

# ONPATTRO<sup>®</sup>

## (patisiran)

### Dosing and Preparation Guide



#### Indication

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

#### Important Safety Information

##### Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

onpattro<sup>®</sup>  
(patisiran) lipid complex injection  
10 mg/5 mL

# hATTR amyloidosis: a multisystem disease with frequent and early polyneuropathy manifestations<sup>1-5</sup>

Hereditary transthyretin-mediated (hATTR) amyloidosis is caused by a variant in the transthyretin (TTR) gene that results in the accumulation of amyloid deposits in multiple organs of the body.<sup>3,6,7</sup>

## Early symptoms of hATTR amyloidosis may include<sup>3</sup>:



### Peripheral sensory-motor neuropathy

(e.g., neuropathic pain, paresthesia, weakness, bilateral carpal tunnel syndrome, difficulty walking)



### Autonomic neuropathy

(e.g., orthostatic hypotension, recurrent urinary tract infections, sexual dysfunction, sweating abnormalities, urinary retention)



### Gastrointestinal manifestations

(e.g., diarrhea, nausea, vomiting, unintentional weight loss)

## hATTR amyloidosis has a heterogeneous symptom presentation.

## Other symptoms that may raise clinical suspicion include<sup>3,8</sup>:

- **Cardiovascular manifestations**  
(e.g., arrhythmias, conduction abnormalities, heart failure)
- **Renal abnormalities**  
(e.g., renal impairment, cardiorenal syndrome)
- **Ocular involvement**  
(e.g., vitreous opacity, glaucoma)

## ONPATTRO® (patisiran) does not treat all of the symptoms of hATTR amyloidosis.

## Important Safety Information

### Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO 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 ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum 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).

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# ONPATTRO<sup>®</sup> (patisiran)—the first FDA-approved RNAi therapeutic

## ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

- ONPATTRO is a double-stranded small interfering ribonucleic acid (siRNA) formulated as lipid nanoparticles for targeted delivery to hepatocytes, the primary source of TTR protein production<sup>9,10</sup>
- ONPATTRO is administered via intravenous (IV) infusion once every 3 weeks. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg<sup>9</sup>
- ONPATTRO is supplied as a 10 mg/5 mL solution in a single-dose glass vial<sup>9</sup>

ONPATTRO is a white to off-white, opalescent, homogeneous solution.<sup>9</sup> Note that there may be a white coating visible on the inner surface of the vial. This is normal and does not impact the product quality.



## APOLLO study: ONPATTRO demonstrated a significant improvement versus placebo across multiple endpoints at 18 months<sup>9</sup>

- ONPATTRO-treated patients had an 84% mean reduction of serum TTR at 18 months<sup>9,11</sup>
- For the primary endpoint, mNIS+7, LS mean change from baseline was -6.0 points (improvement) for ONPATTRO-treated patients versus 28.0 points (worsening) for patients who received placebo, a difference of -34.0 points<sup>9,12</sup>
  - mNIS+7, an objective 304-point scale, assessed motor strength, reflexes, sensation, nerve conduction, and postural blood pressure
- For the key secondary endpoint, Norfolk QoL-DN, LS mean change from baseline was -6.7 points (improvement) with ONPATTRO compared with 14.4 points (worsening) with placebo, a difference of -21.1 points<sup>9,13</sup>
  - Norfolk QoL-DN score is a patient-reported assessment that evaluated neuropathy in domains such as physical functioning, activities of daily living, symptoms, and autonomic neuropathy (score ranges from -4 to 136)

LS=least squares; mNIS+7=modified Neuropathy Impairment Score + 7; Norfolk QoL-DN=Norfolk Quality of Life-Diabetic Neuropathy; RNA=ribonucleic acid; RNAi=RNA interference.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

**onpattro**<sup>®</sup>  
(patisiran) lipid complex injection  
10 mg/5 mL

# Preparation and dosing

## To prepare ONPATTRO® (patisiran), you will need:

- ✓ DEHP-free infusion bag containing 0.9% Sodium Chloride Injection, USP (normal saline solution). Total volume needed: 200 mL  
**Important:** If using a 250 mL infusion bag, it is necessary to remove the calculated volume of ONPATTRO plus 50 mL of normal saline to ensure that the total final volume is 200 mL
- ✓ 0.45 micron PES syringe filter
- ✓ Empty sterile container (e.g., a glass vial or an empty syringe)
- ✓ Syringes, needles, and standard IV preparation materials
- ✓ DEHP-free extension set with 1.2 micron PES in-line infusion filter (for administration of the infusion)

## Dosing<sup>9</sup>

ONPATTRO is supplied as a 10 mg/5 mL solution in a single-dose glass vial.

ONPATTRO is administered via an ~80-minute IV infusion once every 3 weeks.

Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg.

Use the dosing guide on [page 18](#)  
for quick, easy dosing calculations.

DEHP=di(2-ethylhexyl)phthalate; PES=polyethersulfone.

Please see Important Safety Information on [page 16](#)  
and accompanying full [Prescribing Information](#).

# Premedication<sup>9</sup>

All patients should receive premedication prior to ONPATTRO® (patisiran) administration to reduce the risk of infusion-related reactions (IRRs).

Each of the following premedications should be given on the day of the infusion **at least 60 minutes prior to the start of infusion**:

- IV corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- IV H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- IV H2 blocker (e.g., ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions due to the corticosteroid premedication, the corticosteroid dose may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV), or equivalent.

Some patients may require additional or higher doses of 1 or more of the premedications to reduce the risk of IRRs.

## Important Safety Information

### Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

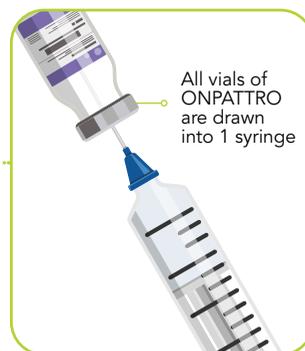
# Preparation and handling<sup>9</sup>

**ONPATTRO® (patisiran) must be filtered and diluted prior to IV infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:**

1. Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.
2. Inspect visually for particulate matter and discoloration. If the vials are discolored or foreign particles are present, do not use the vials and report the issue to Alnylam at 1-877-ALNYLAM.

**Note:** ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white coating may be observed on the inner surface of the vial, typically at the meniscus. This does not impact the quality of the drug. The coating may remain in the vial after withdrawing the solution. This also does not impact product quality.

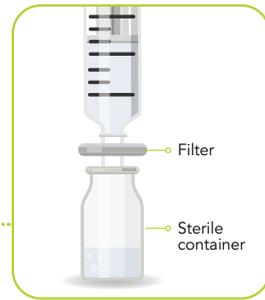
3. Calculate the required dose of ONPATTRO based on the recommended weight-based dosage. **Please see the dosing guide on [page 18](#).**
4. The final total volume of the ONPATTRO infusion should be 200 mL. From the DEHP-free infusion bag containing 0.9% Sodium Chloride Injection, USP, remove the calculated volume of drug plus any extra saline.
  - If using a 250 mL infusion bag, it is necessary to remove the calculated volume of ONPATTRO plus 50 mL of normal saline
5. Withdraw the entire contents of all of the vials needed into a single sterile syringe.



Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Preparation and handling (cont'd)<sup>9</sup>

6. Filter ONPATTRO® (patisiran) through a sterile 0.45 micron PES syringe filter into a sterile container such as a sterile glass vial or sterile syringe. **Do not filter the drug out of the vial directly into an IV bag.**

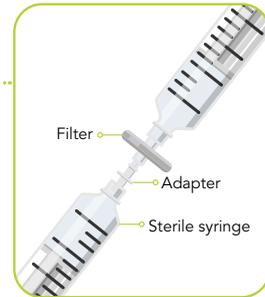


7. If using a sterile glass vial, withdraw the calculated dose of filtered ONPATTRO from the sterile container using a new sterile syringe.



If filtering into a second sterile syringe, ensure that the full calculated dose of ONPATTRO has been filtered into the container.

8. Dilute the required volume of filtered ONPATTRO into a 200 mL DEHP-free infusion bag containing 0.9% Sodium Chloride Injection, USP.



9. Gently invert the infusion bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.

- ONPATTRO should not be delivered via pneumatic tube systems

10. Discard any unused portion of ONPATTRO.



## Important Safety Information

### Adverse Reactions

The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Administration<sup>9</sup>

## The steps below provide the instruction you'll need to administer ONPATTRO<sup>®</sup> (patisiran):

1. Use a dedicated line with an infusion set containing a 1.2 micron PES in-line infusion filter. Use infusion sets and lines that are DEHP-free.
2. Infuse the diluted solution of ONPATTRO intravenously, via an ambulatory infusion pump, over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increase to approximately 3 mL/min for the remainder of the infusion.



The duration of infusion may be extended in the event of an IRR. **See page 10 for details about what to do in the case of IRRs.**

3. Administer only through a free-flowing venous access line. Monitor the infusion site for possible infiltration during drug administration. Suspected extravasation should be managed according to local standard practice for nonvesicants (pH of ONPATTRO solution is ~7.0).
4. After completion of the infusion, flush the IV administration set with 0.9% Sodium Chloride Injection, USP, to ensure that all ONPATTRO has been administered.

Observe the patient during the infusion and, if clinically indicated, following the infusion.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

## Considerations when preparing the dose

Proper preparation of ONPATTRO® (patisiran) requires filtration to remove particulates. An additional vial of ONPATTRO may be required depending on the type of filter used and the amount of product that remains in the filter (hold-up volume).<sup>9</sup> **The dosing guide found on [page 18](#) assumes that 1 mL of drug product remains in the filter when determining the number of vials needed**, based on the manufacturer's information for the Pall PharmAssure® 0.45 micron 32 mm syringe filter with low protein binding Supor® membrane (Product ID HP4644).<sup>14</sup>

The diluted solution should be administered immediately after preparation.

- If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time)
- Do not freeze

## Missed dose<sup>9</sup>

If a dose is missed, administer ONPATTRO as soon as possible.

- If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient's original schedule
- If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter

## Important Safety Information

### Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO 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 ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum 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).

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Infusion-related reactions<sup>9</sup>

IRRs have been observed in patients treated with ONPATTRO<sup>®</sup> (patisiran).

In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a double-blind, placebo-controlled study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients.

- Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time
- Across clinical studies, the most common symptoms (reported in  $\geq 2\%$  of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache
- Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting
- IRRs resulted in permanent discontinuation of ONPATTRO in  $< 1\%$  of patients in clinical studies

## Management of IRRs

- If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment) as clinically indicated



If a patient has a mild to moderate IRR that requires interruption of the infusion, consider resuming the infusion at a slower rate only if symptoms have resolved.

- In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of 1 or more of the premedications with subsequent infusions to reduce the risk of IRRs.

To report suspected adverse reactions, contact Alnylam Pharmaceuticals at 1-877-ALNYLAM (1-877-256-9526), or the FDA at 1-800-FDA-1088, or go to [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

## Storage and handling<sup>9</sup>

- Store ONPATTRO® (patisiran) vials at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen
- If refrigeration is not available, ONPATTRO vials can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days

### After preparation:

ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.

#### Consider home administration



Home administration may be an option for some patients. The decision for a patient to receive home administrations should be made after an evaluation and recommendation by the treating physician, and may not be covered by all insurance plans. Some physicians may choose to have patients receive their first few infusions in the clinic prior to transitioning to home administration. Regardless of the setting, ONPATTRO infusions should be performed by a healthcare professional.

Alnylam Assist™ can help answer questions about home administration.

## Ongoing support from Alnylam Assist

### Alnylam Assist offers a wide range of services to guide your patients through treatment with ONPATTRO, including:

- Disease education and support for your patients that is customized to their communication preferences
- Comprehensive reimbursement education and patient-specific benefit verification
- Ordering assistance and facilitation of delivery via specialty distributor or specialty pharmacy



8AM–6PM, Monday–Friday  
📞: 1-833-256-2748 | 📠: 1-833-256-2747

To learn more visit [www.AlnylamAssist.com](http://www.AlnylamAssist.com).

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Dosing and preparation FAQs

## 1. Are substitutions permitted for the IV premedications? Can they be given orally?

IV equivalents of dexamethasone, diphenhydramine, and ranitidine may be used per the judgment of the prescribing physician. For premedications not available or not tolerated intravenously, equivalents may be administered orally.

## 2. What is the white coating in the ONPATTRO® (patisiran) vial?

ONPATTRO is a white to off-white, opalescent, homogeneous solution. Some of the product residue may be observed on the inner surface of the vial, typically at the meniscus. This coating may remain in the vial after withdrawing the solution and does not impact the quality of the drug.

## 3. How many vials of ONPATTRO are needed to prepare my patient's dose?<sup>9,14</sup>

ONPATTRO is administered via IV infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg. ONPATTRO is supplied as a 10 mg/5 mL (2 mg/mL) solution in a single-dose vial. Proper preparation requires filtration to remove particulates. An additional vial of ONPATTRO may be required to prepare the full recommended dose, depending on the type of filter used and the amount of product that remains in the filter (hold-up volume). The dosing guide on [page 18](#) assumes that 1 mL of drug product remains in the filter when determining the number of vials needed. Consult the dispensing pharmacy or filter manufacturer to determine the expected hold-up volume for the filter used to prepare the ONPATTRO dose.

## 4. What size IV bag is needed to prepare ONPATTRO?

The final total volume of the prepared ONPATTRO dose is 200 mL. If using a 250 mL infusion bag, it is necessary to remove the calculated dose of ONPATTRO plus 50 mL of normal saline to ensure that the total final volume is 200 mL.

## 5. Can I filter ONPATTRO directly out of the vial and into the infusion bag?

ONPATTRO must be filtered through a 0.45 micron PES syringe filter into a sterile container, prior to diluting it into the infusion bag using a sterile syringe. Filtering ONPATTRO directly out of the vial would cause shearing of the lipid nanoparticles due to increased pressure, preventing the active drug from being delivered to the hepatocytes, and therefore is not recommended.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

## **6. What should I use for a sterile container during step 6, on page 7?**

Options for sterile containers include glass containers, vials, or sterile syringes.

## **7. Can a different size PES filter be used during step 6, on page 7?**

If 0.45 micron PES filters are unavailable, 0.2 micron PES filters can be used; however, each vial of ONPATTRO® (patisiran) will require filtration through a separate 0.2 micron filter due to the smaller pore size.

## **8. Why does ONPATTRO preparation require 2 filtration steps?**

The protocol for preparation of ONPATTRO includes filtering the drug through a 0.45 micron PES filter prior to diluting in an infusion bag of normal saline. The prepared drug is then infused from the bag through a second 1.2 micron PES in-line filter. The use of 2 filtration steps ensures delivery of ONPATTRO without residual particles that could cause filter-clogging events during the infusion.

## **9. What should be done if my patient experiences an infusion-related reaction (IRR) during the ONPATTRO infusion?**

If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management if clinically indicated. If the infusion is interrupted, consider resuming at a slower rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

For additional questions regarding ONPATTRO, please contact Alnylam Medical Information at 1-877-ALNYLAM (1-877-256-9526) or [medinfo@alnylam.com](mailto:medinfo@alnylam.com). An electronic version of the Dosing & Preparation Guide and additional resources for healthcare professionals can be found at [www.onpattrohcp.com](http://www.onpattrohcp.com).

Please see Important Safety Information on [page 16](#)  
and accompanying full [Prescribing Information](#).

# Ordering filters through McKesson<sup>a</sup>

## Options for ordering the filters needed to prepare and administer ONPATTRO<sup>®</sup> (patisiran) through McKesson Plasma & Biologics or McKesson Specialty Health

### McKesson Plasma & Biologics



Online: [connect.mckesson.com](https://connect.mckesson.com)



Email: [mpborders@mckesson.com](mailto:mpborders@mckesson.com)



Phone: 1-877-625-2566



Fax: 1-888-752-7626

### McKesson Specialty Health



Online: [mscs.mckesson.com](https://mscs.mckesson.com)



Email: [mshcustomercare-mspl@mckesson.com](mailto:mshcustomercare-mspl@mckesson.com)



Phone: 1-855-477-9800



Fax: 1-800-800-5673

### Filters available for order<sup>b</sup>

Filter Name	Quantity	Manufacturer Product #	McKesson Plasma & Biologics Product #	McKesson Specialty Health Product #
EMD Millipore Millex-HP Syringe Filter Unit, 0.45 µm, PES, 33mm	50	SLHP033RS	3955036	5503021
	250	SLHP033RB	3955028	
B Braun Medical, Inc. Extension Set, 1.2 Micron Filter, Luer Lock Connector, DEHP-Free, 4.3 mL Priming Volume, 10"L, Latex Free	50	473994	3954971	5502260

<sup>a</sup>Cost of filters ordered through McKesson is the responsibility of the healthcare professional and is not covered by Alnylam.

<sup>b</sup>The list of filter options above is not comprehensive. Alnylam does not endorse or recommend any specific filter manufacturer for the preparation and administration of ONPATTRO.

If you do not have a McKesson account, get started by calling 1-877-625-2566 to speak with a McKesson Service Representative.

**Note:** Both a **0.45 micron** PES syringe filter and a **1.2 micron** PES in-line infusion filter are needed to prepare and administer ONPATTRO.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Ordering filters through a specialty pharmacy

## Options for ordering the filters needed to prepare and administer ONPATTRO® (patisiran) through Orsini Healthcare or CVS Specialty Pharmacy

For sites purchasing ONPATTRO through one of the following specialty pharmacies, filters may be available for order.

### Orsini Specialty Pharmacy

1111 Nicholas Boulevard  
Elk Grove Village, IL 60007

 **Phone:** 1-800-690-8236

 **Fax:** 1-877-445-8481

### CVS Specialty Pharmacy

800 Biermann Court, Suite B  
Mount Prospect, IL 60056

 **Phone:** 1-866-526-4984

 **Fax:** 1-855-592-6890



8AM–6PM, Monday–Friday

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

**To learn more visit**  
[www.AlylamAssist.com](http://www.AlylamAssist.com).

Please see Important Safety Information on [page 16](#)  
and accompanying full [Prescribing Information](#).

## Indication

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

## Important Safety Information

### Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

### Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO 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 ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum 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 ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

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

# Dosing guide<sup>9</sup>

ONPATTRO<sup>®</sup> (patisiran) is supplied as a 10 mg/5 mL solution in a single-dose vial.

ONPATTRO is administered via IV infusion once every 3 weeks.

Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg.

Proper preparation of ONPATTRO requires filtration to remove particulates. An additional vial of ONPATTRO may be required depending on the type of filter used and the amount of product that remains in the filter (hold-up volume).<sup>9</sup> **The dosing table below assumes that 1 mL of drug product remains in the filter when determining the number of vials needed**, based on the available manufacturer's information for the Pall PharmAssure<sup>®</sup> 0.45 micron 32 mm syringe filter with low protein binding Supor<sup>®</sup> membrane (Product ID HP4644).<sup>14</sup>

**References:** **1.** Ando Y, Coelho T, Berk JL, et al. *Orphanet J Rare Dis*. 2013;8:31. **2.** Coutinho P, Martins da Silva A, Lopes Lima JL, et al. *Excerpta Medica*. 1980:88-98. **3.** Conceição I, Gonzalez-Duarte A, Obici L, et al. *J Peripher Nerv Syst*. 2016;21(1):5-9. **4.** Ando Y, Nakamura M, Araki S. *Arch Neurol*. 2005;62(7):1057-1062. **5.** Coelho T, Merlini G, Bulawa CE, et al. *Neurol Ther*. 2016;5(1):1-25. **6.** Adams D, Coelho T, Obici L, et al. *Neurology*. 2015;85(8):675-682. **7.** Shin SC, Robinson-Papp J. *Mt Sinai J Med*. 2012;79(6):733-748. **8.** Ruberg FL, Grogan M, Hanna M, et al. *J Am Coll Cardiol*. 2019;73(22):2872-2891. **9.** ONPATTRO Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc. **10.** Gertz MA. *Am J Manag Care*. 2017;23(suppl 7):S107-S112. **11.** Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. *N Engl J Med*. 2018;379(1):11-21. **12.** Adams D, Suhr OB, Dyck PJ, et al. *BMC Neurol*. 2017;17(1):181. **13.** Vinik EJ, Vinik AI, Paulson JF, et al. *J Peripher Nerv Syst*. 2014;19:104-119. **14.** PharmAssure 32 mm syringe filters [manufacturing leaflet]. Port Washington, NY: Pall Corporation; 2010.

Please see Important Safety Information on [page 16](#) and accompanying full [Prescribing Information](#).

# Dosing guide (cont'd)<sup>9</sup>

For patients weighing  $\geq 100$  kg, the recommended dose is 30 mg.

**Note:** The bolded numbers signify weights that may require an additional vial of ONPATTRO<sup>®</sup> (patisiran) due to drug product remaining in the filter.

Body Weight (kg)	mg	mL	Vials	Body Weight (kg)	mg	mL	Vials	Body Weight (kg)	mg	mL	Vials
25	7.5	3.75	1	50	15	7.5	2	75	22.5	11.25	3
26	7.8	3.9	1	51	15.3	7.65	2	76	22.8	11.4	3
27	8.1	4.05	<b>2</b>	52	15.6	7.8	2	77	23.1	11.55	3
28	8.4	4.2	<b>2</b>	53	15.9	7.95	2	78	23.4	11.7	3
29	8.7	4.35	<b>2</b>	54	16.2	8.1	2	79	23.7	11.85	3
30	9	4.5	<b>2</b>	55	16.5	8.25	2	80	24	12	3
31	9.3	4.65	<b>2</b>	56	16.8	8.4	2	81	24.3	12.15	3
32	9.6	4.8	<b>2</b>	57	17.1	8.55	2	82	24.6	12.3	3
33	9.9	4.95	<b>2</b>	58	17.4	8.7	2	83	24.9	12.45	3
34	10.2	5.1	2	59	17.7	8.85	2	84	25.2	12.6	3
35	10.5	5.25	2	60	18	9	2	85	25.5	12.75	3
36	10.8	5.4	2	61	18.3	9.15	<b>3</b>	86	25.8	12.9	3
37	11.1	5.55	2	62	18.6	9.3	<b>3</b>	87	26.1	13.05	3
38	11.4	5.7	2	63	18.9	9.45	<b>3</b>	88	26.4	13.2	3
39	11.7	5.85	2	64	19.2	9.6	<b>3</b>	89	26.7	13.35	3
40	12	6	2	65	19.5	9.75	<b>3</b>	90	27	13.5	3
41	12.3	6.15	2	66	19.8	9.9	<b>3</b>	91	27.3	13.65	3
42	12.6	6.3	2	67	20.1	10.05	3	92	27.6	13.8	3
43	12.9	6.45	2	68	20.4	10.2	3	93	27.9	13.95	3
44	13.2	6.6	2	69	20.7	10.35	3	94	28.2	14.1	<b>4</b>
45	13.5	6.75	2	70	21	10.5	3	95	28.5	14.25	<b>4</b>
46	13.8	6.9	2	71	21.3	10.65	3	96	28.8	14.4	<b>4</b>
47	14.1	7.05	2	72	21.6	10.8	3	97	29.1	14.55	<b>4</b>
48	14.4	7.2	2	73	21.9	10.95	3	98	29.4	14.7	<b>4</b>
49	14.7	7.35	2	74	22.2	11.1	3	99	29.7	14.85	<b>4</b>



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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**ONPATTRO (patisiran) lipid complex injection, for intravenous use**

**Initial U.S. Approval: 2018**

-----**INDICATIONS AND USAGE**-----

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

-----**DOSAGE AND ADMINISTRATION**-----

- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks by intravenous infusion. For patients weighing 100 kg or more, the recommended dosage is 30 mg (2.1)
- Premedicate with a corticosteroid, acetaminophen, and antihistamines (2.2)
- Filter and dilute prior to administration (2.3)
- Infuse over approximately 80 minutes (2.4)

-----**DOSAGE FORMS AND STRENGTHS**-----

Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial (3)

-----**CONTRAINDICATIONS**-----

None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs (5.1)
- 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 (5.2)

-----**ADVERSE REACTIONS**-----

The most frequently reported adverse reactions (that occurred in at least 10% of ONPATTRO-treated patients and at least 3% more frequently than on placebo) were upper respiratory tract infections and infusion-related reactions (6.1)

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

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 01/2023**

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# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

ONPATTRO should be administered by a healthcare professional.

ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.

For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.

For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

#### Missed Dose

If a dose is missed, administer ONPATTRO as soon as possible.

- If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient's original schedule.
- If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter.

### 2.2 Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) [*see Warnings and Precautions (5.1)*]. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs [*see Warnings and Precautions (5.1)*].

## 2.3 Preparation Instructions

ONPATTRO must be filtered and diluted prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.
- Inspect visually for particulate matter and discoloration. Do not use if discoloration or foreign particles are present. ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.
- Calculate the required dose of ONPATTRO based on the recommended weight-based dosage [*see Dosage and Administration (2.1)*].
- Withdraw the entire contents of one or more vials into a single sterile syringe.
- Filter ONPATTRO through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.
- Withdraw the required volume of filtered ONPATTRO from the sterile container using a sterile syringe.
- Dilute the required volume of filtered ONPATTRO into an infusion bag containing 0.9% Sodium Chloride Injection, USP for a total volume of 200 mL. Use infusion bags that are di(2-ethylhexyl)phthalate-free (DEHP-free).
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.
- Discard any unused portion of ONPATTRO.
- ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.

## 2.4 Infusion Instructions

- Use a dedicated line with an infusion set containing a 1.2 micron polyethersulfone (PES) in-line infusion filter. Use infusion sets and lines that are DEHP-free.
- Infuse the diluted solution of ONPATTRO intravenously, via an ambulatory infusion pump, over approximately 80 minutes, at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increase to approximately 3 mL/min for the remainder of the infusion. The duration of infusion may be extended in the event of an IRR [*see Warnings and Precautions (5.1)*].
- Administer only through a free-flowing venous access line. Monitor the infusion site for possible infiltration during drug administration. Suspected extravasation should be managed according to local standard practice for non-vesicants.
- Observe the patient during the infusion and, if clinically indicated, following the infusion [*see Warnings and Precautions (5.1)*].
- After completion of the infusion, flush the intravenous administration set with 0.9% Sodium Chloride Injection, USP to ensure that all ONPATTRO has been administered.

### **3 DOSAGE FORMS AND STRENGTHS**

Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) white to off-white, opalescent, homogeneous solution in a single-dose vial.

### **4 CONTRAINDICATIONS**

None.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Infusion-Related Reactions**

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache [see *Adverse Reactions (6.1)*]. Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion [see *Dosage and Administration (2.2)*]. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs [see *Dosage and Administration (2.2)*].

#### **5.2 Reduced Serum Vitamin A Levels and Recommended Supplementation**

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. 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 ONPATTRO, 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 described elsewhere in the labeling:

- Infusion-Related Reactions [see *Warnings and Precautions (5.1)*]

## 6.1 Clinical Trials Experience

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

A total of 224 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received ONPATTRO in the placebo-controlled and open-label clinical studies, including 186 patients exposed for at least 1 year, 137 patients exposed for at least 2 years, and 52 patients exposed for at least 3 years. In the placebo-controlled study, 148 patients received ONPATTRO for up to 18 months (mean exposure 17.7 months). Baseline demographic and disease characteristics were generally similar between treatment groups. The median age of study patients was 62 years and 74% were male. Seventy-two percent of study patients were Caucasian, 23% were Asian, 2% were Black, and 2% were reported as other. At baseline, 46% of patients were in Stage 1 of the disease and 53% were in Stage 2. Forty-three percent of patients had Val30Met mutations in the transthyretin gene; the remaining patients had 38 other point mutations. Sixty-two percent of ONPATTRO-treated patients had non-Val30Met mutations, compared to 48% of the placebo-treated patients.

Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.

Patients were instructed to take the recommended daily allowance of vitamin A [see *Warnings and Precautions (5.2)*]. Sixty-four percent of patients treated with ONPATTRO had normal vitamin A levels at baseline, and 99% of those with a normal baseline developed low vitamin A levels. In one case, the decreased vitamin A level was reported as an adverse reaction.

Table 1 lists the adverse reactions that occurred in at least 5% of patients in the ONPATTRO-treated group and that occurred at least 3% more frequently than in the placebo-treated group in the randomized controlled clinical trial.

**Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-treated Patients and at Least 3% More Frequently than in Placebo-treated Patients**

Adverse Reaction	ONPATTRO N=148 %	Placebo N=77 %
Upper respiratory tract infections <sup>a</sup>	29	21
Infusion-related reaction <sup>b</sup>	19	9
Dyspepsia	8	4
Dyspnea <sup>c, d</sup>	8	0
Muscle spasms <sup>c</sup>	8	1
Arthralgia <sup>c</sup>	7	0
Erythema <sup>c</sup>	7	3
Bronchitis <sup>e</sup>	7	3
Vertigo	5	1

<sup>a</sup> Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.

<sup>b</sup> Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

<sup>c</sup> Not part of an infusion-related reaction.

<sup>d</sup> Includes dyspnea and exertional dyspnea.

<sup>e</sup> Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

Four serious adverse reactions of atrioventricular (AV) heart block (2.7%) occurred in ONPATTRO-treated patients, including 3 cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

Ocular adverse reactions that occurred in 5% or less of ONPATTRO-treated patients in the controlled clinical trial, but in at least 2% of ONPATTRO-treated patients, and more frequently than on placebo, include dry eye (5% vs. 3%), blurred vision (3% vs. 1%), and vitreous floaters (2% vs. 1%).

Extravasation was observed in less than 0.5% of infusions in clinical studies, including cases that were reported as serious. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

## 6.2 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, 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 to ONPATTRO in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies to ONPATTRO were evaluated by measuring antibodies specific to PEG<sub>2000</sub>-C-DMG, a lipid component exposed on the surface of ONPATTRO. In the placebo-controlled and open-label clinical studies, 7 of 194 (3.6%) patients with hATTR amyloidosis developed anti-drug antibodies during treatment with ONPATTRO. One additional patient had pre-existing anti-drug antibodies. There was no evidence of an effect of anti-drug antibodies on clinical efficacy, safety, or the pharmacokinetic or pharmacodynamic profiles of ONPATTRO. Although these data do not demonstrate an impact of anti-drug antibody development on the efficacy or safety of ONPATTRO in these patients, the available data are too limited to make definitive conclusions.

## 6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ONPATTRO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Symptoms of infusion-related reactions have included syncope [*see Warnings and Precautions (5.1)*] and pruritus.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-877-256-9526 or by contacting [anlylampregnancyprogram@iqvia.com](mailto:anlylampregnancyprogram@iqvia.com).

## Risk Summary

There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. 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 ONPATTRO and of vitamin A supplementation are unknown [see *Clinical Pharmacology (12.2), Warnings and Precautions (5.2)*].

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats (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*

Intravenous administration of patisiran LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. In a separate study, patisiran-LC (0, 0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific surrogate (1.5 mg/kg) to pregnant rats every week 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 ONPATTRO 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 ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG<sub>2000</sub>-C-DMG) were present in milk.

## **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

## 8.5 Geriatric Use

No dose adjustment is required in patients  $\geq 65$  years old [see *Clinical Pharmacology (12.3)*]. A total of 62 patients  $\geq 65$  years of age, including 9 patients  $\geq 75$  years of age, received ONPATTRO in the placebo-controlled study. 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 Hepatic Impairment

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

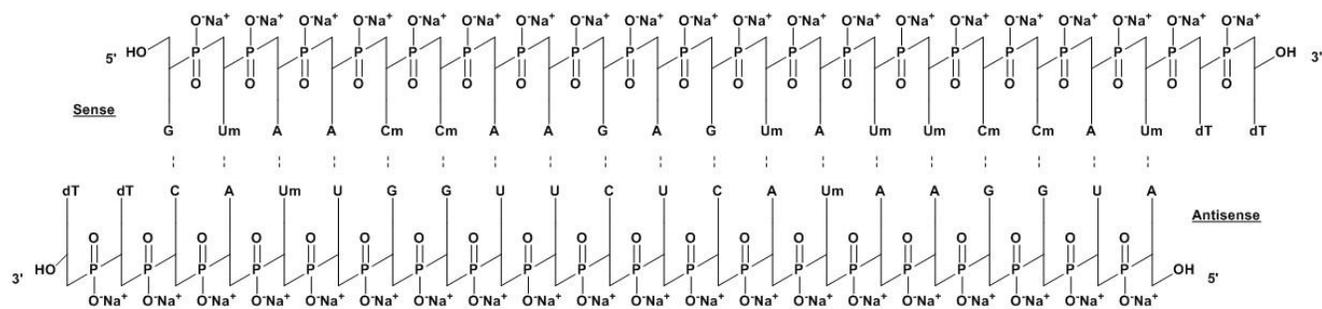
## 8.7 Renal Impairment

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

## 11 DESCRIPTION

ONPATTRO contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA), formulated as a lipid complex for delivery to hepatocytes. Patisiran specifically binds to a genetically conserved sequence in the 3' untranslated region (3'UTR) of mutant and wild-type transthyretin (TTR) messenger RNA (mRNA).

The structural formula is:



A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-O-methylcytidine; Um, 2'-O-methyluridine; dT, thymidine

ONPATTRO is supplied as a sterile, preservative-free, white to off-white, opalescent, homogeneous solution for intravenous infusion in a single-dose glass vial. Each 1 mL of solution contains 2 mg of patisiran (equivalent to 2.1 mg of patisiran sodium). Each 1 mL also contains 6.2 mg cholesterol USP, 13.0 mg (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), 3.3 mg 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1.6 mg  $\alpha$ -(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)- $\omega$ -methoxy, polyoxyethylene (PEG<sub>2000</sub>-C-DMG), 0.2 mg potassium phosphate monobasic anhydrous NF, 8.8 mg sodium chloride USP, 2.3 mg sodium phosphate dibasic heptahydrate USP, and Water for Injection USP. The pH is  $\sim 7.0$ .

The molecular formula of patisiran sodium is C<sub>412</sub> H<sub>480</sub> N<sub>148</sub> Na<sub>40</sub> O<sub>290</sub> P<sub>40</sub> and the molecular weight is 14304 Da.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Patisiran is a double-stranded siRNA 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 ONPATPRO were evaluated in hATTR amyloidosis patients treated with 0.3 mg/kg ONPATPRO via intravenous infusion once every 3 weeks.

Mean serum TTR was reduced by approximately 80% within 10 to 14 days after a single dose. With repeat dosing every 3 weeks, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 84%, respectively. The mean maximum reduction of serum TTR over 18 months was 88%. Similar TTR reductions were observed regardless of TTR mutation, sex, age, race, or prior liver transplantation. In a dose-ranging study, greater TTR reduction was maintained over the dosing interval with the recommended dosing regimen of 0.3 mg/kg every 3 weeks compared to 0.3 mg/kg every 4 weeks.

Serum TTR is a carrier of retinol binding protein, which is involved in the transport of vitamin A in the blood. Mean reductions in serum retinol binding protein of 45% and serum vitamin A of 62% were observed over 18 months [see *Warnings and Precautions (5.2)*].

### 12.3 Pharmacokinetics

Following a single intravenous administration, systemic exposure to patisiran increases in a linear and dose-proportional manner over the range of 0.01 to 0.5 mg/kg. Greater than 95% of patisiran in the circulation is associated with the lipid complex. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, steady state is reached by 24 weeks of treatment. The estimated mean  $\pm$  SD steady state peak concentrations ( $C_{max}$ ), trough concentrations ( $C_{trough}$ ), and area under the curve ( $AUC_{\tau}$ ) were  $7.15 \pm 2.14$   $\mu\text{g/mL}$ ,  $0.021 \pm 0.044$   $\mu\text{g/mL}$ , and  $184 \pm 159$   $\mu\text{g}\cdot\text{h/mL}$ , respectively. The accumulation of  $AUC_{\tau}$  was 3.2-fold at steady state, compared to the first dose. In the placebo-controlled study, inter-patient variability in patisiran exposure did not result in differences in clinical efficacy (mNIS+7 change from baseline) or safety (adverse events, serious adverse events).

#### Distribution

Plasma protein binding of ONPATPRO is low, with  $\leq 2.1\%$  binding observed *in vitro* with human serum albumin and human  $\alpha 1$ -acid glycoprotein. ONPATPRO distributes primarily to the liver. At the recommended dosing regimen of 0.3 mg/kg every 3 weeks, the mean  $\pm$  SD steady state volume of distribution of patisiran ( $V_{ss}$ ) was  $0.26 \pm 0.20$  L/kg.

#### Elimination

The terminal elimination half-life (mean  $\pm$  SD) of patisiran is  $3.2 \pm 1.8$  days. Patisiran is mainly cleared through metabolism, and the total body clearance (mean  $\pm$  SD) at steady state ( $CL_{ss}$ ) is  $3.0 \pm 2.5$  mL/h/kg.

#### *Metabolism*

Patisiran is metabolized by nucleases to nucleotides of various lengths.

#### *Excretion*

Less than 1% of the administered dose of patisiran is excreted unchanged into urine.

### Specific Populations

Age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of patisiran or TTR reduction. Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR  $\geq 30$  to  $< 90$  mL/min/1.73m<sup>2</sup>) or mild hepatic impairment (bilirubin  $\leq 1$  x ULN and AST  $> 1$  x ULN, or bilirubin  $> 1.0$  to  $1.5$  x ULN) on patisiran exposure or TTR reduction. ONPATTRO has not been studied in patients with severe renal impairment, end-stage renal disease, or moderate or severe hepatic impairment.

### Drug Interaction Studies

No formal clinical drug interaction studies have been performed. The components of ONPATTRO are not inhibitors or inducers of cytochrome P450 enzymes or transporters at clinically relevant plasma concentrations. Patisiran is not a substrate of cytochrome P450 enzymes. In a population pharmacokinetic analysis, concomitant use of strong or moderate CYP3A inducers and inhibitors did not impact the pharmacokinetic parameters of patisiran. ONPATTRO is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes.

## **13 NONCLINICAL TOXICOLOGY**

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

#### Carcinogenesis

Patisiran-LC was not carcinogenic in TgRasH2 mice when administered at intravenous (IV) doses of 0, 0.5, 2, or 6 mg/kg every two weeks for 26 weeks.

#### Mutagenesis

Patisiran-LC was negative for genotoxicity in *in vitro* (bacterial mutagenicity assay, chromosomal aberration assay in human peripheral blood lymphocytes) and *in vivo* (mouse bone marrow micronucleus) assays.

#### Impairment of Fertility

Intravenous (IV) administration of patisiran-LC (0, 0.03, 0.1, or 0.3 mg/kg) or a rodent-specific (pharmacologically active) surrogate (0.1 mg/kg) to male rats every two weeks prior to and throughout mating to untreated females produced no adverse effects on fertility.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or on embryofetal development.

Intravenous administration of patisiran-LC (0, 0.3, 1, or 2 mg/kg) to adult monkeys every three weeks for 39 weeks produced no adverse effects on male reproductive organs or on sperm morphology or count.

## **14 CLINICAL STUDIES**

The efficacy of ONPATTRO was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (NCT 01960348). Patients were randomized in a 2:1 ratio to receive ONPATTRO 0.3 mg/kg (N=148) or placebo (N=77), respectively, via intravenous infusion once every 3 weeks for 18 months. All patients received premedication with a corticosteroid, acetaminophen, and H1 and H2

blockers. Ninety-three percent of ONPATTRO-treated patients and 62% of placebo-treated patients completed 18 months of the assigned treatment.

The primary efficacy endpoint was the change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7). The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified +7 (+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 maximum possible score was 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 18 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 version of the Norfolk QoL-DN that was used in the trial had a total score range from -4 to 136, with higher scores representing greater impairment.

The changes from baseline to Month 18 on both the mNIS+7 and the Norfolk QoL-DN significantly favored ONPATTRO (Table 2, Figure 1 and Figure 3). The distributions of changes in mNIS+7 and Norfolk QoL-DN scores from baseline to Month 18 by percent of patients are shown in Figure 2 and Figure 4, respectively.

The changes from baseline to Month 18 in modified body mass index (mBMI) and gait speed (10-meter walk test) significantly favored ONPATTRO (Table 2).

**Table 2: Clinical Efficacy Results from the Placebo-Controlled Study**

Endpoint <sup>a</sup>	Baseline, Mean (SD)		Change from Baseline to Month 18, LS Mean (SEM)		ONPATTRO-Placebo Treatment Difference, LS Mean (95% CI)	p-value
	ONPATTRO N=148	Placebo N=77	ONPATTRO	Placebo		
<b>Primary</b>						
mNIS+7 <sup>b</sup>	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0 (-39.9, -28.1)	p<0.001
<b>Secondary</b>						
Norfolk QoL-DN <sup>b</sup>	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	p<0.001
10-meter walk test (m/sec) <sup>c</sup>	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	p<0.001
mBMI <sup>d</sup>	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	p<0.001

CI, confidence interval; LS, least squares; 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

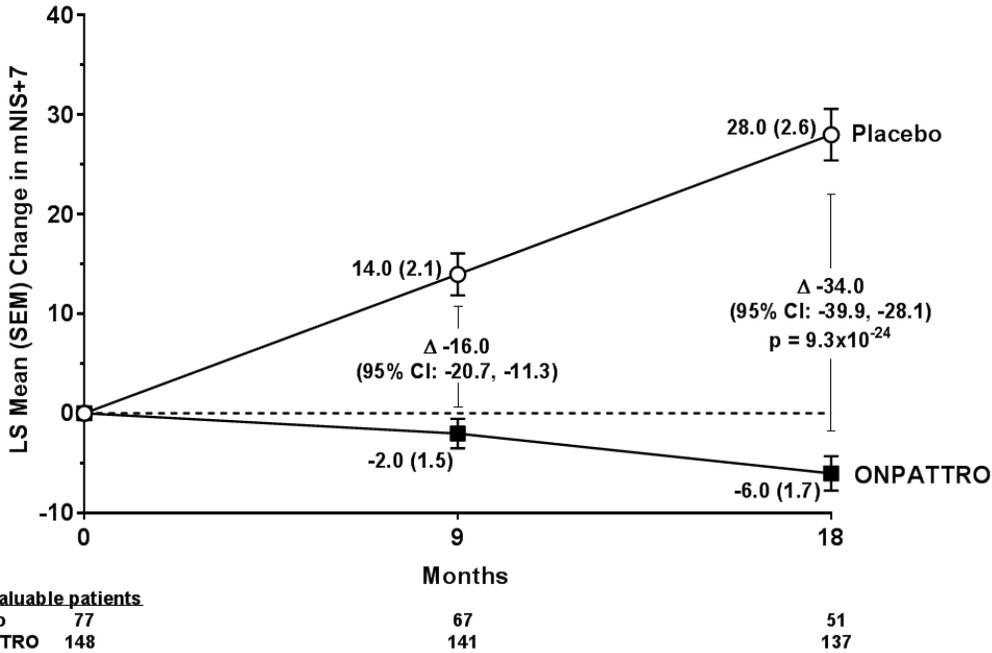
<sup>a</sup> All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.

<sup>b</sup> A lower value indicates less impairment/fewer symptoms.

<sup>c</sup> A higher number indicates less disability/less impairment.

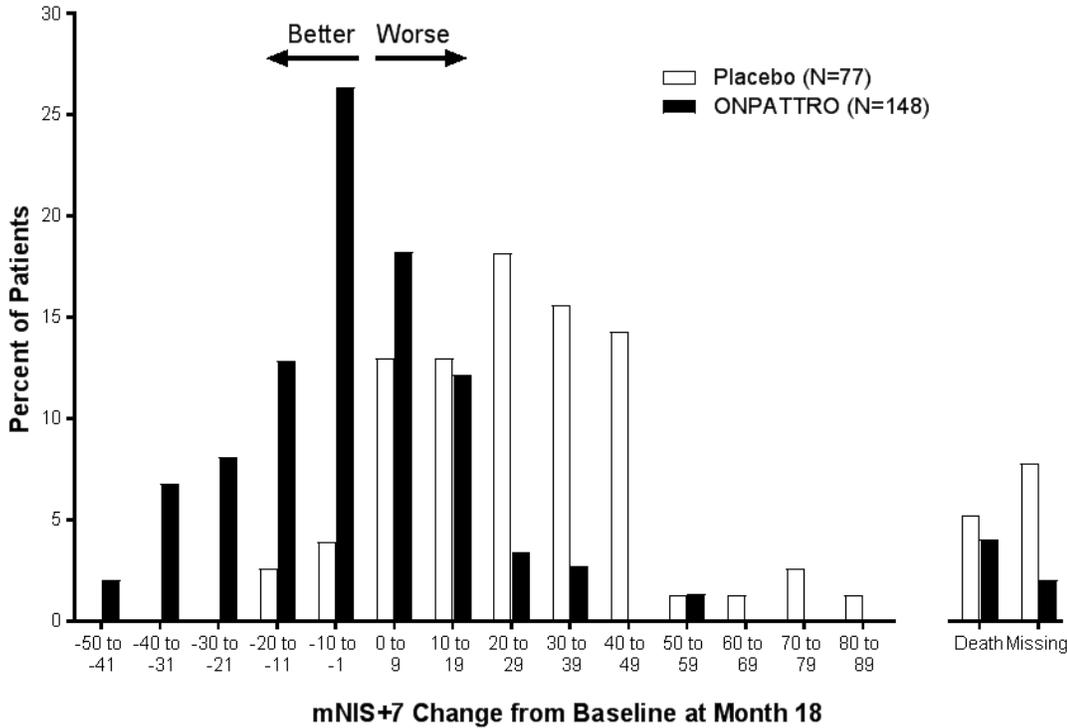
<sup>d</sup> mBMI: body mass index (BMI; kg/m<sup>2</sup>) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

**Figure 1: Change from Baseline in mNIS+7**



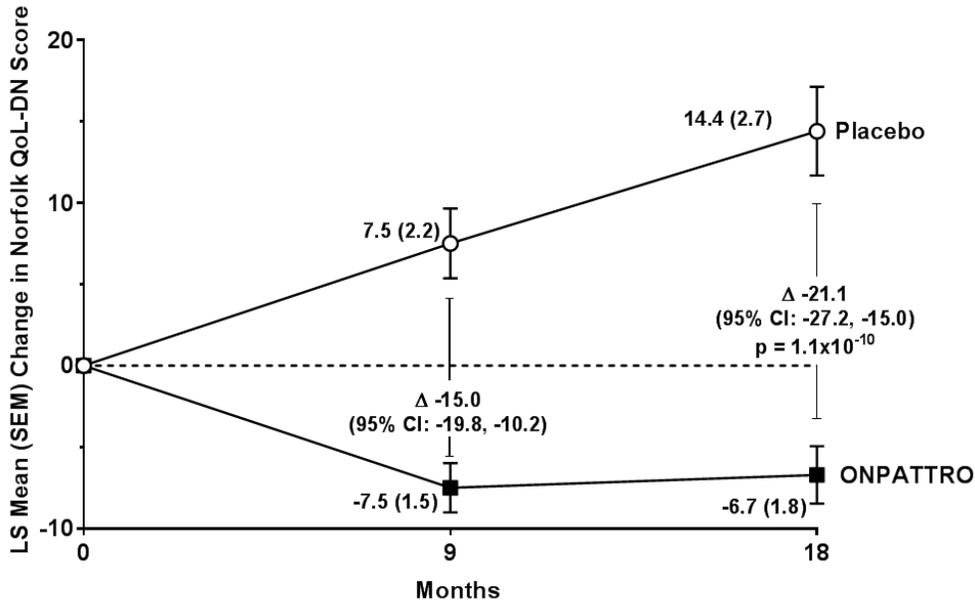
A decrease in mNIS+7 indicates improvement.  
 Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

**Figure 2: Histogram of mNIS+7 Change from Baseline at Month 18**



mNIS+7 change scores are rounded to the nearest whole number; last available post-baseline scores were used.  
 Categories are mutually exclusive; patients who died before 18 months are summarized in the “Death” category only.

**Figure 3: Change from Baseline in Norfolk QoL-DN Score**



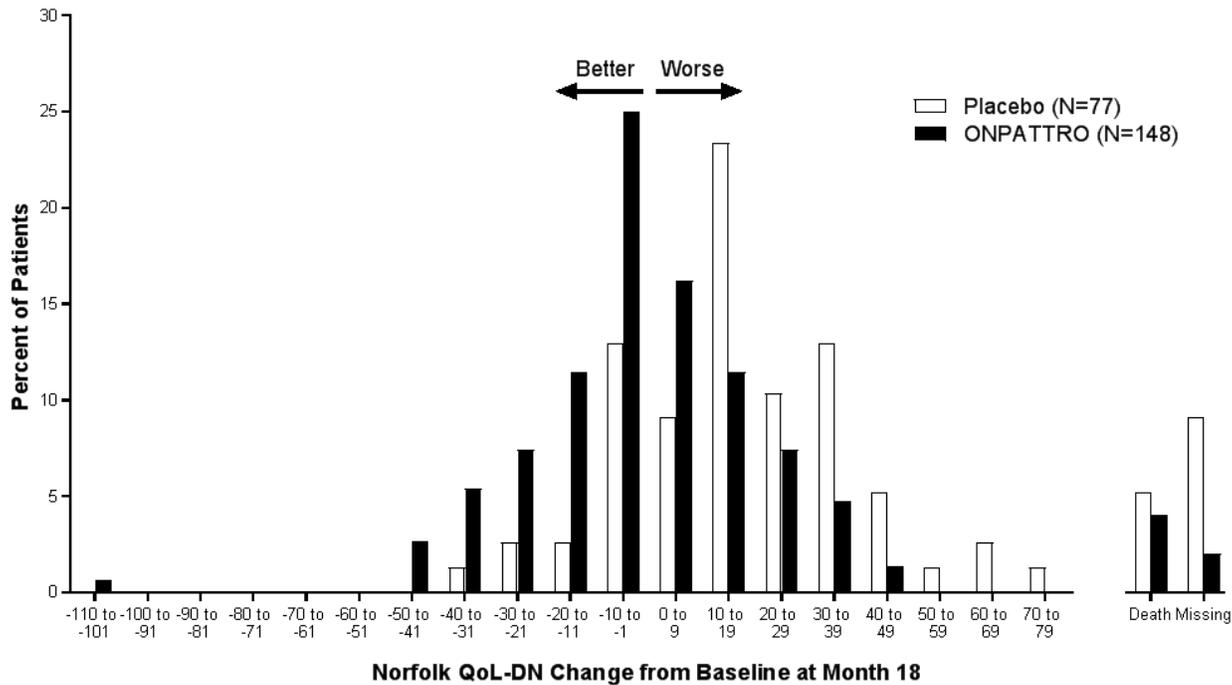
**N of evaluable patients**

Placebo	76	65	48
ONPATTRO	148	141	136

A decrease in Norfolk QoL-DN score indicates improvement.

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

**Figure 4: Histogram of Norfolk QoL-DN Change from Baseline at Month 18**



Norfolk QoL-DN change scores are rounded to the nearest whole number; last available post-baseline scores were used.

Categories are mutually exclusive; patients who died before 18 months are summarized in the “Death” category only.

Patients receiving ONPATTRO experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, Val30Met mutation status, and disease stage.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

ONPATTRO is a sterile, preservative-free, white to off-white, opalescent, homogeneous solution for intravenous infusion supplied as a 10 mg/5 mL (2 mg/mL) solution in a single-dose glass vial. The vial stopper is not made with natural rubber latex. ONPATTRO is available in cartons containing one single-dose vial each.

The NDC is: 71336-1000-1.

### 16.2 Storage and Handling

Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen.

If refrigeration is not available, ONPATTRO can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days.

For storage conditions of ONPATTRO after dilution in the infusion bag, see Dosage and Administration (2.3).

## 17 PATIENT COUNSELING INFORMATION

### Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions (e.g., flushing, dyspnea, chest pain, syncope, rash, increased heart rate, facial edema). Advise patients to contact their healthcare provider immediately if they experience signs and symptoms of infusion-related reactions [*see Warnings and Precautions (5.1)*].

### Recommended Vitamin A Supplementation

Inform patients that ONPATTRO treatment leads to a decrease in vitamin A levels measured in the serum. 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 (5.2)*].

### Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO [*see Use in Specific Populations (8.1)*].

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