

AMVUTTRA® (vutrisiran)
JUST THE TICKET
FOR ATTR-CM

**TALK TO YOUR
DOCTOR TODAY**



Actor portrayals

**PROVEN TO HELP PEOPLE LIVE LONGER
AND HAVE FEWER HEART-RELATED HOSPITAL VISITS**

INDICATION

WHAT IS AMVUTTRA?

AMVUTTRA is a prescription medicine that treats the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce heart-related death, hospital stays and urgent visits.

IMPORTANT SAFETY INFORMATION

WHAT ARE THE MOST IMPORTANT THINGS I SHOULD KNOW ABOUT AMVUTTRA?

AMVUTTRA can cause low vitamin A levels

Treatment with AMVUTTRA lowers the amount of vitamin A in your blood. Your doctor will tell you to take a vitamin A supplement every day. You should not take more than the amount of vitamin A recommended by your doctor.

Low vitamin A levels can affect vision. If you have problems with your vision (e.g., night blindness) while taking AMVUTTRA, talk to your doctor. Your doctor may refer you to an eye specialist.

**Please see additional Important Safety Information on page 11,
and full Prescribing Information.**

amvuttra
(vutrisiran) injection
25 mg/0.5 mL

ENVISION A DIFFERENT JOURNEY WITH ATTR-CM



Please see additional Important Safety Information on page 11,
and full Prescribing Information.

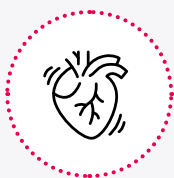
amvuttra 
(vutrisiran) injection
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WHAT TO KNOW ABOUT ATTR-CM

The cardiomyopathy of ATTR amyloidosis (ATTR-CM) can be caused by changes associated with aging (called wild-type ATTR) or by an inherited gene variant passed down through families (called hereditary ATTR). In both types, a protein called transthyretin (TTR) changes shape and builds up in your heart and other tissues in the body. This buildup, also known as amyloid deposits, can cause a variety of symptoms.

SYMPTOMS OF ATTR-CM CAN AFFECT THE HEART AND OTHER PARTS OF THE BODY

In people with ATTR-CM, the heart's ability to pump blood is reduced—a condition known as cardiomyopathy, which can lead to heart failure. Below are some, but not all, of the heart-related symptoms that can occur with ATTR-CM:



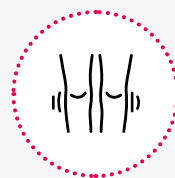
Irregular heartbeat



Shortness of breath



Fatigue



Leg swelling



Fainting

People may also have symptoms that are not related to the heart, which may include:

- Digestive issues
- Dizziness upon standing
- Abnormal sweating
- Sexual dysfunction
- Weakness
- Pain or tingling in arms or legs
- Kidney dysfunction
- Carpal tunnel syndrome

You may not have all of these symptoms at once or experience all of them over time. Each person with ATTR-CM has a different experience.

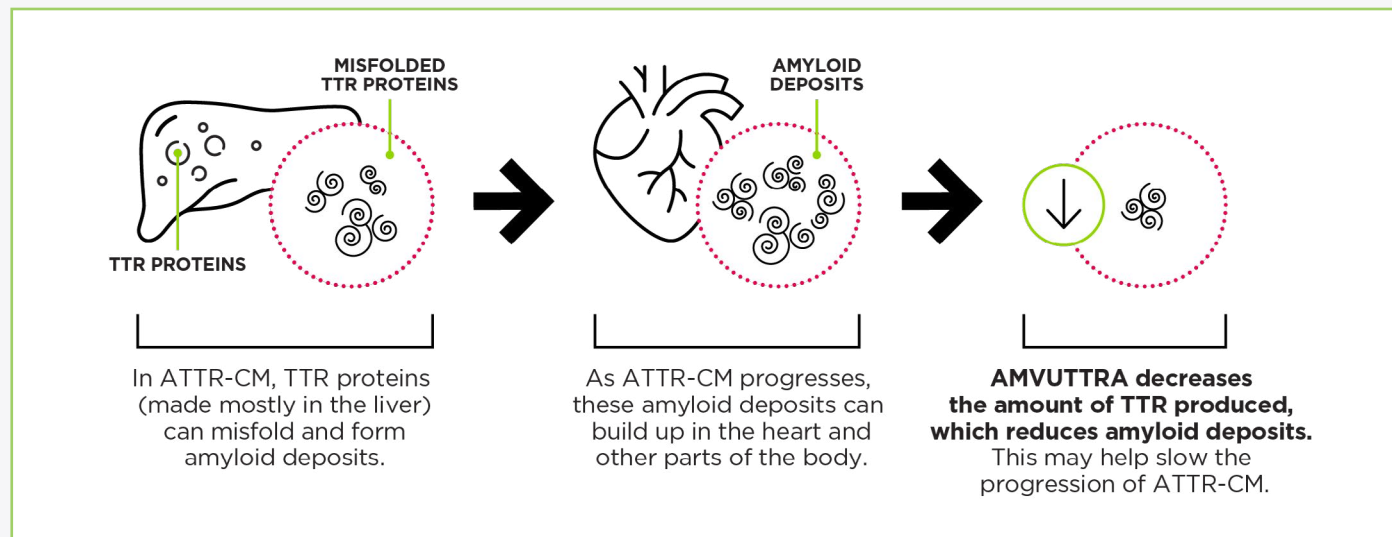
YOU MAY BE ABLE TO CHANGE THE COURSE OF ATTR-CM

The symptoms of ATTR-CM get worse over time and can make it more difficult to walk distances, climb stairs, do things for yourself like daily chores, or enjoy outings with friends and family. If you've been diagnosed, talk to your doctor about ways to manage your condition to help slow its progression.

**ATTR-CM often leads to heart failure.
Talk to your doctor if you have new or worsening symptoms.**

TAKE ON ATTR-CM AT THE SOURCE

AMVUTTRA® (vutrisiran) is the **first and only silencer for ATTR-CM**. It works with your body to reduce the production of TTR in the liver, where most of it is made.



RAPIDLY KNOCKS DOWN TTR

In a clinical study, AMVUTTRA started reducing TTR blood levels after the first dose. It rapidly knocked down TTR as early as 6 weeks.

↓ 87%
**REDUCTION IN
TTR LEVELS**
with 2.5 years of
treatment*

*Individual results may vary.

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amvuttra
(vutrisiran) injection
25 mg/0.5 mL

PEOPLE LIVED LONGER AND HAD FEWER HOSPITAL VISITS

The clinical study of AMVUTTRA® (vutrisiran) included 654 adults with wild-type or hereditary ATTR-CM. Effectiveness was determined by comparing the results of people treated with AMVUTTRA to those who received placebo (a treatment without any medication).

The main measure of effectiveness was the combined risk of death and heart-related hospital stays and urgent visits over 3 years.

**↓ 28% | LOWER RISK OF DEATH AND
HEART-RELATED HOSPITAL VISITS***

*Most deaths were heart-related. Hospital visits included hospital stays and urgent visits.



IMPORTANT SAFETY INFORMATION

WHAT ARE THE COMMON SIDE EFFECTS OF AMVUTTRA?

The most common side effects of AMVUTTRA were pain in the arms or legs, pain in the joints, shortness of breath, and low vitamin A levels.

These are not all the possible side effects of AMVUTTRA. Talk to your doctor about side effects that you experience. You are encouraged to report negative side effects of prescription drugs to the U.S. Food and Drug Administration (FDA). Visit www.fda.gov/medwatch, or call **1-800-FDA-1088**.

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PEOPLE LIVED LONGER WITH CONTINUED TREATMENT

After the first 3 years of the study, people receiving placebo switched to AMVUTTRA® (vutrisiran) so that everyone still in the study received AMVUTTRA for up to an additional 6 months.

The study then measured the risk of death over 3.5 years, and compared people who originally received AMVUTTRA to those who originally received placebo.

↓ 36%

**LOWER RISK
OF DEATH***



*Most deaths were heart-related.

Ask your doctor what these results may mean for you.

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SLOWED DISEASE PROGRESSION COMPARED TO PLACEBO

The study also measured physical activity and health-related quality of life at 2.5 years.



IMPACT ON PHYSICAL ACTIVITY

People receiving AMVUTTRA® (vutrisiran) were able to walk 72 feet farther than people receiving placebo.

These results are based on the 6-minute walk test (6-MWT),* which measures the distance someone can walk in 6 minutes.



IMPACT ON QUALITY OF LIFE

People receiving AMVUTTRA reported a significantly better health status and health-related quality of life compared to placebo.

These results were measured using a questionnaire called KCCQ,* which asked patients about their heart failure symptoms, ability to perform routine tasks and participate in social activities, and the impact heart failure had on their quality of life.

KCCQ=Kansas City Cardiomyopathy Questionnaire.

*Patients receiving AMVUTTRA and patients receiving placebo walked a shorter distance and had lower KCCQ overall summary scores than at the start of the study.

IMPORTANT SAFETY INFORMATION

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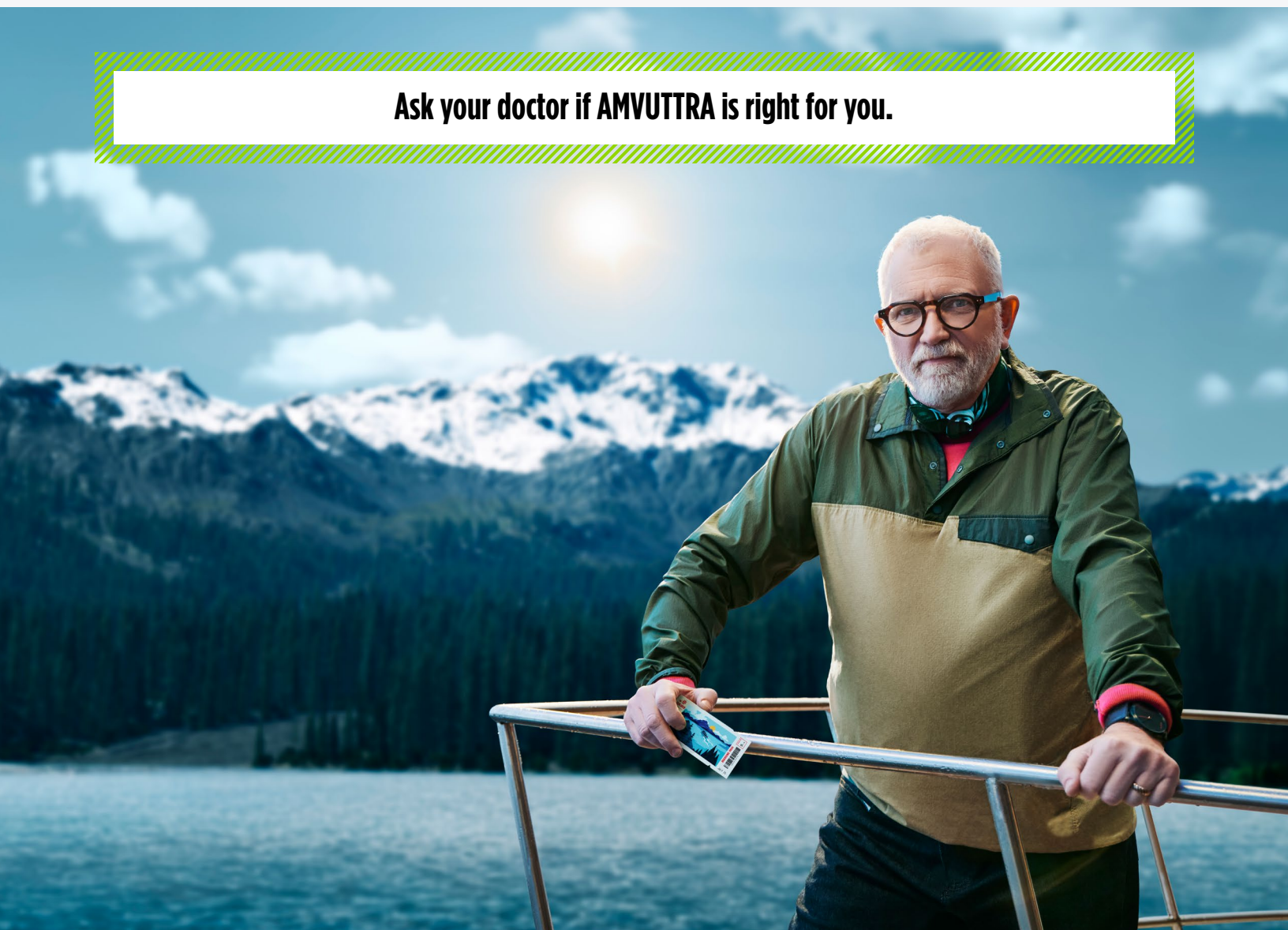
amvuttra
(vutrisiran) injection
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SAFETY OF AMVUTTRA® (vutrisiran)

- The most common side effects of AMVUTTRA included pain in the arms or legs, pain in the joints, and shortness of breath
- AMVUTTRA also lowers vitamin A levels, which can affect vision. Your doctor will tell you to take a vitamin A supplement every day
- Talk to your doctor about side effects that you experience

Please see additional Important Safety Information on page 11, and full Prescribing Information.

Ask your doctor if AMVUTTRA is right for you.



amvuttra 
(vutrisiran) injection
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STAY ON COURSE WITH JUST 4 DOSES A YEAR



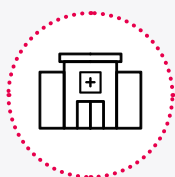
Given by a healthcare provider

AMVUTTRA® (vutrisiran) injections are given by a healthcare provider once every 3 months so you can feel confident you're getting the full dose.



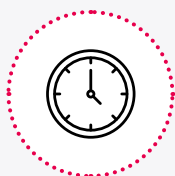
Injected under the skin

AMVUTTRA is a subcutaneous injection that can be given in the thigh, abdomen, or upper arm with a prefilled syringe. AMVUTTRA may cause reactions at the injection site such as bruising, redness, pain, itching, and warmth.



Convenient treatment center options

Receive AMVUTTRA at your doctor's office or a participating nearby clinic. It can even be given at home by a healthcare provider, if covered by your insurance.



Administration process may take a few minutes

A healthcare provider will clean the injection site, pinch the skin, and then inject AMVUTTRA with a short needle.

Watch a video about how AMVUTTRA is given.

IMPORTANT SAFETY INFORMATION

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ALNYLAM ASSIST® PROVIDES SUPPORT THROUGHOUT YOUR JOURNEY

Services and resources designed to help you and your care partners navigate your treatment journey.

Alnylam Assist® offers support with insurance coverage, financial assistance, disease and treatment education, and starting AMVUTTRA® (vutrisiran).

- **Alnylam Patient Education Liaisons (PELs)** provide ATTR-CM and AMVUTTRA education to patients, their families and caregivers
 - **Request to connect with a PEL**
 - Alnylam PELs do not offer medical advice. Please talk to your doctor for specific concerns
- **One-on-one support in understanding insurance coverage and starting treatment** through Alnylam Case Managers
- **Alnylam offers multiple financial assistance programs*** that can help with your medication cost:
 - Alnylam Assist® Copay Program† covers certain out-of-pocket costs for eligible patients with commercial insurance
 - Alnylam Assist® Patient Assistance Program (PAP) provides AMVUTTRA at no cost to eligible patients, primarily the uninsured, who meet specified eligibility criteria
 - Additional programs may help if you have a delay or change in insurance coverage



Visit **AlnylamAssist.com** to learn more.

Call **1-833-256-2748**, Monday-Friday, 8AM-6PM.

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

†Patients with Medicare, Medicaid, or other government-sponsored insurance are not eligible for the Alnylam Assist® Copay Program. Out-of-pocket costs for the administration of AMVUTTRA will not be covered for patients residing where it is prohibited by law or where otherwise restricted.



INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

WHAT IS AMVUTTRA® (vutrisiran)?

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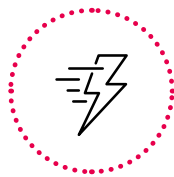
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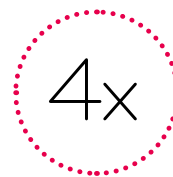
TAKE THE FIRST STEP—TALK TO YOUR DOCTOR ABOUT AMVUTTRA® (vutrisiran)



**Proven to help people
live longer and have fewer
heart-related hospital visits**



**The first and only silencer for
ATTR-CM that works to rapidly
knock down TTR at the source**



**4 doses a year given as
an injection every 3 months
by a healthcare provider**

Request more information today.

INDICATION

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AMV-USA-00884



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

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17 PATIENT COUNSELING INFORMATION

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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 \(2.2\)](#)].

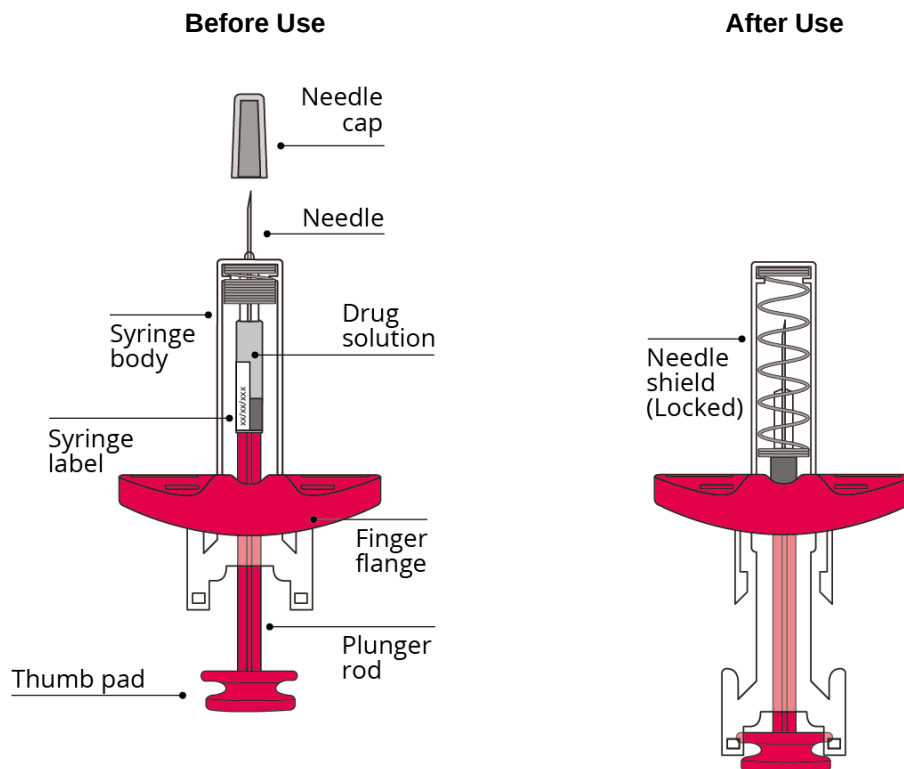
Missed Dose

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



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.

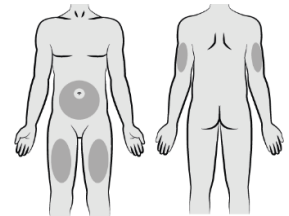
2. *Choose and prepare the injection site*

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.

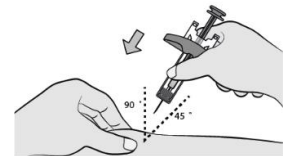
Do not use the syringe if it is dropped.



4. *Perform the injection*

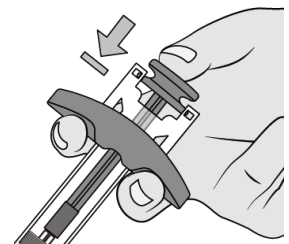
Pinch the cleaned skin.

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



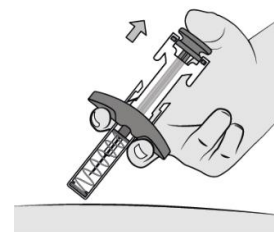
Inject all of the medication.

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.

Safety and effectiveness in pediatric patients have not been established.

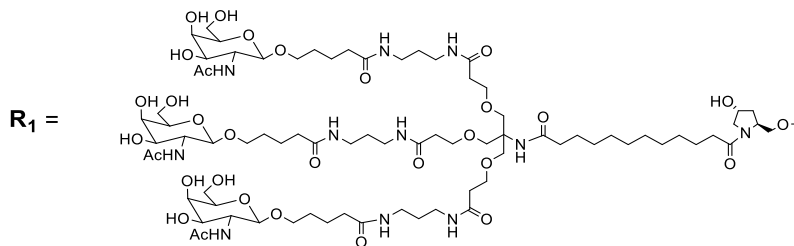
No dose adjustment is required in patients ≥ 65 years of age [see [Clinical Pharmacology \(12.3\)](#)]. In HELIOS-A, a total of 46 (38%) patients ≥ 65 years of age, including 7 (6%) patients ≥ 75 years of age, received AMVUTTRA. In HELIOS-B, a total of 299 (92%) patients ≥ 65 years old, including 203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

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 m²) [see [Clinical Pharmacology \(12.3\)](#)]. AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

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

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

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



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

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 m²), 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 x 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

The change from baseline to Month 9 in modified body mass index nominally favored AMVUTTRA [Table 3].

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)

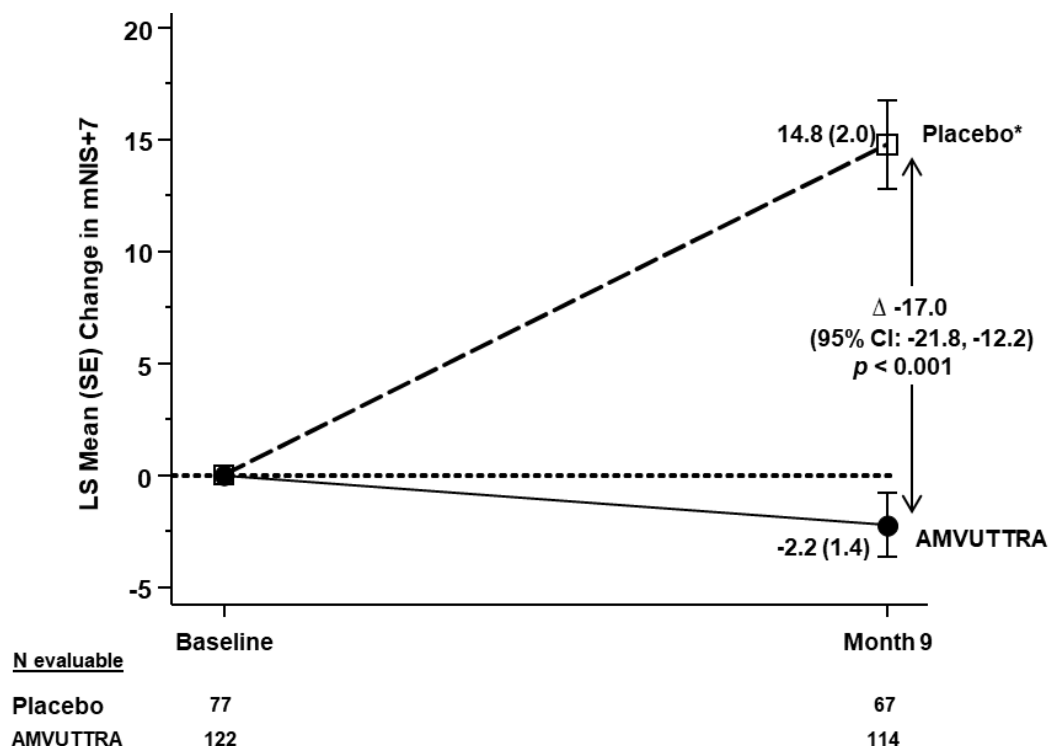
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)

‡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/m²) 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*)

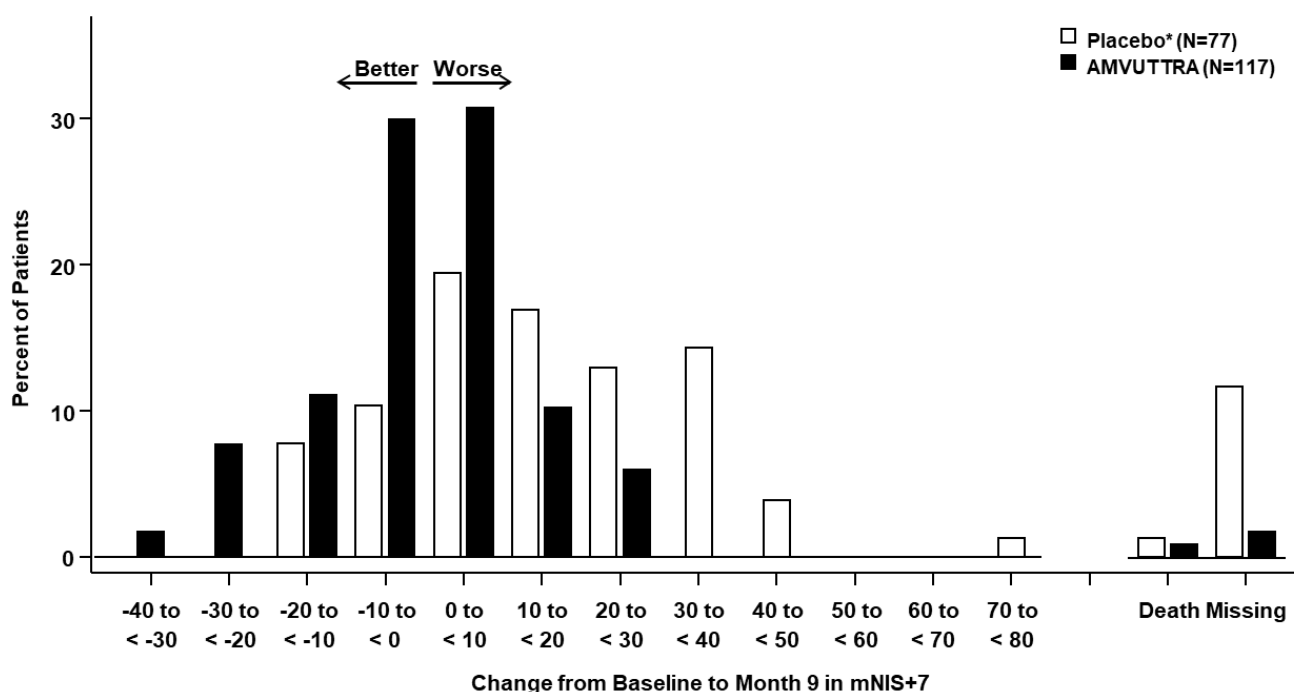


A decrease in mNIS+7 indicates improvement

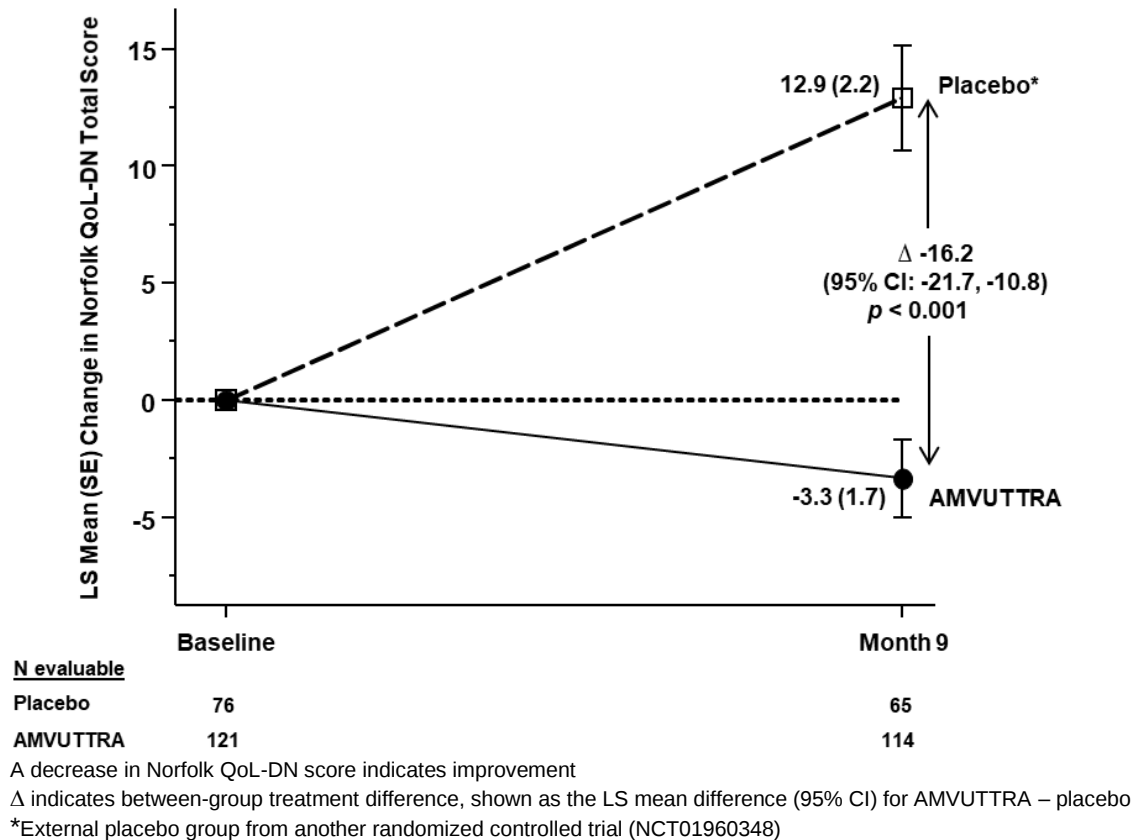
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA – placebo

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

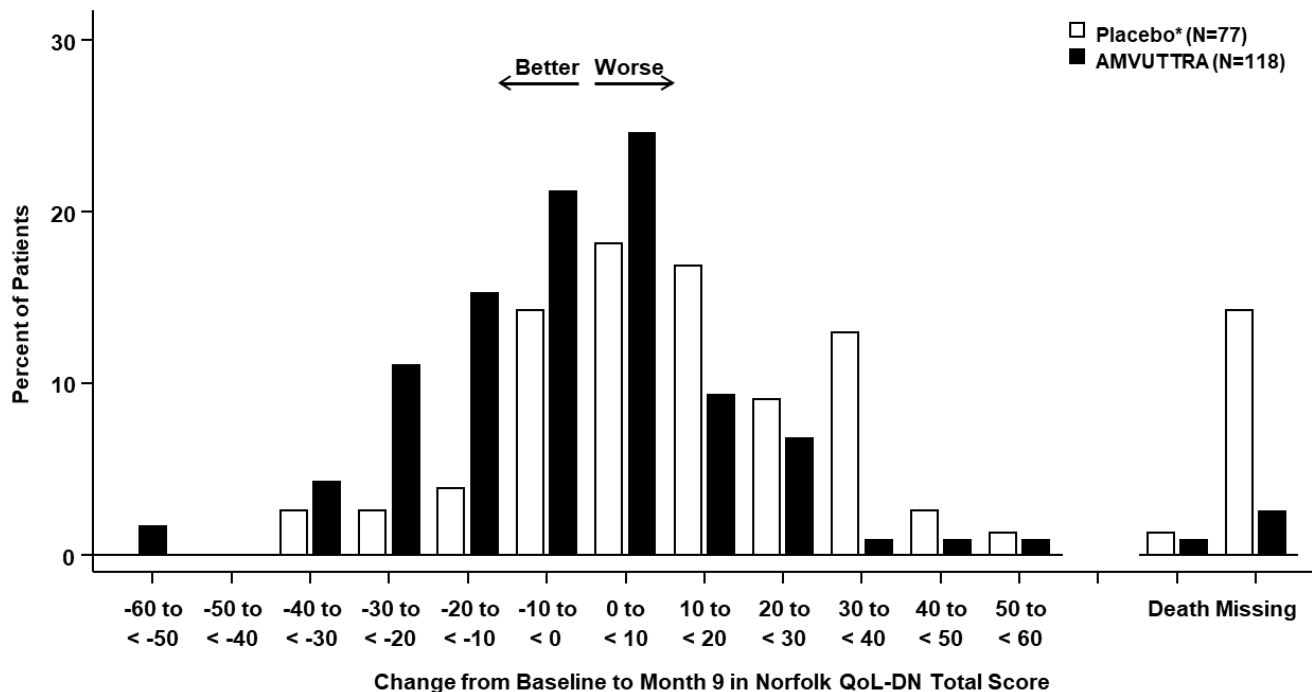
Figure 2: Histogram of mNIS+7 Change from Baseline at Month 9
(Comparison of AMVUTTRA Treatment in HELIOS-A to an External Placebo Control*)



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



**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).

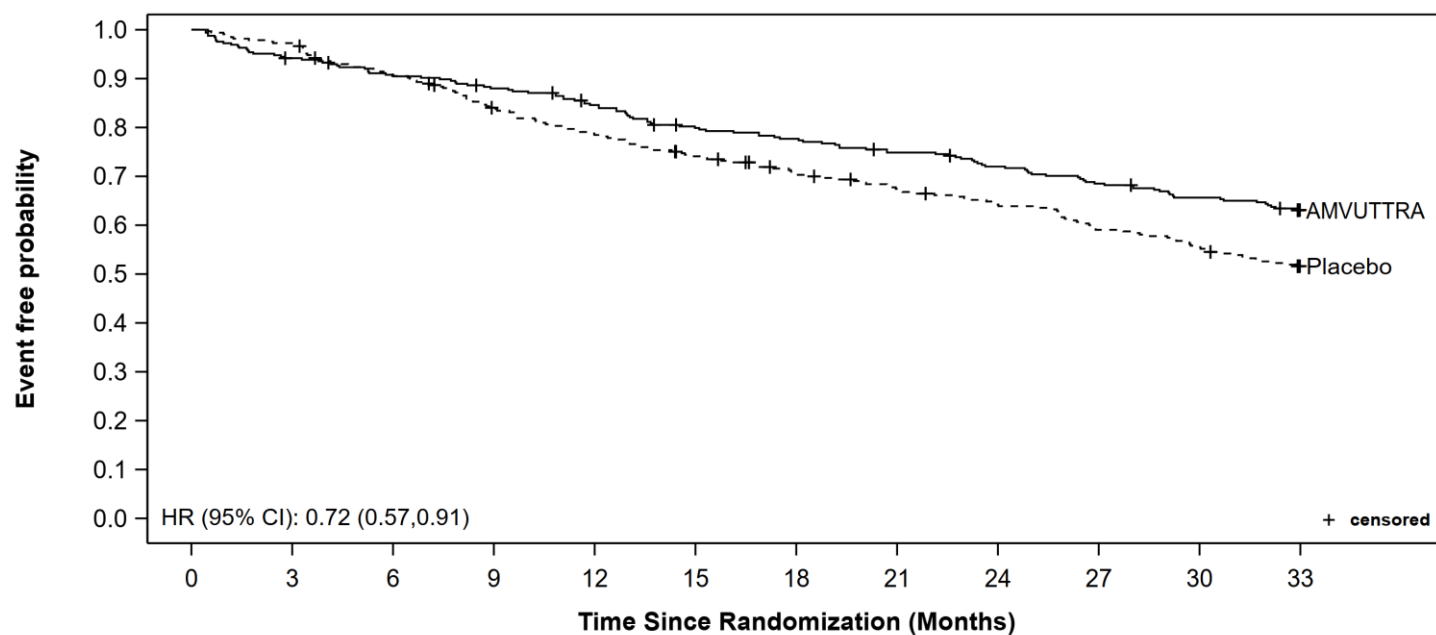
AMVUTTRA led to significant reduction in the risk of all-cause mortality and recurrent CV events compared to placebo in the overall and monotherapy population of 28% and 33%, respectively (Table 4). The majority of the deaths (77%) were CV-related. A Kaplan-Meier curve illustrating time to first CV event 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) [†] <i>p</i> -value [†]	0.72 (0.55, 0.93) 0.01		0.67 (0.49, 0.93) 0.02	
Components of the Primary Composite Endpoint					
All-cause mortality	Hazard Ratio (95% CI) [‡]	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 <i>p</i> -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)



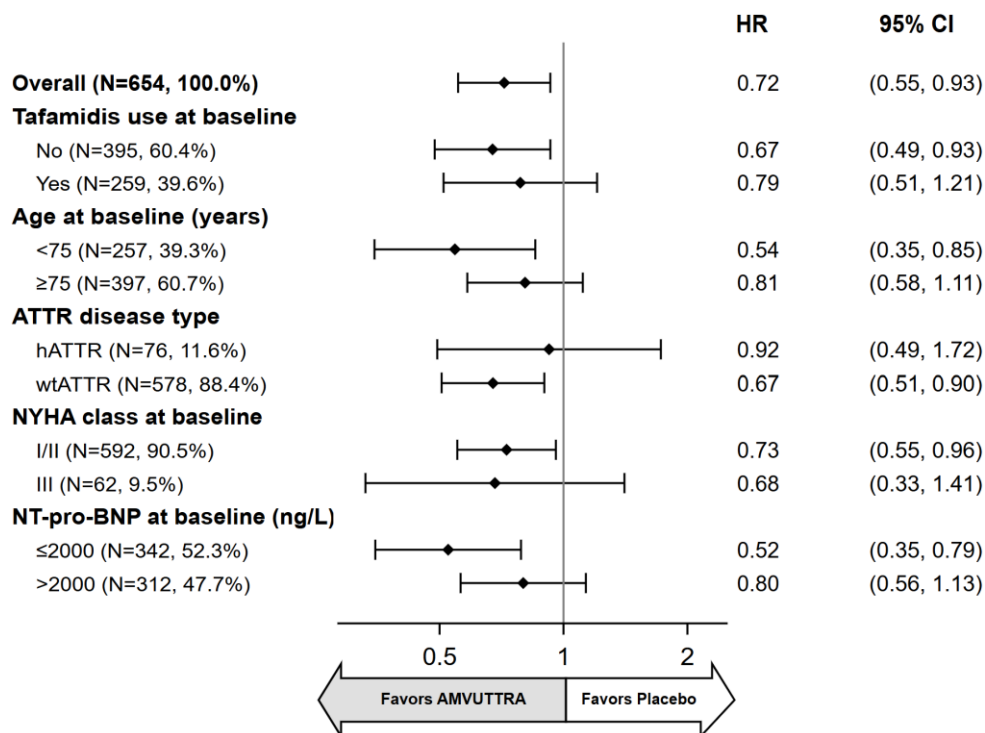
	No. at Risk (Cumulative No. of Events)											
AMVUTTRA	326(0)	306(19)	294(30)	284(39)	271(50)	254(65)	247(72)	237(81)	227(90)	216(101)	206(110)	185(118)
Placebo	328(0)	317(11)	295(31)	270(53)	253(70)	237(84)	221(96)	210(105)	199(115)	183(131)	172(142)	155(154)

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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