CAREGIVER BROCHURE

AMVUTTRA® (vutrisiran) may help

BRING LIFE'S MOMENTS WITHIN REACH

Patient portrayal.

AMVUTTRA is the first and only injection given 4 times a year to treat the polyneuropathy of hereditary ATTR (hATTR) amyloidosis in adults*

Patients receiving AMVUTTRA had significantly improved nerve function and quality of life at 9 months and continued to improve throughout an 18-month study compared to patients receiving placebo in a similar study.

*Dosing once every 3 months by a healthcare professional.

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. (Continued on page 2)

Please see additional Important Safety Information on page 6 and full Prescribing Information.

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Offering support as a caregiver

When a family member receives a diagnosis of hATTR amyloidosis and is prescribed AMVUTTRA® for the polyneuropathy caused by the disease, navigating symptoms of the disease and multiple doctor appointments can mean that loved ones have to become caregivers.

The role of a caregiver is a significant responsibility and can present challenges that require lifestyle changes for you and your loved one.

We're here to help. This guide provides you with information, tips, and suggestions that can help you support your loved one.

Important Safety Information

What are the most important things I should know about AMVUTTRA?
AMVUTTRA can cause:

- **Low Vitamin A Levels (cont.)**
  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.

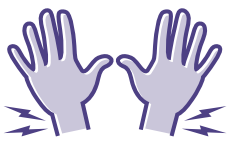
Please see additional Important Safety Information on page 6 and full Prescribing Information.

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Understanding hATTR amyloidosis

hATTR amyloidosis is a rare, inherited condition that affects multiple parts of the body. As a caregiver, it's important for you to be aware of the symptoms of hATTR amyloidosis, so you can help keep track of your loved one's condition and communicate effectively with their doctor.

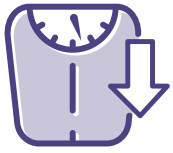
Many of the symptoms of hATTR amyloidosis can affect a loved one's daily life, including:



Carpal tunnel syndrome

Altered sensation or loss of sensitivity

Severe stomach issues



Unintentional weight loss

Loss of mobility

Dizziness upon standing

This is not a complete list of symptoms that may be experienced with hATTR amyloidosis.

AMVUTTRA® does not treat all of the symptoms of hATTR amyloidosis.

Please see Important Safety Information on page 6 and full Prescribing Information.

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Your guide to AMVUTTRA®

Important things to remember

BEFORE	DURING	AFTER
Keep track of appointment details: • Take note of topics you may want to discuss with your loved one's doctor • Plan reliable transportation to and from the appointment	**Become familiar** with how AMVUTTRA is administered: • AMVUTTRA is an injection given by a healthcare professional, such as a doctor or nurse • AMVUTTRA is administered under the skin, in the upper arms, thighs, or abdomen	**Make the next appointment** to stay on schedule: • AMVUTTRA is administered once every 3 months • You can work with your loved one's doctor to choose where they receive AMVUTTRA—their doctor's office, a local clinic, or their own home (depending on insurance)
With AMVUTTRA treatment, no premedications or laboratory monitoring are required.		

To learn more about AMVUTTRA, visit www.amvuttra.com

Important Safety Information

What are the common side effects of AMVUTTRA?
The most common side effects of AMVUTTRA are pain in the arms or legs, pain in the joints (arthralgia), shortness of breath (dyspnea), 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.

Please see additional Important Safety Information on page 6 and full Prescribing Information.

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Helpful tips for you

Caring for someone with a rare condition may require lifestyle changes. The following tips may offer you some help as you care for a loved one with the disease.

Learn about your loved one's condition—Understanding the symptoms of the disease and what to expect from treatment with AMVUTTRA® may help you feel more prepared for conversations with your loved one and their doctors.

Make a plan—Creating a schedule, including setting treatment appointments once every 3 months, can help you establish a routine with your family member that ensures they receive their treatment as prescribed.

Have an open dialogue—Talking with your loved one may help you form a stronger bond and allow you to share insights with doctors about their health and emotional well-being.

Take notes—Taking notes may make it easier to remember important information when talking to their doctors.

Explain your circumstances to others—Acting as a caregiver may sometimes require adjustments to your schedule or routine. You may need to explain to your employer, for example, how the condition impacts your loved one and disclose that you may need to occasionally take extra time to help them get to their doctor appointments.

Take time to care for yourself. It's important to look out for your own well-being when taking care of others. Continue to focus on your health with exercise, sleep, and a balanced diet.

Please see Important Safety Information on page 6 and full Prescribing Information.

Indication and Important Safety Information

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Indication

What is AMVUTTRA® (vutrisiran)?
AMVUTTRA is a prescription medicine that treats the polyneuropathy caused by an illness called hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). AMVUTTRA is used in adults only.

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.

What are the common side effects of AMVUTTRA?
The most common side effects of AMVUTTRA are pain in the arms or legs, pain in the joints (arthralgia), shortness of breath (dyspnea), 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.

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

Finding help and resources

amvuttra (vutrisiran) injection 25 mg/0.5 mL

Connect with an Alnylam Educator

An Alnylam Patient Education Liaison (PEL) can provide education to help you and your loved one better understand the disease and answer your questions about AMVUTTRA®.

Alnylam PELs do not offer medical advice. Please talk to your loved one's doctor for specific concerns.

Visit www.amvuttraPEL.com to connect with an Alnylam Educator

Get patient support services through Alnylam Assist®

Alnylam Assist is a patient support program designed to help your loved one get started on treatment, understand their insurance coverage, determine eligibility for financial assistance, and provide ongoing support in their treatment journey with AMVUTTRA.

An Alnylam Case Manager will work with your loved one to begin treatment with and maintain access to AMVUTTRA.

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

Financial assistance programs[a] may include:

Alnylam Assist Commercial Copay Program[b] 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 financial criteria.

Alnylam ASSIST®

To learn more, visit www.AlnylamAssist.com.

[a]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.

[b]Patients with Medicare, Medicaid, or other government-sponsored insurance are not eligible for the Alnylam Assist Commercial 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.

Connect with someone who understands

There are advocacy and support groups locally and nationally that can help you connect with people who share similar caretaking experiences, questions, and concerns.

Amyloidosis Foundation
www.amyloidosis.org

Amyloidosis Research Consortium
www.arci.org

Amyloidosis Support Groups
www.amyloidosissupport.org

Caregiver Action Network (CAN)
www.caregiveraction.org

The Foundation for Peripheral Neuropathy
www.foundationforpn.org

Global Genes
www.globalgenes.org

National Alliance for Caregiving (NAC)
www.caregiving.org

National Organization for Rare Disorders
www.rarediseases.org

To learn more about AMVUTTRA® (vutrisiran), please scan the QR code or visit www.amvuttra.com

Please see Important Safety Information on page 6 and 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

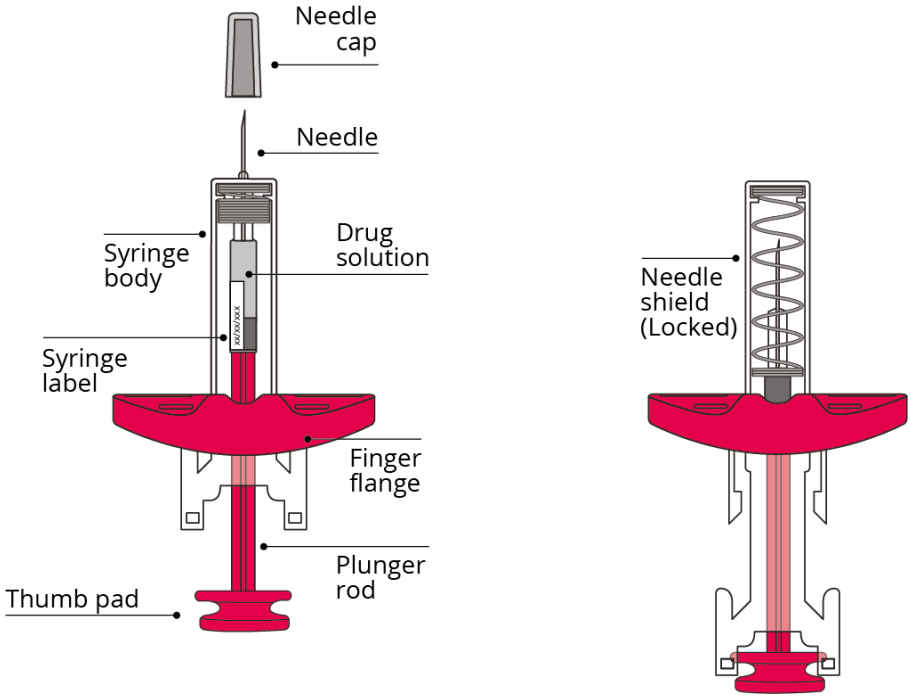
If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

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.

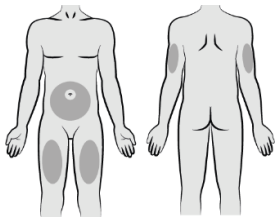
2. *Choose and prepare the injection site*

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.

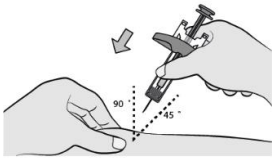
Do not recap the syringe.

Do not use the syringe if it is dropped.

4. *Perform the injection*

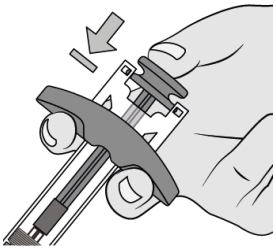
Pinch the cleaned skin.

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



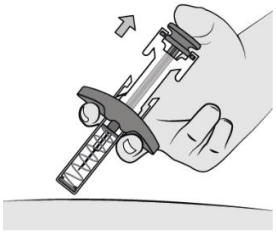
Inject all of the medication.

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.

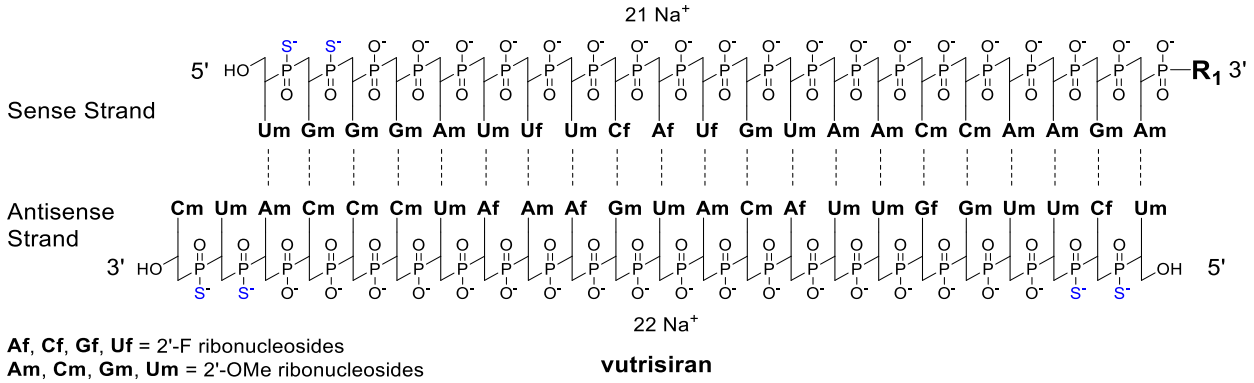
8.7 Hepatic Impairment

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.

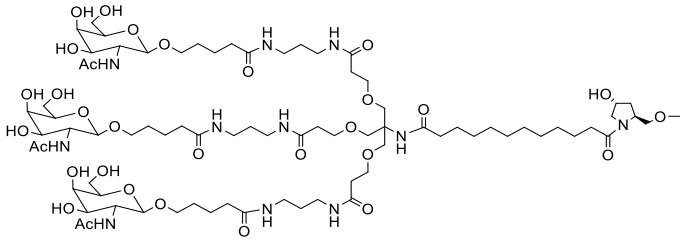
The structural formula of vutrisiran sodium is presented below.



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].

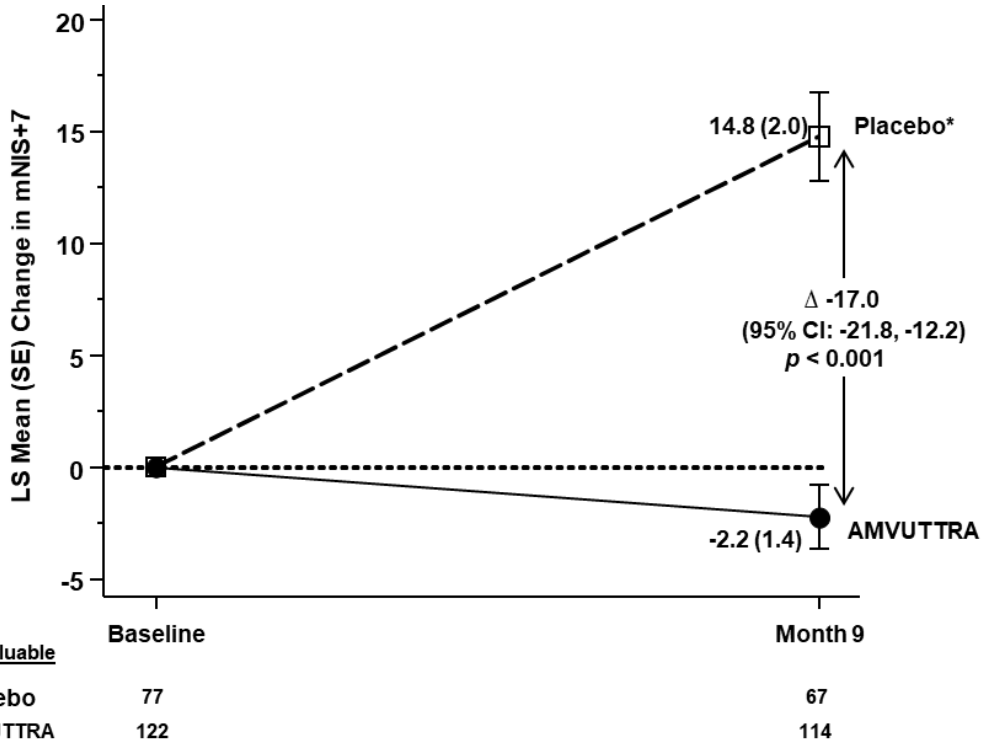
Table 3: Clinical Efficacy Results (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)

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

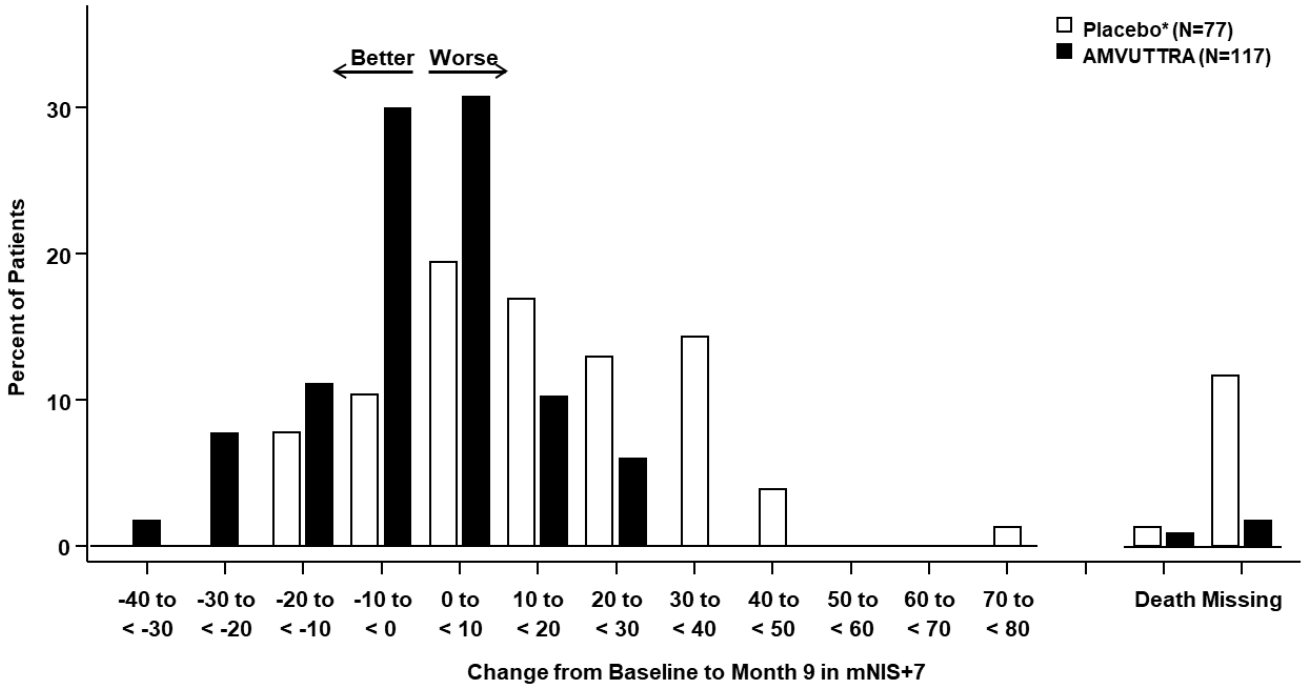
*External placebo group from another randomized controlled trial (NCT01960348)
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)
‡A lower number indicates less impairment/fewer symptoms
§A higher number indicates less disability/less impairment
¶mBMI: 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)

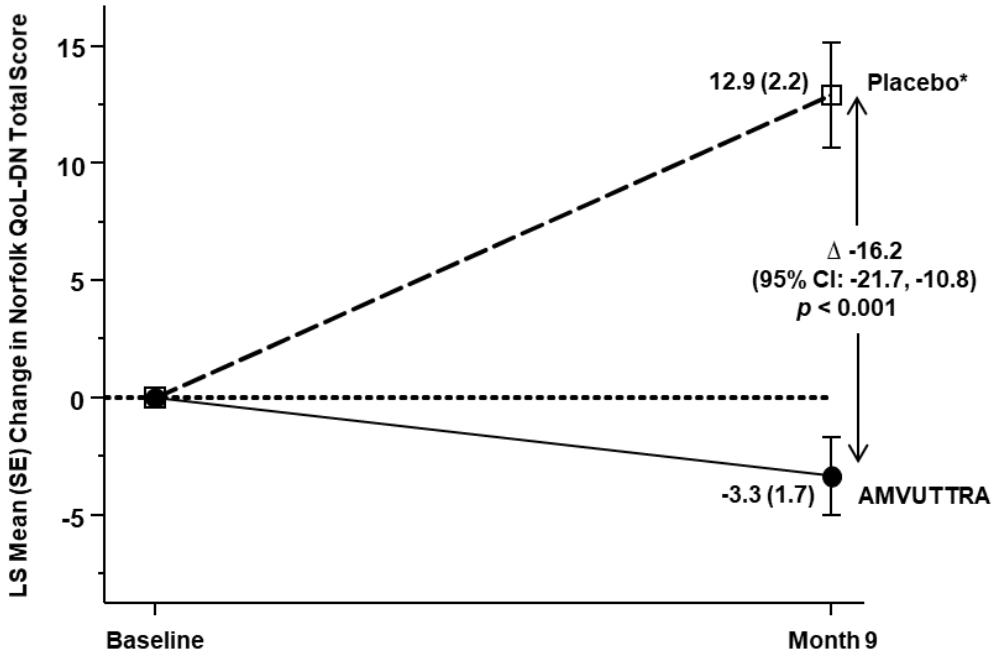
Figure 2: Histogram of mNIS+7 Change from Baseline at Month 9
(Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)



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*)



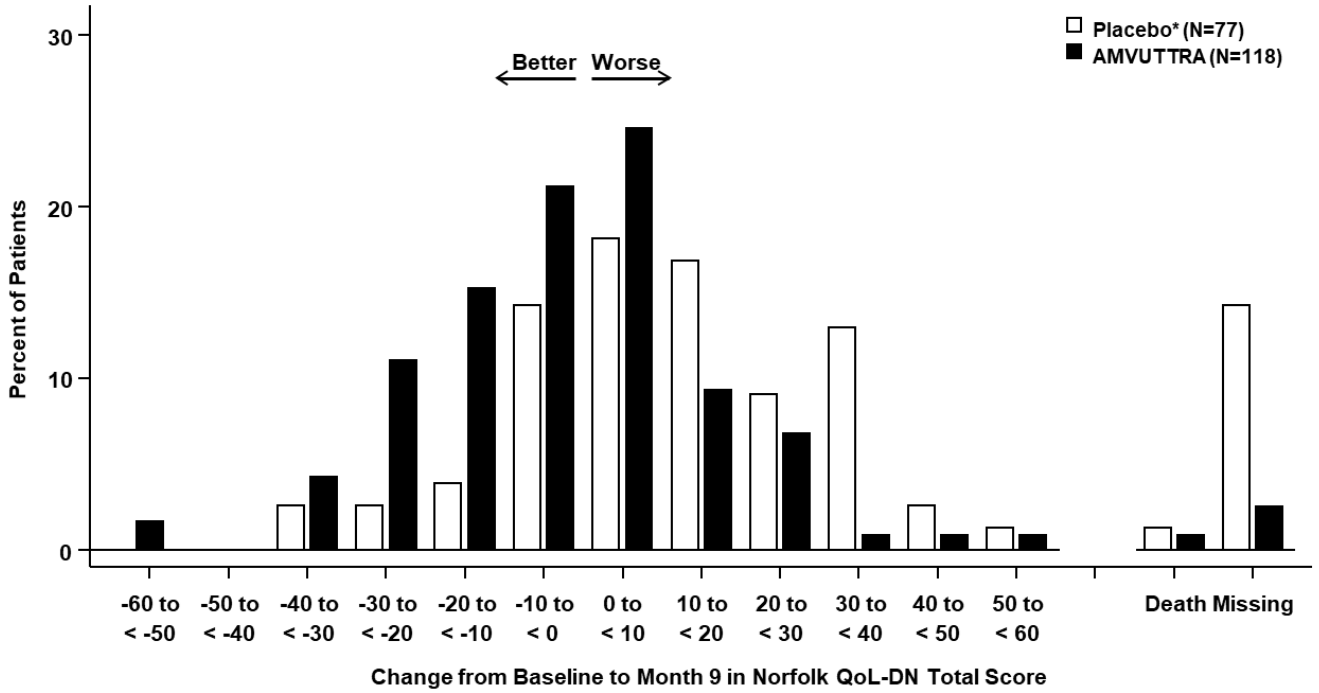
N evaluable		
Placebo	76	65
AMVUTTRA	121	114

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)]*.

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