



**How to Complete the
ONPATTRO® (patisiran)
Start Form**

Please see Important Safety Information on page 7
and accompanying full [Prescribing Information](#).

onpattro
(patisiran) lipid complex injection
10 mg/5 mL

How to complete the ONPATTRO[®] (patisiran) Start Form

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

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

- ▶ Ensure highlighted key areas are correctly filled out
- ▶ Confirm that you and your patient sign where indicated
- ▶ Make sure the Infusion Center Location information is provided for patients not receiving home infusions, if known

Options for getting started

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

— OR —

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

— OR —

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



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

For patients

Already Enrolled?

Patients currently prescribed an Alnylam medicine who are enrolled in Alnylam Assist™ through previous submission of a Start Form do not need to complete Sections 1 – 5.

Preferred Phone Number & Voicemail Checkbox

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


Language Translation?

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

Insurance Information

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

Start Form



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

▶ **Patients currently prescribed an Alnylam medicine who are enrolled in Alnylam Assist do not need to complete Sections 1 – 5**

For Patients

Alnylam Assist Enrollment

(Sections 1 – 5 to be read and completed by **Patient** or **Patient's Authorized Representative**)

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

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

1. Patient Information

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

Date of Birth: Month/Day/Year 05/14/1956 Email: LNReeley@email.com

Street Address: 1020 Generic Ave.

City: Springfield State: MA Zip: 15123

Preferred Phone Number: **Okay to leave voicemail** (555) 137-1634 Alternative Phone Number (if available): **Okay to leave voicemail**

Caregiver Name (optional): Diane Reeley Caregiver Relationship to Patient (optional): Wife Caregiver Phone (optional): **Okay to leave voicemail** (555) 136-1522

Caregiver Email (optional): _____ Language translation? Yes, translation needed No
If yes, please indicate language: Portuguese


2. Insurance Information

Attach a copy of both sides of your medical INSURANCE and PRESCRIPTION insurance cards
 Check if you do not have insurance

Primary Insurance Provider: <u>ABC Insurance Co.</u>	Employer Name: <u>Company Inc.</u>	Policy Number: <u>123456789101</u>	Group Number: <u>12-34567</u>
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year	Insurance Phone: <u>(555) 136-2222</u>
Pharmacy Plan Provider (if applicable):	Policy Number:	Group Number:	Rx Bin Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year	Insurance Phone:
Secondary Insurance Provider (if applicable):		Policy Number:	Group Number:
Policyholder Name (First, MI, Last), if other than the patient:		Policyholder Date of Birth: Month/Day/Year	Insurance Phone:

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

Please see Important Safety Information on page 4, and full Prescribing Information available from your Alnylam representative or at www.onpatrohcp.com.

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

Start Form

onpattro
(patisiran) lipid complex injection
10 mg/5 mL

3. Authorization to Share Protected Health Information

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

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

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

Lawrence N. Reece <small>Print Patient or Authorized Patient Representative Name</small>	<input checked="" type="checkbox"/> <i>Lawrence N. Reece</i> <small>Signature of Patient or Authorized Patient Representative</small>
	January 1, 2022 <small>Date</small>
<small>Relationship to Patient</small>	<small>Date</small>

4. Authorization for Alnylam Assist and Communications

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

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

Lawrence N. Reece <small>Print Patient or Authorized Patient Representative Name</small>	<input checked="" type="checkbox"/> <i>Lawrence N. Reece</i> <small>Signature of Patient or Authorized Patient Representative</small>
	January 1, 2022 <small>Date</small>
<small>Relationship to Patient</small>	<small>Date</small>

5. Opt-in to Receive Marketing Communications (optional)

By checking this box, I authorize Alnylam, and companies working with Alnylam, to contact me by mail, email, fax, and/or telephone regarding marketing and promotional communications, customer surveys, or for market research surveys. **I understand that I am not required to provide this consent as a condition of receiving any Alnylam medicine or services from Alnylam.**

Please see Important Safety Information on page 4, and full Prescribing Information available from your Alnylam representative or at www.onpattrohcp.com.

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Alnylam
ASSIST

Signature of Patient

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

For healthcare providers/prescriber declaration

Infusion Center Location

Ensure that infusion center information has been provided, if known. Please note that home infusion may also be an option.^a

Product Acquisition


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

ONPATTRO® (patisiran) Dosing Information

Make sure to include the primary diagnosis code and patient's weight (kg).

Signature of Prescriber

- ▶ Confirm that your patient is being prescribed ONPATTRO as indicated by checking the box
- ▶ Ensure the **prescriber's signature** and **date** are included in Section 8



Start Form For Healthcare Providers

(Sections 6 – 8 to be read and completed by **Healthcare Provider**)

6. Prescriber Information

Name (First, Last): Charles Sample			Office/Clinic/Institution Name: Sample Co.		Specialty: Neurology	
Office/Clinic/Institution Street Address: 530 Pioneer Road				City: Easton		State: MA
Zip: 40520	Phone: (555) 876-5309	Fax:	National Provider ID (NPI) #: 1234567890	State License Number: S943072	Tax ID #: 123-45-6789	
Office Contact Name: Jane Smith			Phone: (555) 652-5678		Email: SampleDoc@email.com	
Infusion Center Location Name & Address (if different from above): 202 Another Street					Anticipated First Infusion Date: February 14, 2022	
Infusion Center Contact Name: Richard I. Vaile			Phone: (555) 555-5055		Email:	

Product Acquisition:

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

7. ONPATTRO® (patisiran) Dosing Information


Patient Name (First, MI, Last):		Patient Date of Birth: Month/Day/Year:	
Primary Diagnosis Code: E85.1, Neuroopathic hereditary amyloidosis			
Dose: (Recommended dose is 0.3 mg/kg supplied as 10 mg/5 mL vials) ONPATTRO (patisiran) 21 mg IV every 3 weeks		Number of Vials: 3	Patient Weight (kg): 70 kg

8. Prescriber Declaration


By signing below, I certify that:

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

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

 Prescriber signature <small>(stamps not acceptable)</small>	January 1, 2022 Date
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Please see Important Safety Information on page 4, and full Prescribing Information available from your Alnylam representative or at www.onpattrohcp.com.



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

ONPATTRO® (patisiran) Indication and Important Safety Information

Start Form



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 full Prescribing Information available from your Alnylam representative or at www.onpattrohcp.com.

Fax the completed Start Form
to 1-833-256-2747

Call Alnylam Assist™ at 1-833-256-2748
8AM–6PM, Monday–Friday

For more information
visit www.AlnylamAssist.com

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Indication

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

Important Safety Information

Infusion-Related Reactions

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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](#).

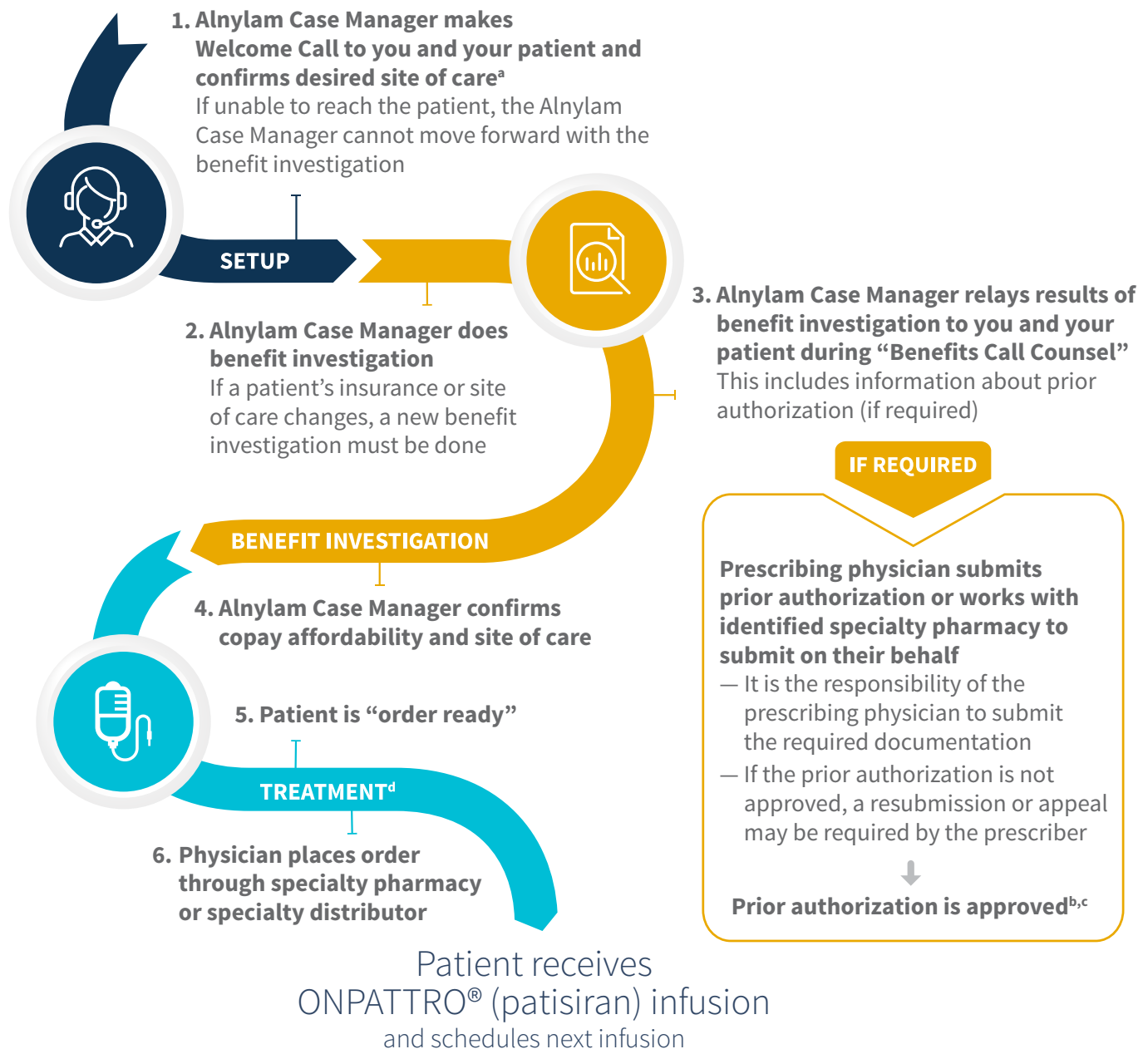


8AM–6PM, Monday–Friday

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

To learn more,
visit www.AlylamAssist.com.

Once the completed Start Form is received by Alnylam Assist™



^aIf no infusion center has been identified, Alnylam Case Manager can do a search for infusion centers near the patient's preferred geographic location and confirm their in-/out-of-network status during the benefit investigation.

^bIf a reauthorization is required, a new request must be submitted.

^cAlnylam Assist can provide education on prior authorization requirements and processes, but cannot guarantee that a patient's prior authorization will be approved.

^dIf your patient has a new prescribing physician, a new Start Form is required and the process must be repeated.

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



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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2022

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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 ^a	29	21
Infusion-related reaction ^b	19	9
Dyspepsia	8	4
Dyspnea ^{c, d}	8	0
Muscle spasms ^c	8	1
Arthralgia ^c	7	0
Erythema ^c	7	3
Bronchitis ^e	7	3
Vertigo	5	1

^a Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.

^b 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.

^c Not part of an infusion-related reaction.

^d Includes dyspnea and exertional dyspnea.

^e 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 PEG₂₀₀₀-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 alnylampregnancyprogram@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 PEG₂₀₀₀-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 ≥ 65 years old [see *Clinical Pharmacology (12.3)*]. A total of 62 patients ≥ 65 years of age, including 9 patients ≥ 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.

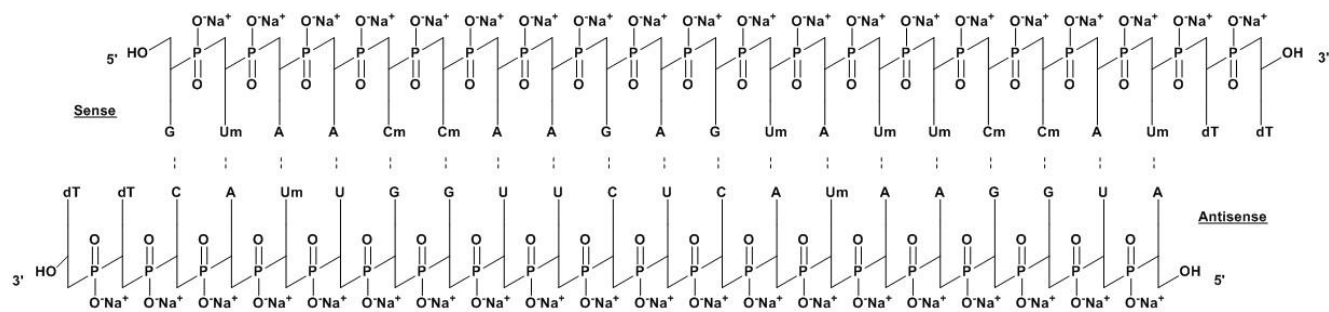
8.7 Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73m²) [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 α -(3'-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)- ω -methoxy, polyoxyethylene (PEG₂₀₀₀-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 ~ 7.0 .

The molecular formula of patisiran sodium is C₄₁₂ H₄₈₀ N₁₄₈ Na₄₀ O₂₉₀ P₄₀ 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, or race. 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_{τ}) were 7.15 ± 2.14 $\mu\text{g/mL}$, 0.021 ± 0.044 $\mu\text{g/mL}$, and 184 ± 159 $\mu\text{g}\cdot\text{h/mL}$, respectively. The accumulation of AUC_{τ} 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 ± 0.20 L/kg.

Elimination

The terminal elimination half-life (mean \pm SD) of patisiran is 3.2 ± 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 ± 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), and sex 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 ≥ 30 to < 90 mL/min/1.73m²) or mild hepatic impairment (bilirubin ≤ 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, moderate or severe hepatic impairment, or in patients with prior liver transplant.

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 ^a	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		
Primary						
mNIS+7 ^b	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
Secondary						
Norfolk QoL-DN ^b	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) ^c	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 ^d	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

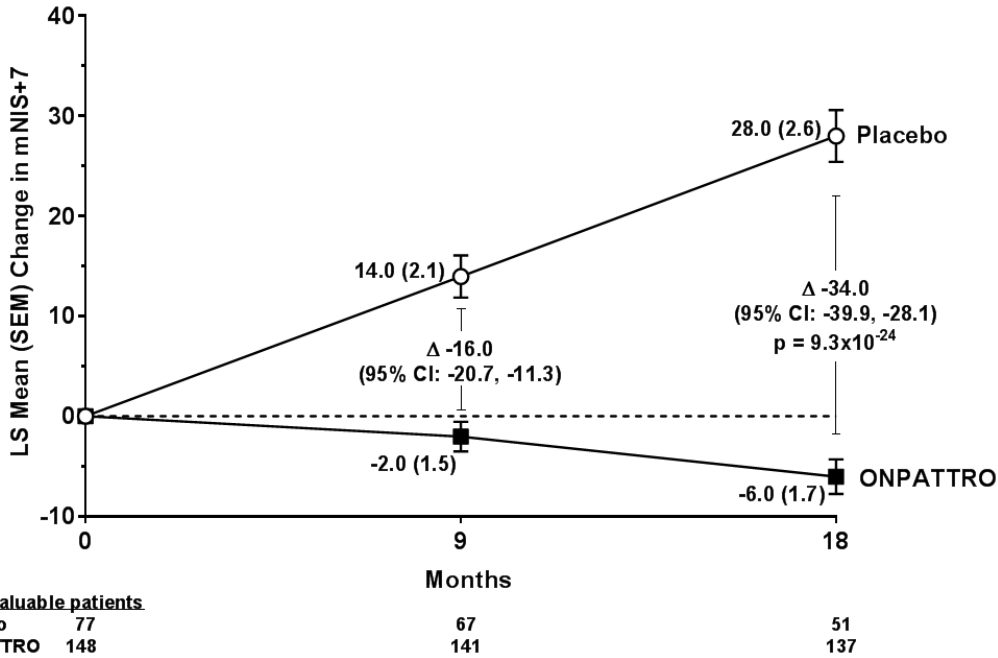
^a All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.

^b A lower value indicates less impairment/fewer symptoms.

^c A higher number indicates less disability/less impairment.

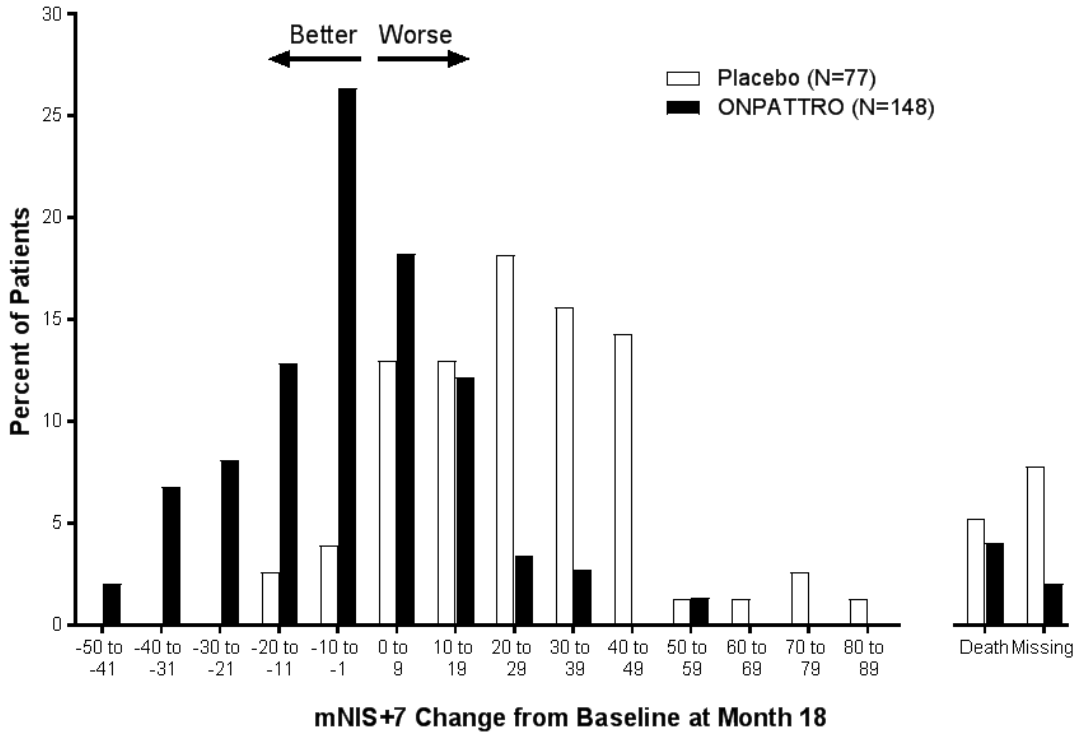
^d mBMI: body mass index (BMI; kg/m²) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

Figure 1: Change from Baseline in mNIS+7



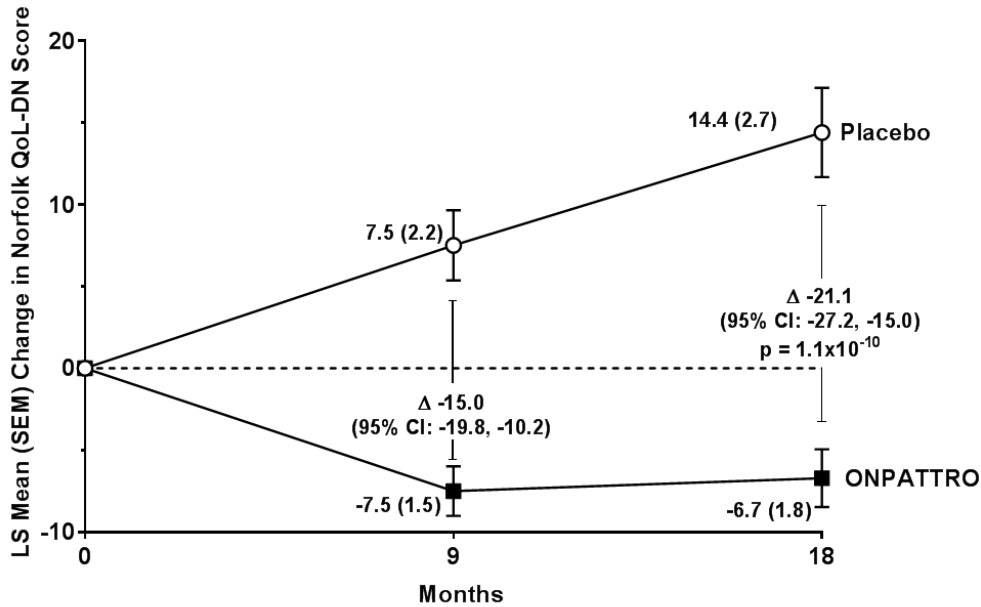
A decrease in mNIS+7 indicates improvement.
 Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

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



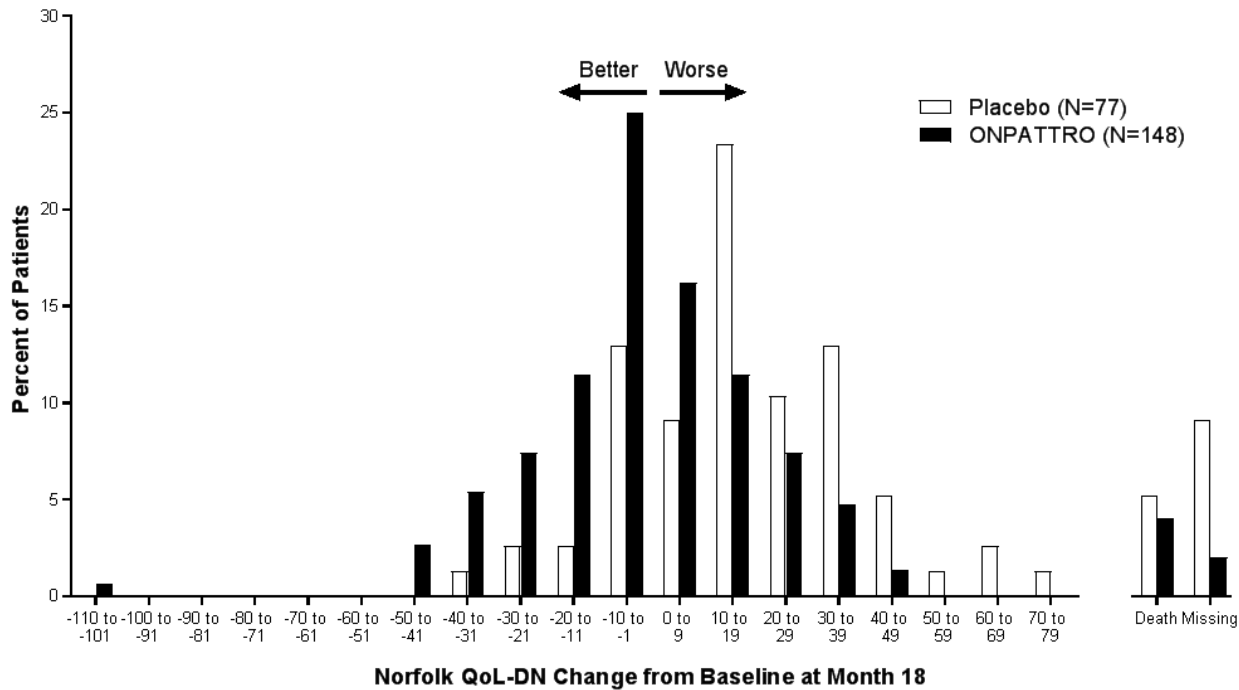
N of evaluable patients

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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