmaceuticals, Inc., its affiliates, representatives, agents, and contractors ("Alnylam"). Alnylam Assist provides Patient Support to eligible patients who have been prescribed an Alnylam medicine. This includes: (1) providing reimbursement and financial support to eligible patients (such as investigating your insurance coverage, confirming out-of-pocket costs, and reviewing eligibility for financial assistance); (2) working with you and your provider to fill your prescription; (3) providing you with disease and medication-related educational resources and communications; and (4) contacting you to participate in disease and medication-related market research panels or surveys. Your authorization in this form will relate to information and support with respect to any Alnylam medicine you have been prescribed or may be prescribed in the future.

Please read this form carefully and ask any questions that you may have before signing.

1. Patient Information

Name (First, MI, Last): Lawrence N. Reele

Date of Birth: Month/Day/Year: 05/14/1956

Email: LNReele@email.com

Street Address: 1020 Generic Ave.

City: Springfield | State: MA | Zip: 15123

Preferred Phone Number: ☑ **Okay to leave voicemail** (555) 137–1634

Alternative Phone Number (if available): ☐ **Okay to leave voicemail**

Caregiver Name (optional): Diana Reele | Caregiver Relationship to Patient (optional): Wife | Caregiver Phone (optional): ☑ **Okay to leave voicemail** (555) 136–1522

Caregiver Email (optional):

Language translation? ☑ Yes, translation needed ☐ No

If yes, please indicate language: Portuguese

2. Insurance Information

Attach a copy of both sides of your medical INSURANCE and PRESCRIPTION insurance cards

☐ **Check if you do not have insurance**

Primary Insurance Provider:	Employer Name:	Policy Number:	Group Number:
ABC Insurance Co.	Company Inc.	123456789101	12–34567
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year	Insurance Phone: (555) 136–2222

Pharmacy Plan Provider (if applicable):	Policy Number:	Group Number:	Rx Bin Number:	Rx PCN Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year		Insurance Phone:

Secondary Insurance Provider (if applicable):	Employer Name:	Policy Number:	Group Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year	Insurance Phone:

▷ Continue to page 2 to complete the patient portion of the Start Form

Please see Important Safety Information on page 4, and full Prescribing Information.

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Authorization to share protected health information/ authorization for Alnylam Assist® enrollment

Start Form

amvuttra (vutrisiran) injection 25 mg/0.5 mL

3. Authorization to Share Protected Health Information

By signing below, I authorize my healthcare providers, including my physicians and pharmacies ("My Providers") and my health insurance plan ("My Plan") to share my medical information (such as information about my diagnosis, prescriptions, and treatment) and my insurance information ("My Information") with Alnylam so that Alnylam can provide Patient Support. I authorize My Providers to use My Information to provide me with certain offerings related to my treatment and any Alnylam medicine My Providers may prescribe for me at any time. I understand that my pharmacy will receive payment from Alnylam for disclosing My Information to Alnylam. I understand that once My Information has been disclosed, federal privacy laws may no longer protect the information. However, I understand that Alnylam agrees to protect My Information by using and disclosing it only for purposes described in this Authorization or as required by law. I understand that I may refuse to sign this Authorization, and that my treatment, insurance enrollment, and eligibility for insurance benefits are not conditioned upon signing this Authorization.

I also understand, however, that refusing to sign this Authorization means that I may not participate in Alnylam Assist® and may not be able to take advantage of other offerings by Alnylam. I may cancel or revoke this Authorization at any time by mailing a letter to Privacy Officer at Alnylam, Attn: Legal Department, 675 West Kendall Street, Cambridge, MA 02142 or by sending an email to privacy@alnylam.com. I understand that if I revoke this Authorization, My Providers and Alnylam will stop using and sharing My Information under this Authorization, but my revocation will not affect uses and disclosures of My Information prior to my revocation in reliance upon this Authorization.

This Authorization expires ten (10) years from the date signed below, or earlier if required by state or local law, unless I revoke it before then. I understand that I may receive a copy of this Authorization.

For information about how your personal data are processed as a part of our program, please visit www.alnylampolicies.com/privacy.

Lawrence N. Reele	X [signature]
Print Patient or Authorized Patient Representative Name	Signature of Patient or Authorized Patient Representative
	August 1, 2022
Relationship to Patient	Date

4. Authorization for Alnylam Assist and Communications

By signing below, I confirm I would like to enroll in the Alnylam Assist program and authorize Alnylam to provide me with Patient Support. I understand that Alnylam Assist is an optional program.

I agree that Alnylam may use My Information and share it with My Providers or My Plan in connection with providing the Patient Support, administering the Alnylam Assist program, or as otherwise required by Alnylam to meet its legal obligations. For example, Alnylam may communicate with me (such as by mail, phone, email, and/or text message) or my caregiver, use My Information to tailor the Alnylam Assist–related communications to my needs, and share information with My Providers about dispensing Alnylam medicine to me. I understand that Alnylam may de-identify My Information, combine it with information about other patients, and use the resulting information for Alnylam's business purposes.

Lawrence N. Reele	X [signature]
Print Patient or Authorized Patient Representative Name	Signature of Patient or Authorized Patient Representative
	August 1, 2022
Relationship to Patient	Date

Please see Important Safety Information on page 4, and full Prescribing Information.

Alnylam ASSIST

AMV-USA-00015-V3 — 2 of 4 —

Signature of Patient

The signature of the patient or authorized patient representative, with the date, is required **twice** on this page in Sections 3 and 4 unless the patient is currently prescribed an Alnylam medicine and is already enrolled in Alnylam Assist.

Alnylam ASSIST

For healthcare providers

Product Acquisition

Select your preferred method of product acquisition (specialty pharmacy or specialty distributor). If acquisition method is unknown, select *Unknown*.

AMVUTTRA® (vutrisiran) Prescription

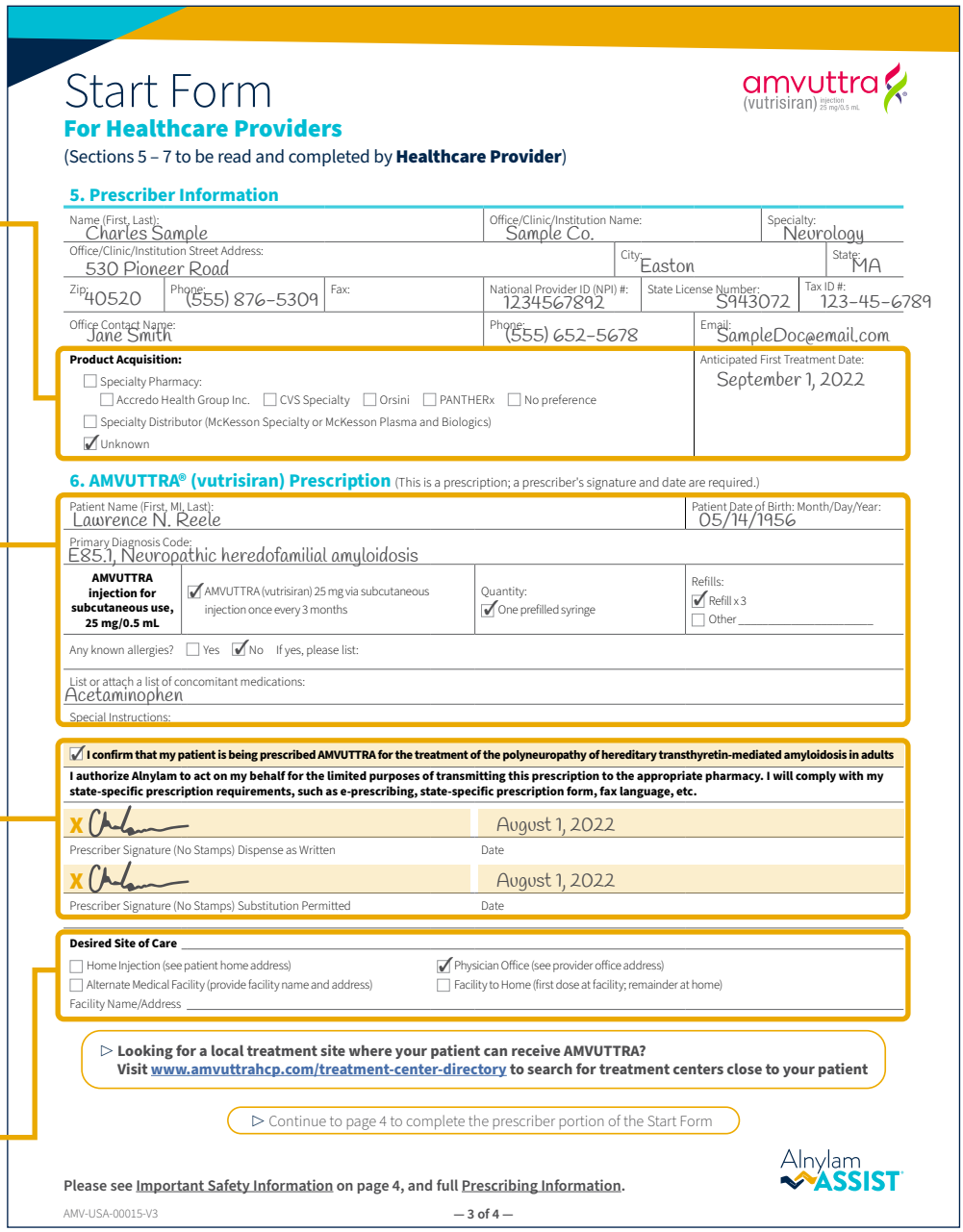
- Ensure you fill in the prescription fields
- Make sure to include the primary diagnosis code

Signature of Prescriber

- Confirm that your patient is being prescribed AMVUTTRA as indicated by checking the box
- Ensure the prescriber's signature and date are included in Section 6

Desired Site of Care

Ensure that your patient's desired site of care has been provided. Please note that home administration may also be an option.[a]



Start Form

amvuttra (vutrisiran) injection 25 mg/0.5 mL

For Healthcare Providers

(Sections 5 – 7 to be read and completed by **Healthcare Provider**)

5. Prescriber Information

Name (First, Last): Charles Sample		Office/Clinic/Institution Name: Sample Co.		Specialty: Neurology	
Office/Clinic/Institution Street Address: 530 Pioneer Road			City: Easton		State: MA
Zip: 40520	Phone: (555) 876-5309	Fax:	National Provider ID (NPI) #: 1234567892	State License Number: S943072	Tax ID #: 123-45-6789
Office Contact Name: Jane Smith		Phone: (555) 652-5678		Email: SampleDoc@email.com	

Product Acquisition:

☐ Specialty Pharmacy:
☐ Accredo Health Group Inc. ☐ CVS Specialty ☐ Orsini ☐ PANTHERx ☐ No preference
☐ Specialty Distributor (McKesson Specialty or McKesson Plasma and Biologics)
☑ Unknown

Anticipated First Treatment Date: September 1, 2022

6. AMVUTTRA® (vutrisiran) Prescription (This is a prescription; a prescriber's signature and date are required.)

Patient Name (First, MI, Last): Lawrence N. Reele			Patient Date of Birth: Month/Day/Year: 05/14/1956
Primary Diagnosis Code: E85.1, Neuropathic heredofamilial amyloidosis			
AMVUTTRA injection for subcutaneous use, 25 mg/0.5 mL	☑ AMVUTTRA (vutrisiran) 25 mg via subcutaneous injection once every 3 months	Quantity: ☑ One prefilled syringe	Refills: ☑ Refill x 3 ☐ Other _____

Any known allergies? ☐ Yes ☑ No If yes, please list:

List or attach a list of concomitant medications: Acetaminophen

Special Instructions:

☑ **I confirm that my patient is being prescribed AMVUTTRA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults**

I authorize Alnylam to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy. I will comply with my state-specific prescription requirements, such as e-prescribing, state-specific prescription form, fax language, etc.

X [signature]	August 1, 2022
Prescriber Signature (No Stamps) Dispense as Written	Date
X [signature]	August 1, 2022
Prescriber Signature (No Stamps) Substitution Permitted	Date

Desired Site of Care _____

☐ Home Injection (see patient home address) ☑ Physician Office (see provider office address)
☐ Alternate Medical Facility (provide facility name and address) ☐ Facility to Home (first dose at facility; remainder at home)
Facility Name/Address _____

▷ **Looking for a local treatment site where your patient can receive AMVUTTRA?**
Visit www.amvuttrahcp.com/treatment-center-directory to search for treatment centers close to your patient

▷ Continue to page 4 to complete the prescriber portion of the Start Form

Alnylam ASSIST

Please see Important Safety Information on page 4, and full Prescribing Information.

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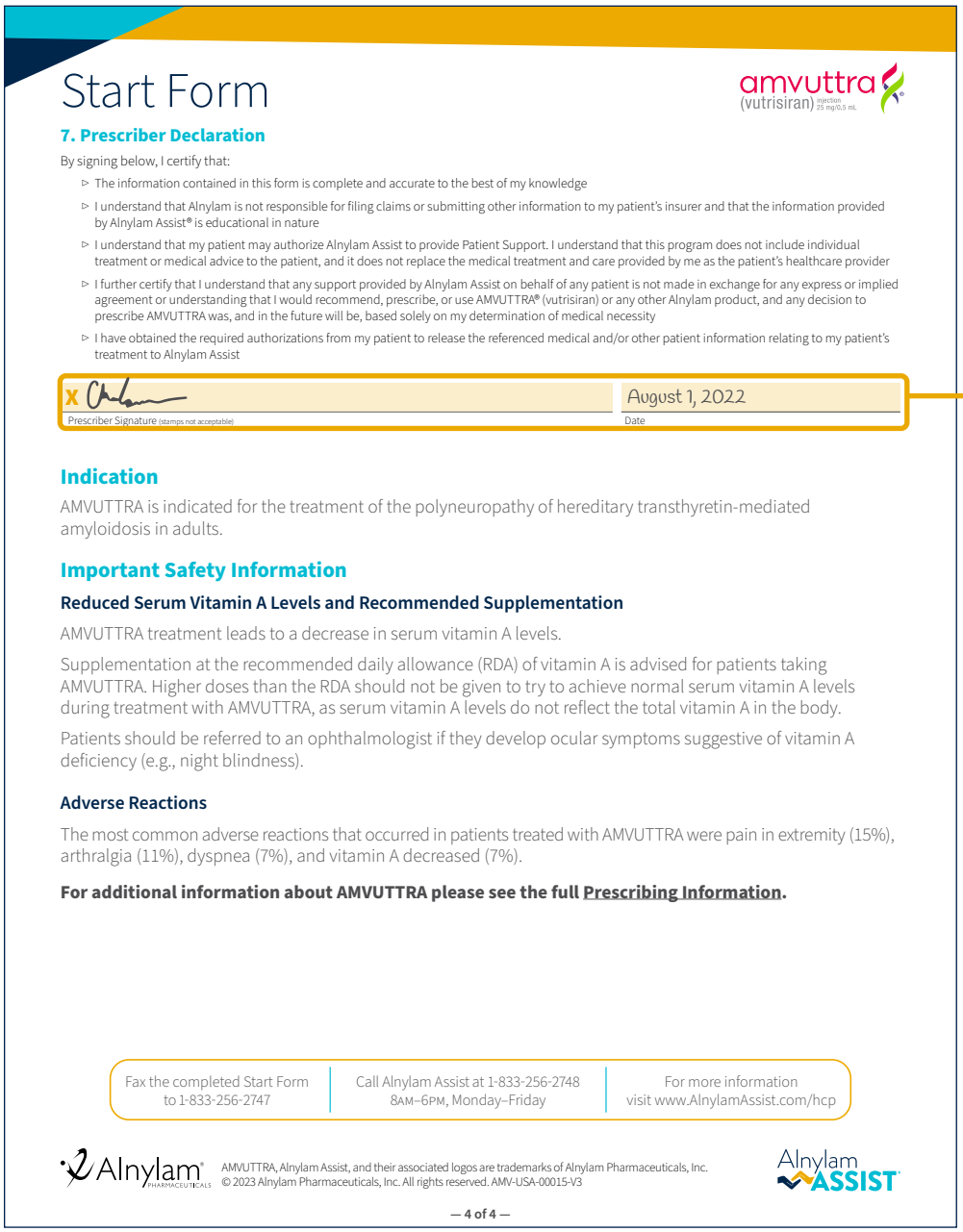
[a]Home administration may be an option for some patients. The decision for a patient to receive home administration should be made after evaluation and recommendation by the treating physician and may not be covered by all insurance plans.

Alnylam ASSIST®

Please see Important Safety Information on page 7 and full Prescribing Information.

Prescriber declaration/AMVUTTRA® (vutrisiran) Indication and Important Safety Information



Start Form

amvuttra (vutrisiran) injection 25 mg/0.5 mL

7. Prescriber Declaration

By signing below, I certify that:

- The information contained in this form is complete and accurate to the best of my knowledge
- I understand that Alnylam is not responsible for filing claims or submitting other information to my patient's insurer and that the information provided by Alnylam Assist® is educational in nature
- I understand that my patient may authorize Alnylam Assist to provide Patient Support. I understand that this program does not include individual treatment or medical advice to the patient, and it does not replace the medical treatment and care provided by me as the patient's healthcare provider
- I further certify that I understand that any support provided by Alnylam Assist on behalf of any patient is not made in exchange for any express or implied agreement or understanding that I would recommend, prescribe, or use AMVUTTRA® (vutrisiran) or any other Alnylam product, and any decision to prescribe AMVUTTRA was, and in the future will be, based solely on my determination of medical necessity
- I have obtained the required authorizations from my patient to release the referenced medical and/or other patient information relating to my patient's treatment to Alnylam Assist

X [signature] | August 1, 2022

Prescriber Signature (stamps not acceptable) | Date

Indication

AMVUTTRA 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.

Fax the completed Start Form to 1-833-256-2747 | Call Alnylam Assist at 1-833-256-2748 8AM–6PM, Monday–Friday | For more information visit www.AlnylamAssist.com/hcp

Alnylam PHARMACEUTICALS

Alnylam ASSIST

— 4 of 4 —

Signature of Prescriber

Ensure the **prescriber's signature** and **date** are included in Section 7.

Please see Important Safety Information on page 7 and full Prescribing Information.

Alnylam ASSIST®

Indication

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

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

Alnylam ASSIST®

8AM–6PM, Monday–Friday

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

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

Please see Important Safety Information on page 7 and full Prescribing Information.

Alnylam ASSIST®

Once the completed Start Form is received by Alnylam Assist®

1. Alnylam Case Manager makes Welcome Call to you and your patient and confirms desired site of care[a]
If unable to reach the patient, the Alnylam Case Manager cannot move forward with the benefit investigation

2. Alnylam Case Manager does benefit investigation
If a patient's insurance or site of care changes, a new benefit investigation must be done

3. Alnylam Case Manager relays results of benefit investigation to you and your patient during "Benefits Call Counsel"
This includes information about prior authorization (if required)

IF REQUIRED

Prescribing physician submits prior authorization or works with identified specialty pharmacy to submit on their behalf
- It is the responsibility of the prescribing physician to submit the required documentation
- If the prior authorization is not approved, a resubmission or appeal may be required by the prescriber

Prior authorization is approved[b,c]

4. Alnylam Case Manager confirms copay affordability and site of care

5. Patient is "order ready"

6. Physician places order through specialty pharmacy or specialty distributor

Patient receives AMVUTTRA® (vutrisiran) treatment and schedules next treatment

[a]If no site of care has been identified, Alnylam Case Manager can do a search for sites of care near the patient's preferred geographic location and confirm their in-/out-of-network status during the benefit investigation.
[b]If a reauthorization is required, a new request must be submitted.
[c]Alnylam Assist can provide education on prior authorization requirements and processes, but cannot guarantee that a patient's prior authorization will be approved.
[d]If your patient has a new prescribing physician, a new Start Form is required and the process must be repeated.

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

Alnylam® PHARMACEUTICALS

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

----------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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

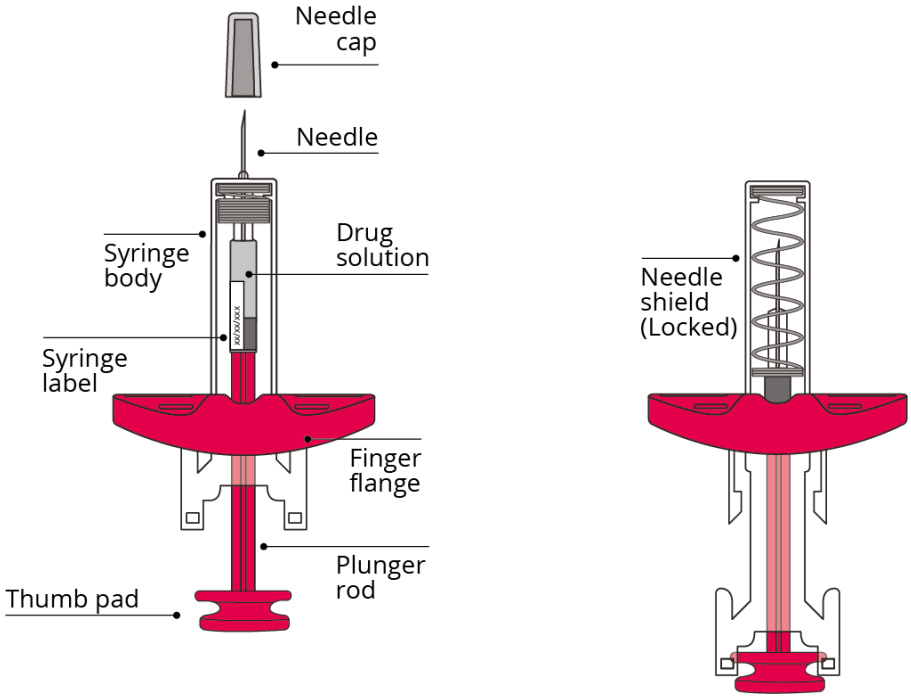
If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

2.2 Administration Instructions

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

Syringe Appearance Before and After Use

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.

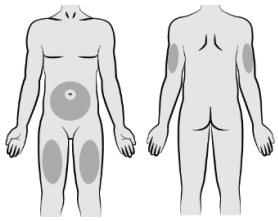
2. *Choose and prepare the injection site*

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.

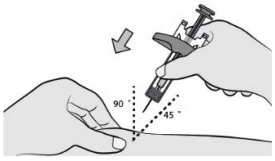
Do not recap the syringe.

Do not use the syringe if it is dropped.

4. *Perform the injection*

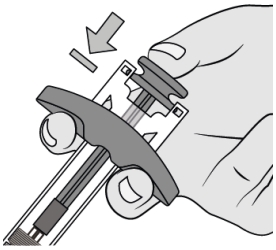
Pinch the cleaned skin.

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



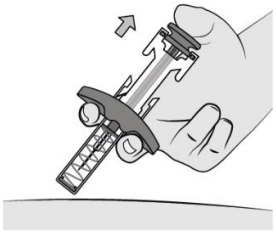
Inject all of the medication.

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.

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 ≥65 years of age *[see Clinical Pharmacology (12.3)]*. A total of 46 (38%) patients ≥65 years of age, including 7 (6%) patients ≥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] ≥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.

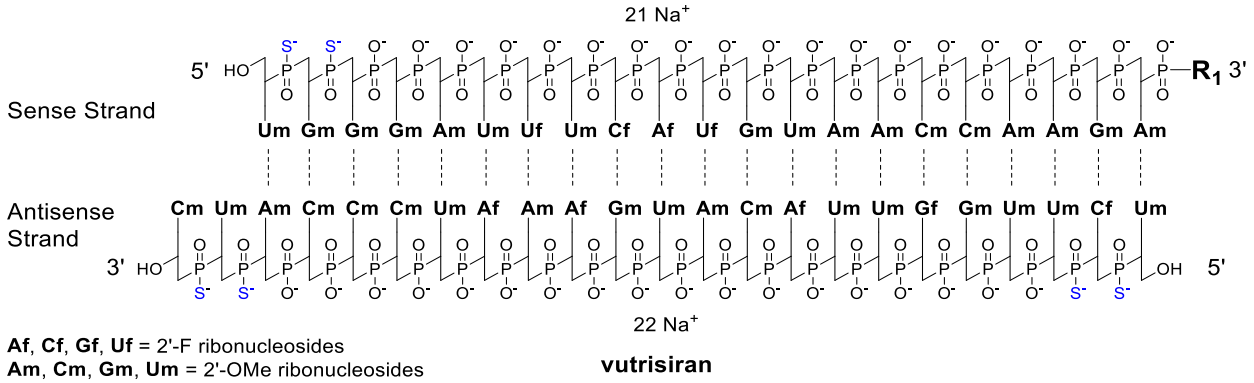
8.7 Hepatic Impairment

No dose adjustment is recommended in patients with mild 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) *[see Clinical Pharmacology (12.3)]*. AMVUTTRA has not been studied in patients with moderate or 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.

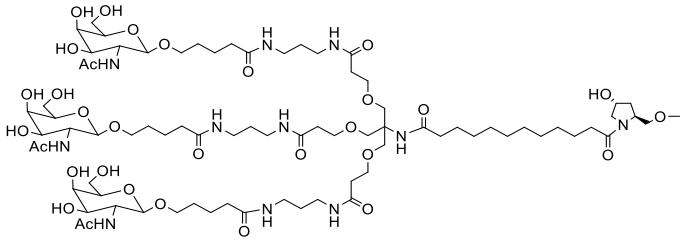
The structural formula of vutrisiran sodium is presented below.



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

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.

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

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 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].

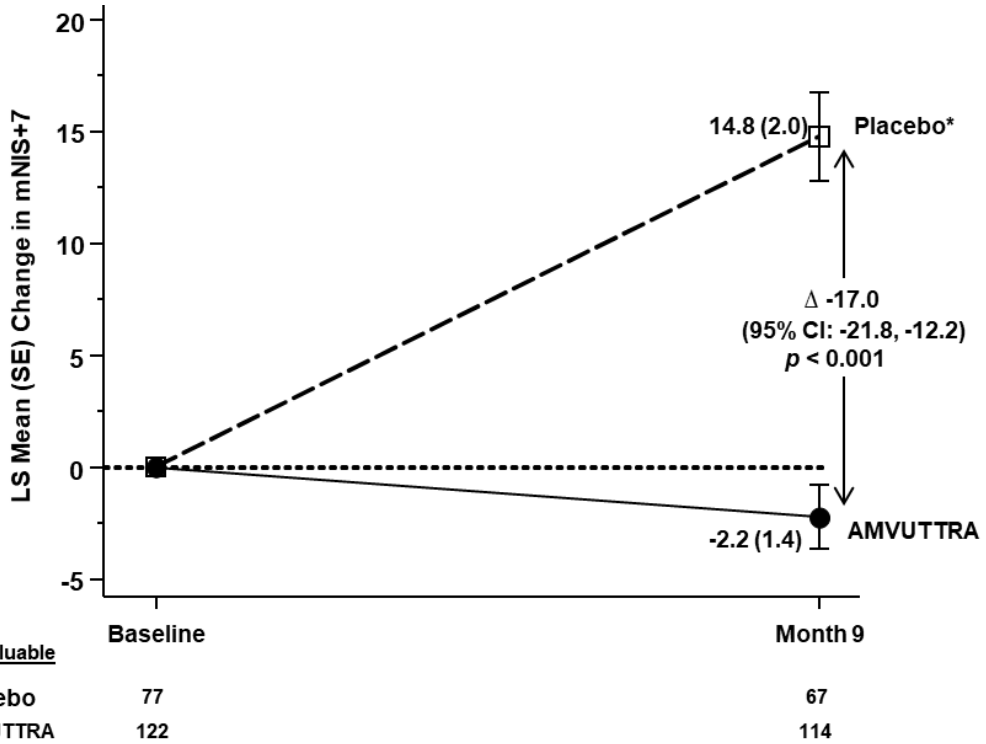
Table 3: Clinical Efficacy Results (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)

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

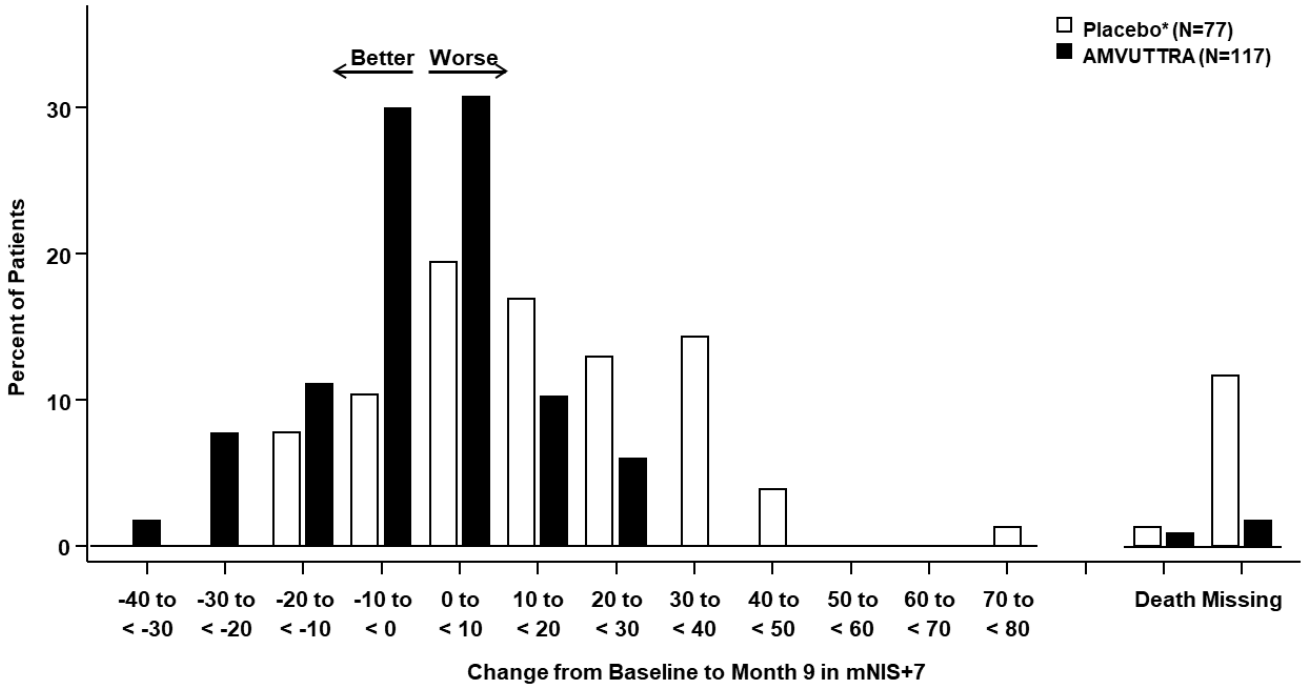
*External placebo group from another randomized controlled trial (NCT01960348)
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)
‡A lower number indicates less impairment/fewer symptoms
§A higher number indicates less disability/less impairment
¶mBMI: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

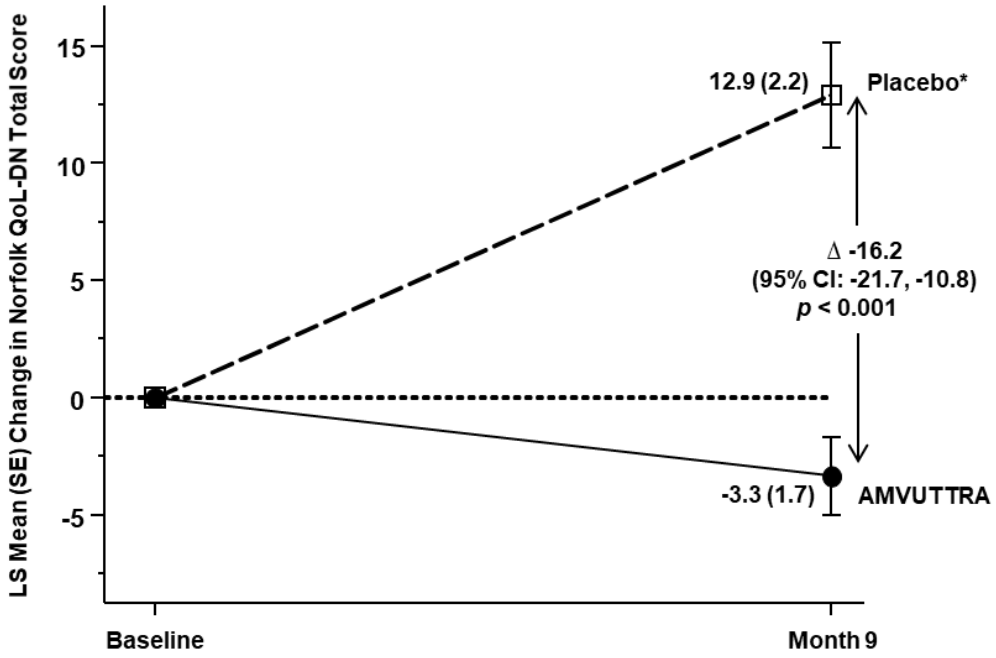
Figure 2: Histogram of mNIS+7 Change from Baseline at Month 9
(Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



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*)



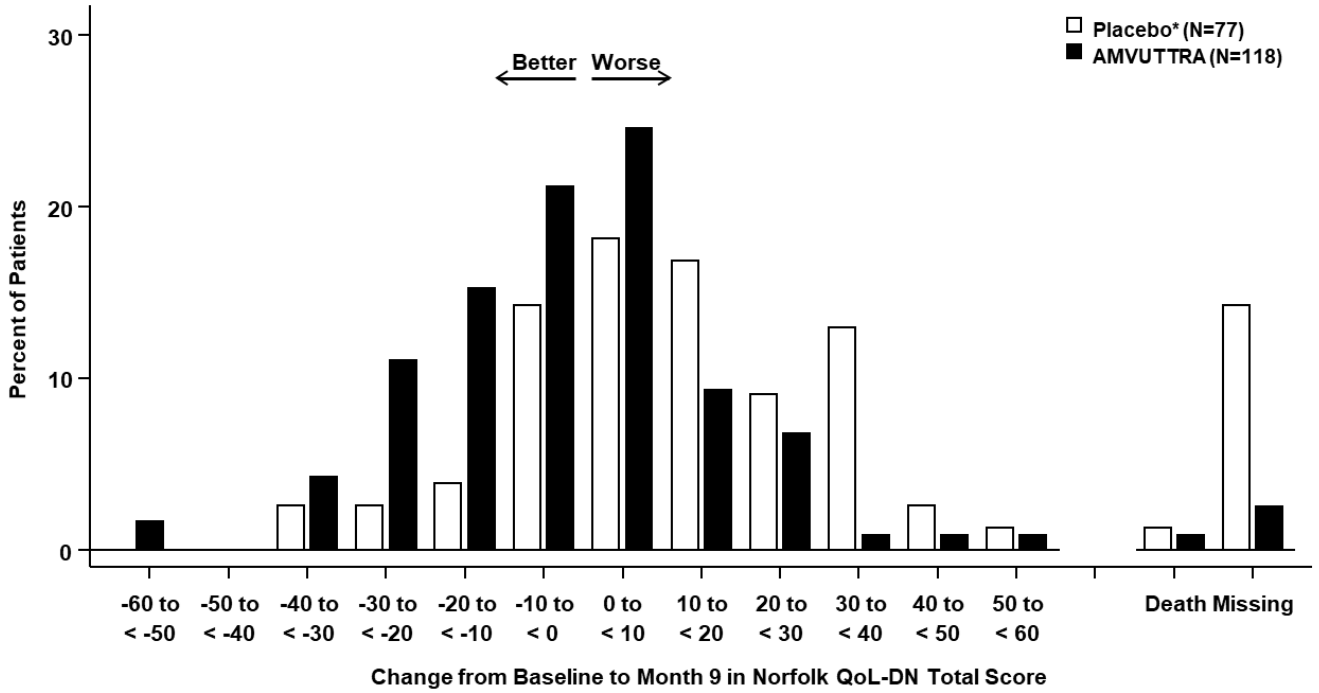
N evaluable		
Placebo	76	65
AMVUTTRA	121	114

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 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