PATISIRAN (ALN-TTR02)

ALN-TTR02-006

A MULTICENTER, OPEN-LABEL, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF PATISIRAN IN PATIENTS WITH FAMILIAL AMYLOIDOTIC POLYNEUROPATHY WHO HAVE COMPLETED A PRIOR CLINICAL STUDY WITH PATISIRAN

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4.0 - Global	28 March 2018	Incorporating Global Amendment 3 (including UK, Argentina, and Brazil-specific changes)

The study will be completed according to guidelines of Good Clinical Practice (GCP). Compliance with this practice provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

SPONSOR PROTOCOL APPROVAL

I have read this Protocol and I approve the design of this study.

[redacted]

28 MAR 2018

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTR02-006 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SYNOPSIS

Name of Sponsor/Company:
Alnylam Pharmaceuticals, Inc

Name of Investigational Product:
Patisiran

Title of Study:
A Multicenter, Open-Label, Extension Study to Evaluate the Long-term Safety and Efficacy of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Completed a Prior Clinical Study with Patisiran

Study Centers:
This study will be conducted at multiple sites worldwide that have enrolled patients in a previous patisiran study.

Objectives:
To assess the safety and efficacy of long-term dosing with patisiran in patients with transthyretin-mediated amyloidosis (ATTR amyloidosis).

Methodology:
This is a multicenter, multinational, open-label extension study to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have previously completed a patisiran study.

Consented eligible patients will enroll in this study and receive 0.3 mg/kg patisiran intravenously (IV) once every 3 weeks (q3w) for the duration of the study. In order to maintain the q3w dosing schedule from the parent study, patients are expected to have their first visit (Day 0) in this study 3 weeks after their last dose visit in the parent study. However, if necessary, a patient may initiate dosing in this study up to 45 days from the time of the last dose in the parent study. Exceptions to this timing may be allowed for medical or regulatory considerations only after consultation with the Medical Monitor. The last testing visit in the parent study will serve as the baseline for this study, unless more than 45 days have elapsed, in which case the baseline tests will need to be repeated on Day 0. Eligibility for this study will be confirmed before administration of the first dose on Day 0.

After the Day 0 visit, patients should return to the site for patisiran dosing q3w. Where applicable country and local regulations allow, patients may receive the patisiran infusions at home by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion. Patients who are receiving patisiran infusions at home will have a phone contact with the site at least every 30 (±5) days. Patients will also have visits at the clinical site at approximately 12, 26 and 52 weeks, and yearly thereafter.

A complete set of efficacy assessments will be done at 52 weeks, followed by more limited efficacy assessments yearly thereafter. In order to decrease the variability in the efficacy assessment testing during the study, there will be a number of sites within any one territory that conduct these efficacy assessments (referred to as "Central Assessment Sites [CAS]"); these sites can also dose and manage patients. There will also be sites that can dose and manage the patients ("Patient Care Sites [PCS])", while sending the patients to the nearest CAS for their efficacy assessments. Every effort should be made for the patient to return to the same CAS center that the patient attended in the parent study.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at 12, 26 and 52 weeks after the first dose in this study during the first year and yearly thereafter. Patients will be continually assessed throughout the study for adverse events (AEs).

Unscheduled visits for study assessments may occur if deemed necessary by the study personnel.

Number of patients (planned):

All patients who have previously completed a patisiran study may be enrolled if they meet the eligibility criteria for this study.

Diagnosis and eligibility criteria:

To be enrolled in the study, patients must meet the following criteria before administration of patisiran on Day 0:

1. Have completed a patisiran study (ie, completed the last efficacy visit in the parent study) and, in the opinion of the investigator, tolerated study drug
2. Be considered fit for the study by the Investigator
3. Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)
4. Have a total bilirubin within normal limits. A patient with total bilirubin ≤2 x ULN is eligible if the elevation is secondary to documented Gilbert's syndrome (elevation of unconjugated bilirubin with normal conjugated bilirubin) and the patient has ALT and AST levels within normal ranges.
5. Have a serum creatinine ≤2 × ULN
6. Women of child-bearing potential must have a negative pregnancy test, cannot be breastfeeding, and must be using 2 highly effective methods of contraception prior to dosing in this study and agree to use 2 highly effective methods of contraception throughout study participation and for 12 weeks after last dose of patisiran in this study.
7. Be willing and able to comply with the protocol-required visit schedule and visit requirements and provide written informed consent

A patient will be excluded if they meet any of the following criteria before dosing on Day 0:

1. Has an active infection requiring systemic antiviral or antimicrobial therapy that will not be completed before the first dose of patisiran administration
2. Has poorly controlled diabetes mellitus
3. Has uncontrolled cardiac arrhythmia or unstable angina
4. Is currently taking tafamidis, diflunisal, doxycycline, or tauroursodeoxycholic acid (TUDCA), unless previously allowed per the parent study
5. Is unable to take the required premedications, unless modifications to the premedication regimen were previously allowed per the parent study
6. Is under legal protection (defined as "any person who becomes incapable of protecting his/her interests due to a medically diagnosed impairment of his/her mental faculties that may limit or prevent the expression of his will"), decided by a court

Investigational product, dosage and mode of administration:

Patisiran (comprising a small interfering ribonucleic acid [siRNA] targeting mutant and wild type transthyretin [TTR] messenger RNA [mRNA]), in a lipid nanoparticle formulation for IV administration, 0.3 mg/kg q3w administered as an IV infusion over approximately 80 minutes (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minute for the remainder of the infusion) by a controlled infusion device.

Patients will receive the following premedications at least 60 minutes before the start of the patisiran infusion:

- Intravenous dexamethasone (10 mg) or equivalent
- Oral paracetamol/acetaminophen (500 mg) or equivalent
- Intravenous H2 blocker (ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose)
- Intravenous H1 blocker: diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the study site). Hydroxyzine 25 mg per os (PO, orally) or fexofenadine 30 mg or 60 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blocker.

Duration of treatment:

The duration of the study has been determined to allow the collection of long-term safety, tolerability and efficacy data of patisiran in patients with hATTR amyloidosis who have completed a prior study with patisiran. The estimated duration of the study treatment for each patient is 5 years.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy:

The efficacy of patisiran will be assessed by the following evaluations:

- Neurological impairment assessed using the Neuropathy Impairment Score (NIS), Modified NIS (mNIS +7) composite score, and NIS+7
- Patient-reported quality of life (QOL) using the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) and the EuroQOL (EQ-5D) questionnaires
- Disability reported by patients using the Rasch-built Overall Disability Scale (R-ODS)
- Autonomic symptoms assessed using the Composite Autonomic Symptom Score (COMPASS 31)
- Motor function assessments, including NIS-Weakness (NIS-W), timed 10-meter walk test, and grip strength test
- Polyneuropathy disability (PND) score and FAP stage
- Nutritional status using modified body mass index (mBMI)
- Pathologic evaluation of sensory and autonomic innervation evaluated by intraepidermal nerve fiber density (IENFD) analysis and quantitation of dermal sweat gland nerve fibers (SGNFD), and amyloid burden characterization via tandem 3 mm skin punch biopsies; one set of biopsies will be taken from the distal lower leg and one set from the distal thigh (only for patients having this assessment in the parent study)

- Magnetic resonance (MR) neurography (as regionally applicable)
- Cardiac structure and function through echocardiograms and serum levels of terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin I
- New York Heart Association (NYHA) classification of heart failure
- Disease burden and healthcare utilization assessed using a patient-reported pharmacoeconomics questionnaire

Pharamcodynamic:

- Serum TTR
- Vitamin A

Safety:

Safety assessments will include monitoring for AEs (including serious AEs [SAEs]); clinical laboratory tests, including hematology, clinical chemistry, urinalysis, thyroid stimulating hormone (TSH), coagulation and pregnancy testing;; vital signs; physical examinations; ophthalmology examinations; and assessment of suicidal ideation and behavior.

Immunogenicity:

- Anti-drug antibodies (ADA)

Statistical methods:

This is an open-label extension study enrolling patients who have previously completed a patisiran study; the size of the study is not determined via power analysis of particular hypotheses tests.

Associations between pharmacodynamic and efficacy data will be explored via correlation.

Descriptive statistics will be provided for clinical efficacy data, clinical laboratory data, vital signs data, and ADA data, presented as both actual values and changes from baseline relative to each on-study evaluation. Laboratory shift tables from baseline to worst values will be presented.

Table 1: Schedule of Assessments

Window	Day 0 Visit ≤45 Days from Last Dose[a]	12 Week Visit ±4 Weeks	26 Week Visit ±4 Weeks	Year 1 52 Week Visit ±4 Weeks	Year 2[ee], Year 3[ee], Year 4, and Year 5 Annual Visit ±6 Weeks	End of Study 4 (+1) Weeks from Last Dose	Early Withdrawal Visit[bb] 4 (+1) Weeks from Last Dose
Procedure							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X[b]						
Demographics	X[c]						
Physical Examination	X[d]			X	X	X[o]	X[o]
Weight	X Prior to Each Dose					X[o]	X[o]
mBMI[e]	X[d]			X	X	X[o]	X[o]
Height	X[c]						
FAP Stage and PND Score	X[d]			X	X	X[o]	X[o]
Karnofsky Performance Status	X			X	X		[X][f]
NYHA Classification	X			X	X		[X][f]
Vital Signs[g]	X Prior to Each Dose						
Safety Laboratory Assessments[h]	X[d]	X	X	X	X	X	X

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Procedure							
INR[y]	X						
Pregnancy Test (urine)[cc]	X[i]		X	X	X	X	X
C-SSRS Questionnaire			X	X	X	X	X
TTR Protein (ELISA)	X[d]		X	X	X	X	X
TSH and Vitamin A				X	X	X[o]	X[o]
Blood Sample for Long-term Storage	X	X	X	X	X	X	X
mNIS+7[j]	X[d]			X	X[dd]		[X][f]
NIS+7[k]	X[d]			X			[X][f]
NIS only					X[l]	X[m]	X[m]
Grip Strength Test[n]	X[d]			X			[X][f]
10-Meter Walk Test[p]	X[d]			X	X		[X][f]
Ophthalmology Examination[q]	X[d]			X	X	X[o]	X[o]
Skin Punch Biopsy (IENFD and SGNFD)[r]				X	X	X[o]	X[o]
MR Neurography[s] (*Germany & France only)*	X		X	X	X	X[o]	X[o]

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Procedure							
Pharmacoeconomics Questionnaire	X			X	X	X[o]	X[o]
Norfolk QOL-DN[t]	X[d]			X	X	X[o]	X[o]
COMPASS 31 Questionnaire	X[d]			X			[X][f]
R-ODS Disability	X[d]			X	X		[X][f]
EQ-5D QOL	X[d]			X	X	X[o]	X[o]
Echocardiogram	X[d,u]			X	X		[X][f]
Troponin I and NT-proBNP	X[d]			X	X		[X][f]
Anti-Drug Antibody Testing[v]			X	X	X	X	X
Blood sample for genetic sequencing[z]		Blood sample collection at first possible visit[z]					
Premedication / Patisiran Administration[w]	X	At dosing visits[w]-					
Phone Contact[x] *(In applicable regions only)*		X					
Adverse Events	X[b, bb] Continuous Monitoring						
Concomitant Medications and Procedures	X[b] Continuous Monitoring						

Table 1 Footnotes:

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; COMPASS 31 = Composite Autonomic Symptom Score; ELISA = enzyme linked immunosorbent assay; EQ-5D QOL = EuroQOL; FAP = familial amyloidotic polyneuropathy; IENFD = intraepidermal nerve fiber density; INR = internationalized normalized ratio; mBMI = modified body mass index; mNIS = Modified Neuropathy Impairment Score; MR = magnetic resonance; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; QOL-DN = Quality of Life-Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; SGNFD = sweat gland nerve fiber density; TSH = thyroid stimulating hormone; TTR = transthyretin

a. Every effort should be made to perform Day 0 visit 3 weeks (±3 days) from the last dose of study drug in the parent study. However, the Day 0 visit may occur within 45 days after the last dose in the parent study. Exceptions may be made for medical or regulatory considerations only after consultation with the Medical Monitor.
b. Medical history includes TTR genotype. Ongoing AEs from the parent study will be captured as Medical History on the case report form (CRF). Similarly concomitant medications that continue from the parent study will be entered into the database.
c. Assessment does not need to be repeated. Information will be obtained from parent study.
d. Assessment/procedure does not need to be repeated if performed during the parent study within 45 days of first dose in this study.
e. mBMI will be calculated within the clinical database; this calculation does not need to be performed at the study center.
f. Assessment/procedure required only if patient withdraws before the 52-week visit.
g. Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. Collected supine using an automated instrument after patient rests for 10 minutes. Must be performed pre-dose.
h. Includes serum chemistry, hematology, and urinalysis. Refer to Section 9.1.5 for specific laboratory assessments.
i. Assessment does not need to be repeated if the patient had a negative pregnancy test (urine or serum) within 14 days of the first dose.
j. The mNIS+7 consists of the modified NIS tool (weakness and reflexes), nerve conduction studies (NCS) 5 attributes (Σ5), quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), and postural blood pressure. Two assessments of the mNIS+7 will be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site will make every effort to have these assessments at the visit performed by the same study personnel who performed the assessments for the patient in the patisiran study in which they were previously enrolled.
k. The NIS+7 consists of the NIS tool (weakness, sensation, and reflexes), NCS Σ5, vibration detection threshold (VDT), and heart rate response to deep breathing (HRdB). Two assessments of the NIS+7 will be performed oapproximately 24 hours apart from each other but not more than 7 days apart. Each site will make every effort to have these assessments at the Week 52 visit performed by the same study personnel who performed the assessments for the patient in the patisiran study in which they were previously enrolled.
l. Two independent assessments of the NIS will be performed at each specified visit and must be performed by a neurologist approximately 24 hours apart from each other but not more than 7 days apart.
m. Assessment of NIS only does not need to be repeated if done as part of the NIS+7 at the End of Study or Early Withdrawal visit or if done within the previous 26 weeks.
n. Grip strength will be measured in triplicate using a dynamometer held in the dominant hand. Every effort will be made to use the same device for a patient throughout the duration of the study. Two assessments of the grip strength will be performed on separate days (1 assessment on each day). The second (repeat) assessment must be conducted at least 24 hours (approximately) after the first assessment, but not more than 7 days apart.
o. Assessment does not need to be repeated if done within the previous 26 weeks.
p. The patient will be asked to walk 10 meters. The walk must be completed without assistance from another person; ambulatory aids such as canes and walkers are permitted. The time required for the patient to walk 10 meters will be recorded. Two assessments of the 10-meter walk test will be performed approximately 24 hours apart from each other but not more than 7 days apart.
q. Examination will include visual acuity, visual fields, and slit-lamp evaluation. An electroretinogram may also be performed, as described in Section 9.1.6

r. Optional skin biopsies will only be obtained if the patient had skin biopsies in the parent study and has provided separate informed consent for the skin biopsies in this study. Each skin biopsy assessment will include 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total), including 1 set of biopsies taken from the distal lower leg, and 1 set from the distal thigh, when a patient's clinical status allows.
s. MR neurography will only be conducted at sites in Germany and France. In these countries, neurography may be conductedfor patients who had MR neurography in the parent study and for a subset of patients providing informed consent who did not have MR neurography previously in their parent study. Patients who had imaging in the parent study should have Day 0 imaging if they did not undergo MR neurography within the past 3 months.
t. Patients who are entering this study from a protocol that does not include the Norfolk QOL-DN questionnaire (eg, ALN-TTR02-003) do not have to complete this assessment.
u. Patients entering this study from study ALN-TTR02-003, who were not previously participating in the cardiac subgroup, will be required to have an echocardiogram before dosing on Day 0.
v. Serum samples for anti-drug antibodies will be collected as specified.
w. Patisiran will be administered once every 21 (±3) days (q3w). Every effort should be made to continue dosing from the parent study in the 21 (±3) day timeframe. Doses may be administered at the clinical site or, where applicable country and local regulations allow, at home by a healthcare professional trained in the protocol.
x. Patients who are receiving patisiran infusions at home must be contacted by the clinical site a minimum of every 30 (±5) days for assessment of adverse events and concomitant medication use. During phone contact, patients may also be asked additional questions about their general experience receiving infusions at home.
y. ALN-TTR02-004 coagulation assessment taken at Day 546 may be used for ALN-TTR02-006 qualification.
z. Where allowed per local regulations, IRB/IEC approval, and patient consent (and assent, where applicable), a blood sample should be collected at the first possible visit for genetic sequencing as described in Section 8.1.15.
aa. If available, information from a cardiac technetium scan and/or tissue biopsy testing for amyloid content prior to study enrollment or during the study should be collected and recorded as part of concomitant procedure information.
bb. Patients who discontinue early from the study will have a vital status check approximately 3 months after the last dose.
cc. More frequent pregnancy testing in women of child-bearing potential can be conducted according to country-specific regulations. In Argentina and Brazil, pregnancy testing should be performed prior to each patisiran dose.
dd. The mNIS+7 will be performed at Year 2 and Year 3, and will not be performed in Year 4 or Year 5 (see Section 8.1.1 for details).
ee. Patients who completed the Year 2 or Year 3 visit but did not have additional assessments performed at that annual visit (ie, mNIS+7, R-ODS, 10-MWT, ECHO, collection of blood for cardiac biomarker testing, NYHA classification, and KPS), should return to the site within 6 months of that visit to complete the additional assessments. If more than 6 months has passed since the Year 2 or Year 3 visit, then patients should proceed to have their assessments performed at the next scheduled annual visit.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
ATTR	transthyretin-mediated amyloidosis
BUN	blood urea nitrogen
CAS	Central Assessment Sites
CFR	Code of Federal Regulations
COMPASS 31	Composite Autonomic Symptom Score
CRF	case report form
CRO	clinical research organization
CYP	cytochrome P450
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DN	diabetic neuropathy
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EP	European Pharmacopoeia
EQ-5D	EuroQOL
EU	European Union
Σ5	5 attributes
FAC	familial amyloidotic cardiomyopathy also known as hATTR amyloidosis with cardiomyopathy
FAP	familial amyloidotic polyneuropathy also known as hATTR amyloidosis with polyneuropathy
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hATTR	Hereditary transthyretin-mediated amyloidosis
HEENT	head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act of 1996

Abbreviation	Definition
HP	heat pain
HRdb	heart rate response to deep breathing
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IENFD	intraepidermal nerve fiber density
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRS	interactive response system
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
LNP	lipid nanoparticle
mBMI	modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
mNIS	Modified Neuropathy Impairment Score
mRNA	messenger RNA
MR	magnetic resonance
NCS	nerve conduction studies
NHP	non-human primate
NIS	Neuropathy Impairment Score
NIS-W	Neuropathy Impairment Score- Weakness
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
OTC	over-the-counter

Abbreviation	Definition
PCS	Patient Care Sites
PD	pharmacodynamic
PEG_{2000}-C-DMG	(R)-methoxy-PEG_{2000}-carbamoyl-di-O-myristyl-sn-glyceride
PK	pharmacokinetic
PND	polyneuropathy disability
PO	per os (orally)
QOL	quality of life
QOL-DN	Quality of Life-Diabetic Neuropathy
QST	quantitative sensory testing
RBC	red blood cell
RBP	retinol binding protein
RNAi	ribonucleic acid interference
R-ODS	Rasch-built Overall Disability Scale
SAE	serious adverse event
SGNFD	sweat gland nerve fiber density
siRNA	small interfering ribonucleic acid
SUSAR	Suspected Unexpected Serious Adverse Reaction
TP	touch pressure
TSH	thyroid stimulating hormone
TTR	transthyretin
TUDCA	tauroursodeoxycholic acid
ULN	upper limit of normal
USP	United States Pharmacopeia
V30M	Val30Met
VDT	vibration detection threshold
WBC	white blood cell
WT	wild type

1. INTRODUCTION

1.1. Disease Overview

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis is a rare autosomal dominant, systemic disease caused by a mutation in the transthyretin (TTR) gene leading to the extracellular deposition of amyloid fibrils containing both mutant and wild type (wt) TTR.[1, 2] The particular TTR mutation and site of amyloid deposition determines the clinical manifestations of the disease, which include sensory and motor neuropathy, autonomic neuropathy, and/or cardiomyopathy. Hereditary ATTR amyloidosis is a progressive disease associated with severe morbidity, with a life expectancy limited to 5 to 15 years from symptom onset.[1] There are more than 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated TTR allele.[3-5] The most common genotype is the valine to methionine mutation at position 30 (V30M), accounting for approximately 50% of cases worldwide, and occurring primarily in families with heritage from Portugal, Sweden, Japan, and Brazil.[5-7]

Historically, due to incomplete understanding of etiology and pathogenesis, 2 clinical syndromes of hATTR amyloidosis have been described in the medical literature: hATTR amyloidosis with polyneuropathy (previously known as familial amyloidotic polyneuropathy, or FAP) and hATTR amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy, or FAC), both of which are characterized by amyloid deposits comprised of both mutant and wt TTR.[1] However, while patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease. Therefore, clinicians caring for these patients have evolved to refer to 1 hereditary disease with a spectrum of clinical manifestations rather than attempt to classify the disease into 2 distinct syndromes.[8]

Reduction of circulating amyloidogenic TTR improves outcomes in patients with hATTR amyloidosis. Orthotopic liver transplantation, which eliminates mutant TTR from the circulation, has improved survival in early stage FAP patients.[1] The TTR tetramer stabilizer tafamidis (Vyndaqel®) was approved in the European Union (EU) for the treatment of stage 1 hATTR amyloidosis with polyneuropathy based on evidence that it may slow neuropathy progression in these patients, but has not been approved for use in other regions of the world. Diflunisal, a generic, nonsteroidal anti-inflammatory drug (NSAID) that is also a tetramer stabilizer, exhibits slowing of neuropathy progression in patients with hATTR amyloidosis, but is not standardly used among practitioners. Thus, there remains an unmet medical need for a potent and effective therapy for patients with hATTR amyloidosis that will have an impact on patients across a broad range of neurologic and cardiac impairment, regardless of their mutation.

1.2. Patisiran

Patisiran (the International Nonproprietary Name [INN] name for the drug substance is a novel investigational agent being developed for the treatment of patients with hATTR amyloidosis. Patisiran comprises a small interfering ribonucleic acid (siRNA) which is specific for TTR, and

is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[9] It is designed to significantly suppress liver production of both wt and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with hATTR amyloidosis.

The nonclinical pharmacology, pharmacokinetics (PK), and toxicology of patisiran were evaluated in a series of in vitro and in vivo studies that have enabled chronic dosing in clinical studies. A summary of the nonclinical data can be found in the patisiran Investigator's Brochure (IB).

1.2.1. Clinical Experience with Patisiran

1.2.1.1. Healthy Volunteers

In a Phase 1 study of patisiran in healthy volunteers (Study ALN-TTR02-001), patisiran was generally well tolerated.[10] Significant pharmacology in terms of a TTR protein-lowering effect (>80% reduction from pretreatment baseline) was observed at the dose of 0.3 mg/kg. TTR levels showed evidence of recovery at Day 28 and return to baseline by Day 70. A Phase 1 study in healthy subjects of Japanese origin (Study ALN-TTR02-005) also showed dose-dependent reduction in serum TTR, similar to that observed in Study ALN-TTR02-001 in non-Japanese subjects; patisiran was generally well tolerated up to 0.3 mg/kg.

1.2.1.2. Phase 2 and Phase 2 Open-label Extension Study

An open-label Phase 2 multiple ascending dose study of patisiran in patients with hATTR amyloidosis (Study ALN-TTR02-002) was conducted to determine the safety and tolerability, PK, and pharmacodynamics of patisiran. The 0.3 mg/kg administered q3w was found to have an acceptable safety profile, with sustained TTR suppression of >80% observed; this dose was selected for subsequent studies.[11]

A Phase 2 open-label, single-arm, long-term follow-up extension study (Study ALN-TTR02-003) in 27 patients from Study ALN-TTR02-002 who received and tolerated at least one dose of patisiran was conducted. Patients in Study ALN-TTR02-003 were treated with patisiran 0.3mg/kg q3w for up to 2 years. Patisiran was generally well tolerated in patients treated for a median duration of 24.7 months. Seven patients experienced serious adverse events (SAEs); no SAEs were considered to be related to study drug. Flushing (25.9%) and infusion-related reactions (IRRs) (22.2%) were the most common related adverse events (AEs); all were mild in severity and did not result in discontinuation from study. A mean reduction in serum TTR levels over 24 months of 82% was achieved, accompanied by a 6.95-point decrease (improvement) in the modified Neuropathy Impairment +7 Score (mNIS+7) at 24 months compared to baseline. These results compared favorably to the 26- to 30-point increase (worsening) in mNIS+7 over 24 months estimated to occur in historic controls with similar baseline disease severity.[12]

1.2.1.3. Phase 3 Study

A randomized, double-blind, placebo-controlled Phase 3 study of patisiran (ALN-TTR02-004; APOLLO) in patients with hATTR amyloidosis with polyneuropathy was completed in August 2017, with a primary endpoint of change in mNIS+7 at 18 months. The main objectives of the study were to demonstrate the clinical efficacy of patisiran and to establish the safety in patients

with hATTR amyloidosis with polyneuropathy. This study met its primary efficacy endpoint (change from baseline in mNIS+7 at 18 months), the key secondary endpoint (change from baseline in Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QOL-DN] at 18 months), and all other secondary endpoints (change from baseline at 18 months for Neuropathy Impairment Score-Weakness [NIS-W], Rasch-built Overall Disability Scale [R-ODS], 10 meter walk test, modified Body Mass Index [mBMI], and Composite Autonomic Symptom Score [COMPASS 31]). Furthermore, the safety profile of patisiran was acceptable. The patisiran and placebo groups had similar frequencies of AEs (96.6% and 97.4%, respectively) and SAEs (36.5% and 40.3%, respectively). AEs reported in ≥10% of patients and occurring more frequently (≥5 percentage point difference) in the patisiran group compared to the placebo group were peripheral edema occurring in 29.7% and 22.1% of patients, respectively, and IRRs, occurring in 18.9% and 9.1% of patients, respectively.

Refer to the patisiran IB for more complete information on this study.

1.3. Study Design Rationale

This is a multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis who have completed a prior study with patisiran.

The nonclinical data and clinical experience with patisiran support the continuation of patisiran treatment in this long-term extension study. All patients will receive patisiran at 0.3 mg/kg administered IV q3w, which is the dose and regimen employed in the Phase 3 study with patisiran. Various clinical evaluations will be performed periodically as outlined in Table 1 to continue to assess the effect of patisiran beyond the completion of previous clinical studies, and will enable all patients who have completed a prior study with patisiran (provided they meet the eligibility criteria of this study), including those previously on placebo, to receive open-label patisiran. The duration of this study will enable collection of long-term safety, tolerability and efficacy data of patisiran in patients with hATTR amyloidosis . The estimated duration of the study is 5 years for each patient.

1.4. Risk-Benefit Assessment

Patisiran is a novel investigational agent intended for the treatment of patients with hATTR amyloidosis, a rare, serious and life-threatening disease with limited treatment options. Patisiran has shown a favorable benefit-risk profile in clinical studies to date. Clinical studies to date have shown a sustained mean serum TTR knockdown of approximately 80% as well as reduction of toxic misfolded TTR oligomers. The Phase 2 OLE study has shown evidence of improvement of neurologic impairment at 24 months, as assessed by the mNIS+7.[13] The randomized, placebo-controlled Phase 3 study met its primary efficacy endpoint (change from baseline in mNIS+7 at 18 months) and all secondary endpoints. Both studies had an acceptable safety profile with similar risks.

To minimize the risk of IRRs, patients must receive premedication prior to dosing with patisiran (Section 6.4.1). The infusion may be interrupted or slowed if an IRR occurs (Section 6.4.2 and Section 6.4.3, respectively). The protocol also includes a recommendation that patients receive oral supplemental vitamin A at the usual recommended daily dose (Section 5.2).

Patisiran is contraindicated in patients with a history of severe hypersensitivity (eg., anaphylaxis or anaphylactoid reactions) to patisiran or any of the excipients.

Further guidance to the investigator can be found in the patisiran IB.

2. STUDY OBJECTIVES

The objective of this study is to assess the safety and efficacy of long-term dosing with patisiran in patients with hATTR amyloidosis .

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, multinational, open-label extension study to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy who have previously completed a patisiran study. Patients in this study will have completed "parent" study ALN-TTR02-003 or ALN-TTR02-004. Note that Study ALN-TTR02-003 was not conducted in Japan.

Consented eligible patients will enroll in this study and receive 0.3 mg/kg patisiran IV q3w for the duration of the study. All dosing visits have a window of ± 3 days. In order to maintain the q3w dosing schedule from the parent study, patients are expected to have their first visit (Day 0) on this study 3 weeks after their last dose visit on the parent study. However, if necessary, a patient may initiate dosing in this study up to 45 days from the time of the last dose in the parent study. Exceptions to this timing may be allowed for medical or regulatory considerations only after consultation with the Medical Monitor. The last testing visit in the parent study will serve as the baseline for this study, unless more than 45 days have elapsed, in which case the baseline tests will need to be repeated on Day 0. Eligibility for this study will be confirmed before administration of the first dose on Day 0.

The duration of the study has been determined to allow the collection of long-term safety, tolerability and efficacy data of patisiran in patients with hATTR amyloidosis who have completed a prior study with patisiran. The estimated duration of the study is 5 years for each patient.

In order to reduce the potential for an IRR with patisiran, all patients on this study will receive premedications at least 60 minutes before the start of the patisiran infusion. Patisiran will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). If the infusion duration for a patient was lengthened beyond 80 minutes due to the occurrence of an IRR while on the parent study, that infusion duration may be continued on this study for that particular patient. Returning the patient's infusion duration to 80 minutes will require a discussion with the Medical Monitor.

After the Day 0 visit, patients should return to the clinical site for patisiran dosing q3w. Where applicable country and local regulations allow, patients may receive the patisiran infusions at home by a healthcare professional trained on the protocol and delivery of premedications and patisiran. Patients who are receiving patisiran infusions at home will have a phone contact with the site at least every 30 (±5) days. Patients will also have visits at the clinical site at approximately 12, 26 and 52 weeks, and yearly thereafter.

A complete set of efficacy assessments will be performed at 52 weeks, followed by more limited efficacy assessments yearly thereafter. In order to decrease the variability in the efficacy assessment testing during the study, there will be a number of sites within any one territory that conduct these efficacy assessments (referred to as "Central Assessment Sites [CAS]"); these sites can dose and manage patients. There will also be sites that can dose and manage the patients ("Patient Care Sites [PCS])", while sending the patients to the nearest CAS for efficacy

assessments. Every effort should be made for the patient to return to the same CAS center that the patient went to in the parent study. Prior to starting the study, the CAS and PCS will create a delegation of responsibilities document that clearly details which site is responsible for which efficacy tests and safety parameters to ensure adherence to the protocol. This document will become part of the study site specific documentation.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at 12, 26, and 52 weeks during the first year and yearly thereafter. Patients will be continually assessed throughout the study for adverse events (AEs). Unscheduled visits for study assessments may occur if deemed necessary by the study personnel.

3.2. Number of Patients

All patients who have previously completed a patisiran study may be enrolled if they meet the eligibility criteria for this study.

3.3. Treatment Assignment

All patients enrolled in this study will receive open-label patisiran at 0.3 mg/kg administered IV q3w days.

The Investigator or his/her delegate will contact the interactive response system (IRS) (via phone or web) after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The patient will then be assigned a patient number that corresponds to their current patient number on the parent study. A combination of the center number, parent study number, enrollment number, and patient initials will create the unique patient identifier. In countries with regulations prohibiting the use of patient initials, a strategy consistent with local regulations will be used to generate replacement values for the patient initials.

3.4. Criteria for Study Termination

The study may be terminated if patisiran does not obtain marketing approval or the development of patisiran is no longer being pursued by the Sponsor (Alnylam Pharmaceuticals, Inc).

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and patisiran supplied for the study must be returned to the Sponsor, and the Investigators, Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

To be enrolled in the study, patients must meet the following criteria before administration of patisiran on Day 0:

1. Have completed a patisiran study (ie, completed the last efficacy visit in the parent study) and, in the opinion of the investigator, tolerated study drug
2. Be considered fit for the study by the Investigator
3. Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)
4. Have a total bilirubin within normal limits. A patient with total bilirubin ≤ 2 X ULN is eligible if the elevation is secondary to documented Gilbert's syndrome (elevation of unconjugated bilirubin with normal conjugated bilirubin) and the patient has ALT and AST levels within normal ranges.
5. Have a serum creatinine ≤2 × ULN
6. Women of child-bearing potential must have a negative pregnancy test, cannot be breastfeeding, and must be using 2 highly effective methods of contraception prior to dosing in this study and agree to use 2 highly effective methods of contraception throughout study participation and for 12 weeks after last dose of patisiran in this study. Highly effective methods of birth control are defined in Section 4.4.
7. Be willing and able to comply with the protocol-required visit schedule and visit requirements and provide written informed consent

4.2. Patient Exclusion Criteria

A patient will be excluded if they meet any of the following criteria before dosing on Day 0:

1. Has an active infection requiring systemic antiviral or antimicrobial therapy that will not be completed before the first dose of patisiran administration
2. Has poorly controlled diabetes mellitus
3. Has uncontrolled cardiac arrhythmia or unstable angina
4. Is currently taking tafamidis, diflunisal, doxycycline, or tauroursodeoxycholic acid (TUDCA), unless previously allowed per the parent study
5. Is unable to take the required premedications, unless modifications to the premedication regimen were previously allowed per the parent study
6. Is under legal protection (defined as "any person who becomes incapable of protecting his/her interests due to a medically diagnosed impairment of his/her mental faculties that may limit or prevent the expression of his will"), decided by a court

4.3. Patient Withdrawal Criteria

Patients are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. For those patients who withdraw, every effort will be made to determine their reason for dropping out, and to complete the Early Withdrawal visit.

The Investigator may withdraw a patient from the study if the patient:

- Is in violation of the protocol
- Experiences a serious or intolerable AE
- Becomes pregnant
- Requires a prohibited medication (see Section 5.2)
- Requests to be withdrawn from the study
- Is found to be substantially noncompliant with the protocol-required patisiran dosing visits

The Investigator will withdraw patients from the study upon the request of the Sponsor, including if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor before discontinuing the patient.

Missing an occasional dose of patisiran will not necessarily result in the patient being withdrawn from the study. However, if a patient misses 3 consecutive doses of patisiran, the Investigator at the clinical site and the Medical Monitor will determine whether the patient should be withdrawn from the study. If the patient is withdrawn from the study, the reason will be noted in the patient medical record and on the case report form (CRF).

In the event a patient is withdrawn from the study, the clinical research organization (CRO) Medical Monitor must be informed immediately.

Definition of Study Completion:

A patient is considered to have completed the study if the patient completed protocol-specified procedures through the 5-year annual assessment visit.

An End-of-Study visit is planned 4 weeks after the last dose of study treatment.

4.4. Pregnancy and Breastfeeding Restrictions / Contraception Requirements

TTR transports vitamin A in plasma; therefore, reductions in circulating vitamin A levels accompany reductions in TTR caused by patisiran. Vitamin A deficiency has known effects on both male and female reproductive performance and embryo/fetal development.[14] It is not known whether decreased levels of vitamin A at efficacious patisiran doses in ATTR patients who are male or who are women of child bearing potential will affect reproduction. Histopathological evaluations of all of the reproductive organs have been conducted in the rat and non-human primate (NHP) toxicology studies including a chronic NHP study in sexually mature animals, where there were no adverse effects in males (including sperm analyses and spermatogenic staging) or females. In a dose range-finding rat embryo/fetal development study conducted with patisiran, there were no effects on mating, fertility, ovarian or uterine parameters,

or fetal development despite reductions (-88% from baseline) in serum vitamin A in the dams dosed with the rat-specific TTR surrogate siRNA.

Women of child-bearing potential are defined as any woman or adolescent who has begun menstruation. A post-menopausal woman is defined as a woman who has 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

In this study, women of child-bearing potential must have a negative pregnancy test, cannot be breastfeeding, and must be using 2 highly effective methods of contraception prior to dosing on Day 0, throughout study participation, and for 12 weeks after last dose of patisiran in this study. Highly effective methods of birth control result in a low failure rate (ie, less than 1% per year). Acceptable forms of effective contraception are defined as follows:

- Hormonal: established use of oral, implantable, injectable, or transdermal hormonal methods of conception
- Placement of an intrauterine device (IUD)
- Placement of an intrauterine system (IUS)
- Mechanical/barrier method of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) in conjunction with spermicide (foam, gel, film, cream or suppository)

  Note: Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient);
- Sexual true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Patients should be instructed to use 2 different forms of effective contraception from the list above. Examples of 2 forms of highly effective contraception are as follows:

- Oral, implantable, injectable, or transdermal contraceptives in conjunction with condom or diaphragm and spermicide
- IUD in conjunction with condom or diaphragm and spermicide
- Surgical sterilization of partner in conjunction with condom or diaphragm and spermicide

Interaction between patisiran and hormonal contraceptives is not anticipated. The patisiran drug substance ALN-18328 (siRNA), and the 2 novel lipid excipients 1,2-Dilinoleyloxy-N,N-

dimethylpropylamine (DLin-MC3-DMA) and (R)-methoxy-PEG$_{2000}$-carbamoyl-di-O-myristyl-sn-glyceride (PEG-$_{2000}$-C-DMG), were evaluated by in vitro human microsomal incubations to determine if any had inhibitory effects on cytochrome P450 (CYP) activity. None of the components displayed an inhibitory effect on any of the CYPs investigated (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5). In addition, there was no induction of CYP1A2, CYP2B6, or CYP3A4 at any of the concentrations studied. These data suggest a low likelihood of patisiran to interfere with the metabolism of hormonal contraceptives.

Contraception is not required in males (refer to the patisiran IB).

In Japan it is recommended that the Investigators select appropriate contraception methods, as available.

Pregnancy reporting guidelines are provided in Section 9.5.2.

5. TREATMENT OF PATIENTS

5.1. Description of Study Drug

Patisiran Solution for intravenous infusion is a ribonucleic acid interference (RNAi) therapeutic consisting of an siRNA targeting TTR messenger RNA (mRNA) formulated in a LNP. The patisiran drug product is a sterile formulation of ALN-18328, an siRNA targeting TTR, formulated as LNPs with lipid excipients (DLin-MC3-DMA, 1,2-Distearoyl-sn-glycero-3-phosphocholine [DSPC], cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for intravenous infusion contains 2 mg/mL of patisiran.

5.2. Concomitant Medications

Use of the following medications/treatments is prohibited during study participation:

- Any investigational agent other than patisiran
- Corticosteroids other than those administered as premedications prior to the dose of patisiran, those used to treat an infusion reaction, or topical or inhaled corticosteroids. However, for patients with chronic inflammatory disorders (eg, asthma, rheumatoid arthritis), systemically administered steroids may be permitted provided that: 1) the dose is <20 mg/day prednisone or equivalent if administered chronically, or 2) for doses ≥20 mg/day, administration is limited to no more than 5 consecutive days.

Use of the medications/treatments listed below is permitted in patients who were already taking such medications while on the parent study in accordance with the rules of that study protocol. For patients who did not take these medications while on the parent study, use of these medications is permitted, if necessary, only after the patient has completed the 52-week visit.

- Tafamidis
- Diflunisal
- Doxycycline/TUDCA

Medications and treatments other than those specified above, including palliative and supportive care approved by the Investigator for disease-related symptoms, are permitted during the study.

All patients will be asked to continue to take the recommended daily allowance of vitamin A. Patients will receive this daily dose for the duration of their participation in the study while being administered patisiran. In Japan, the clinical sites will provide patients with a prescription for vitamin A.

Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. Use of all concomitant medications and treatments will be recorded on the patient's CRF through the end of the patient's participation in the study. This will include all prescription drugs, herbal preparations, over-the-counter (OTC) medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the CRF. Similarly, concomitant medications that continue from the parent study will be entered into the database.

5.3. Treatment Compliance

Compliance with patisiran administration is dependent on the proper preparation and administration of IV infusions by trained personnel and attendance by the patient at the clinic or home for scheduled assessment visits. Compliance with patisiran administration will be verified through observation by study staff or (in applicable regions) trained home healthcare professionals. A dose will be considered completed if 80% or more of the total volume of the IV solution was administered to the patient. Patients will be permitted to miss an occasional dose of patisiran; however, if a patient misses 3 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue on the study.

5.4. Randomization and Blinding

This is an open-label study; however, patients rolling over into this study from a previously blinded study will remain blind to their previous treatment assignment until database lock has occurred in that study.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug Packaging and Labeling

All packaging, labeling, and the preparation of patisiran will be in compliance with Good Manufacturing Practice (GMP) specifications, as described in the Manufacture of Investigational Medicinal Products Volume 4 Annex 13, and any other or local applicable regulations.

Patisiran labels will include all appropriate local labeling requirements on the vial and external label. Sample labels will be submitted to health authorities, per local country submission requirements.

The patisiran drug product is packaged in 10 mL glass vials with a fill volume of 5.5 mL. The container closure system consists of a United States Pharmacopeia/European Pharmacopoeia (USP/EP) Type I borosilicate glass vial, a Teflon-faced butyl rubber stopper, and an aluminium flip-off cap.

6.2. Study Drug Storage

Patisiran will be stored upright and refrigerated at approximately 5 ± 3°C. Any deviation from the recommended storage conditions must be reported to the CRO and/or the Sponsor. For major deviations, as specificed in the Pharmacy Manual, use of patisiran must be halted until authorization for its continued use has been given by the Sponsor or designee.

No special procedures for the safe handling of patisiran are required. A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Patisiran supplied for this study may not be administered to any person not enrolled in the study.

6.3. Study Drug Preparation

Staff at each clinical site or the healthcare professional administering patisiran will be responsible for preparation of patisiran doses, according to procedures detailed in the Pharmacy Manual.

All patients in this study will receive 0.3 mg/kg patisiran q3w (± 3 days). The amount (mg) of patisiran to be administered will be based on the patient's actual body weight (kg). For each dose administered, the weight obtained during the previous dosing visit will be used to calculate the dose of patisiran. In the event that the weight obtained on the previous dosing day is not available, the weight obtained pre-dose on the current dosing day can be used for dose calculation. Patients who weigh 105 kg or more will receive patisiran dosing based on an assumption of a body weight of 104 kg.

Patisiran will be prepared as described in the Pharmacy Manual. The total volume of diluted study drug to be infused into each patient at each dosing visit will be 200 mL.

6.4. Administration

6.4.1. Premedication

Prior to each dose of patisiran, patients will receive the following premedications in order to reduce the risk of experiencing an IRR at least 60 minutes before the infusion:

- Intravenous dexamethasone (10 mg) or equivalent
- Oral paracetamol/acetaminophen (500 mg) or equivalent
- Intravenous H2 blocker (ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose)
- Intravenous H1 blocker: diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the clinical site). Hydroxyzine 25 mg per os (PO, orally) or fexofenadine 30 mg or 60 mg PO or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blocker.

Further details (including a table of equivalent premedications) can be found in the patisiran Pharmacy Manual.

Patients will be started on the above premedication regimen. However, modifications may be made to the premedication regimen after consultation with the medical monitor either due to a patient's inability to tolerate one or more of the premedications or to the occurrence of IRRs unresponsive to slowing of the infusion rate.

- If a patient is having difficulty tolerating the steroid premedication regimen (e.g., patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the steroid premedication may be allowed for that patient after consultation with the medical monitor.
- If after consultation with the medical monitor, it is agreed that an individual patient's steroid premedication will be lowered, then the following steps **must be followed**:
    1) If the current steroid dosage is 10 mg or less of intravenous dexamethasone or equivalent, then the patient may be lowered in increments no greater than 2.5 mg intravenous dexamethasone or equivalent.
    2) After each incremental lowering of intravenous dexamethasone or equivalent, the patient must receive three consecutive intravenous doses of patisiran without IRR and continued signs or symptoms of steroid intolerance before further reductions in steroid premedications.
    3) The premedication steroid dosage should not be reduced below 5 mg intravenous dexamethasone or equivalent.

Alternatively if a patient experiences an IRR when 10 mg or less of IV dexamethasone or equivalent is used as the steroid premedication, then proceed to Section 6.4.3.

If a patient's premedication regimen was modified prior to enrollment in Study TTR02-006, the patient may continue on that modified premedication regimen.

6.4.2. Study Drug Administration

Patisiran will be administered under the supervision of the site personnel q3w (±3 days). Patients who have received at least 3 consecutive doses of patisiran on this study at the clinical site with no evidence of IRRs or other drug-related adverse effects impacting safety and tolerability of the infusion may have patisiran administered at home, where applicable country and local regulations allow. Home administration of patisiran will be performed by a healthcare professional trained on the protocol and administration of premedications and patisiran infusion.

For patients who experience IRRs or other drug-related adverse effects who subsequently would like to participate in home administration, the Alnylam Medical Monitor, using clinical judgement and consulting with the PI, will determine if the patient's clinical status now allows for home administration.

On all dosing days, patisiran will be administered as an approximately 80-minute IV infusion (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minute for the remainder of the infusion).

- If the patient experiences an IRR the infusion time may be extended up to 3 hours in the event of a mild or moderate IRR.
    1) If the patient experiences a mild or moderate IRR that resolves by slowing the infusion rate then no further premedication changes are recommended.
    2) If the patient experiences a severe IRR, then patisiran administration will not be resumed until the case is discussed with the Medical Monitor (see Section 6.4.3).
- If the infusion time for a patient was already extended on the parent study due to an IRR, that modified infusion duration may be continued on this study for that particular patient. Returning the patient's infusion duration to approximately 80 minutes will require a discussion with the Medical Monitor.
- For the first 3 infusions of patisiran on this study, the patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion, and the patient will remain at the clinical site for 1 hour following completion of dosing.

If a patient does not receive a dose of patisiran within the dosing window (±3 days), the dose will be considered missed and not administered.

Additional details can be found in the patisiran Pharmacy Manual.

In addition to study treatment, patients will receive the recommended daily allowance of vitamin A . Patients will receive this daily dose for the duration of their participation in the study while being administered patisiran. In Japan the clinical sites will provide the subjects with a prescription for vitamin A.

6.4.3. Suggested Guidelines for Management of Infusion-Related Reactions

Criteria for categorizing IRRs are provided in Appendix 3.

- In the event of an IRR, the infusion of patisiran may be stopped and the patient closely monitored until resolution of the reaction. Drugs that may be used to facilitate resolution and permit resumption of patisiran administration include, but are not limited to: paracetamol/acetaminophen (or equivalent), additional histamine H1/H2 receptor antagonists (eg, ranitidine), NSAIDs, adrenaline, supplemental oxygen, IV fluids, and/or corticosteroids.
- Following resolution of a mild or moderate IRR that required interruption of the patisiran infusion, resumption of administration may occur at the Investigator's discretion at a slower infusion rate (but not to exceed 3 hours) for that dose and for all subsequent doses of patisiran. If the infusion is delayed, the administration of the infusion should be completed no more than 6 hours from the initial start of the infusion.
- Patisiran administration will not be resumed for any patient following a severe IRR until the case is discussed with the Medical Monitor.
- If after consultation with the Medical Monitor it is agreed that an individual patient's steroid premedication will be increased then the following steps are **recommended**:

    1) If the IRR occurred while the patient received 10 mg intravenous dexamethasone or equivalent at least 60 minutes before the infusion and did not resolve with slowing of the infusion rate, then the patient should be increased by multiples of 5 mg intravenous dexamethasone or equivalent at least 60 minutes before the infusion and/or 5 mg oral dexamethasone or equivalent the night before the intravenous infusion.
    2) Increased dose of premedication steroids should NOT exceed the combination of 20 mg intravenous dexamethasone or equivalent on the day of infusion and 8 mg oral dexamethasone or equivalent taken the night before the infusion.
    3) If the IRR occurred while the patient received less than 10 mg intravenous dexamethasone or equivalent, then the patient should return to the prior dose of intravenous dexamethasone or equivalent that did not result in an IRR.

Patients will be instructed to call the Investigator if they experience symptoms such as fever, chills, myalgia, or nausea/vomiting after discharge from the site.

6.5. Study Drug Accountability

The Investigator or designee (or in Japan, the responsible pharmacist designated according to the Japan local regulations) will maintain accurate records of receipt and the condition of the patisiran supplied for this study, including dates of receipt. In addition, accurate records will be kept of the weight used to calculate each dispensed patisiran dose, and when and how much patisiran is dispensed and used by each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available for verification by the Sponsor or designee.

Further instructions about drug accountability are detailed in the patisiran Pharmacy Manual.

6.6. Study Drug Handling and Disposal

All used, partially used, and unused vials of patisiran will be returned to the Sponsor or its specified designee/depot or destroyed at the site according to applicable regulations.

Patisiran supplied for this study must not be used for any purpose other than the present study. Drug that has been dispensed for a patient and returned unused must not be redispensed.

7. PHARMACOKINETIC ASSESSMENTS

No PK assessments will be performed in this study.

8. ASSESSMENT OF EFFICACY

8.1. Efficacy Parameters

Efficacy assessments may be performed at Day 0 if not performed during the parent study within 45 days of the first dose in this study. Efficacy assessments will occur for all patients at the 52-week visit (Year 1), at Year 2, Year 3, Year 4 and Year 5. Patients will not receive study drug at these visits. The specific timing for each assessment is presented in Table 1.

Patients who completed the Year 2 or Year 3 visit but did not have additional assessments performed at that annual visit (ie, mNIS+7, R-ODS, 10-MWT, ECHO, collection of blood for cardiac biomarker testing, NYHA classification, and KPS), should return to the site within 6 months of that visit to complete the additional assessments. If more than 6 months has passed since the Year 2 or Year 3 visit, then patients should proceed to have their assessments performed at the next scheduled annual visit.

A central neurologic testing core facility will review the mNIS+7 data derived from the various neuropathy measures at each participating site to ensure compliance with testing procedures and quality of the data. A central echocardiography core lab will analyze the echocardiogram data. A core lab will be responsible for processing and analyzing skin punch biopsy samples. Magnetic resonance (MR) neurography data (when performed) will also be centrally read.

Further details on performing the efficacy assessments will be provided in the Study Reference Manual.

8.1.1. Neurological Testing

Neurological testing will be performed and the results of these tests will be used to calculate the Neuropathy Impairment Score (NIS), modified NIS+7 (mNIS+7), and NIS+7.

The NIS will be performed at Day 0 if not performed during the parent study within 45 days of the first dose in this study, at Week 52 (Year 1), and thereafter annually (at the end of Year 2 to Year 5) as specified in Table 1. At Year 1, NIS is collected as part of the NIS+7 assessment. At subsequent visits, only NIS (not NIS+7) is collected.

The mNIS+7 will be performed at Day 0 if not performed during the parent study within 45 days of the first dose in this study, at Week 52 (Year 1), at the end of Year 2, and at the end of Year 3 as specified in Table 1.

Patients who have already had a Year 2 or Year 3 visit but did not have a mNIS+7 assessment, should return to the site within 6 months of that visit to complete the mNIS+7 assessment.

The NIS+7 will be performed at Day 0 if not performed during the parent study within 45 days of the first dose in this study and at Week 52 (Year 1) as specified in Table 1.

8.1.1.1. Modified Neurological Impairment Score +7 and Neurological Impairment Score +7

The mNIS+7 assessment tool is a composite measure of neurologic impairment which includes the following measures:

- Clinical exam-based NIS (weakness and reflexes)
- Electrophysiologic measures of small and large nerve fiber function (+7) including:

  Nerve conduction studies (NCS) 5 attributes (Σ5)

  Quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP)
- Autonomic function (postural blood pressure)

Neurologic impairment will also be assessed by NIS+7. The NIS+7 consists of the following measures:

- Full NIS (including weakness, sensation, and reflexes)
- Electrophysiologic measures of small and large nerve fiber function (+7) including:

  NCS Σ5

  Vibration detection threshold (VDT)
- Heart rate response to deep breathing (HRdb)

The scoring and components of the mNIS+7 and NIS+7 are summarized in Appendix 4. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment.

Every effort will be made to use the same devices for NCS, QST, and VDT for a patient throughout the duration of the study.

For each patient, 2 independent assessments of the mNIS+7 and NIS+7 will be performed by a neurologist at each time point at a CAS. Assessments are to be performed approximately 24 hours apart from each other but not more than 7 days apart. In order to limit potential intra-operator bias, results of any of the prior assessments will not be available to the examiner when performing the second assessment. Each site will make every effort to have these assessments performed by the same study personnel who performed the assessments for the patient in the patisiran study in which they were previously enrolled.

8.1.1.2. Neurological Impairment Score (NIS)

The NIS will be performed at Day 0 if not performed during the parent study within 45 days of the first dose in this study, at Week 52 (Year 1), and thereafter annually (at the end of Year 2 to Year 5) as specificed in Table 1.

At each timepoint 2 independent assessments of the NIS will be performed by a neurologist approximately 24 hours apart from each other but not more than 7 days apart at a CAS or PCS.

8.1.2. Familial Amyloidotic Polyneuropathy Stage and Polyneuropathy Disability Score

Changes in ambulation will be evaluated through the polyneuropathy disability (PND) score and FAP stage (see Appendix 5 and Appendix 6, respectively).

8.1.3. Intraepidermal Nerve Fiber Density and Sweat Gland Nerve Fiber Density

Quantification of nerve fibers in skin will be assessed via intraepidermal nerve fiber density (IENFD) and sweat gland nerve fiber density (SGNFD). For patients who had skin biopsies on the parent study and who have provided additional voluntary consent for skin biopsy on this study, 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total) for IENFD,SGNFD and amyloid burden characterization will be obtained at each time point. One set of biopsies will be taken from the distal lower leg, and 1 set from the distal thigh, when a patient's clinical status allows.

Details on sample collection, processing, and storage will be provided in the Study Laboratory Manual.

Skin biopsies will be performed at a CAS or PCS.

8.1.4. Magnetic Resonance Neurography (Germany and France Only)

Magnetic resonance (MR) neurography will only be performed at sites in Germany and France. Magnetic resonance neurography enables direct high-resolution longitudinal and cross-sectional images for the evaluation of peripheral nerve disorders.[15] This procedure produces detailed images of nerve morphology to evaluate degeneration and regeneration. Nerves in the lumbar plexus and lower extremity may be imaged for patients in Germany and France who have previously had MR neurography in the parent study and for a subset of patients providing informed consent who did not have MR neurography previously in the parent study. A central reader will be used for MR neurography.

8.1.5. Modified Body Mass Index

Sites will measure body weight on all dosing days. Using that data, the modified body mass index (mBMI) will be calculated (BMI × albumin) programmatically in the clinical database and does not need to be performed at the study center.

8.1.6. Timed 10-meter Walk Test

To perform the timed 10-meter walk test, the patient will be asked to walk 10 meters. The walk must be completed without assistance from another person; ambulatory aids such as canes and walkers are permitted. The time required for the patient to walk 10 meters will be recorded.

At each annual visit or at the time points specified in Table 1, 2 assessments of the 10-meter walk test are to be conducted approximately 24 hours apart from each other but not more than 7 days apart. Each site will make every effort to have this assessment performed by the same Investigator.

8.1.7. Grip Strength Test

Hand grip strength is to be measured by dynamometer. Sites will be trained on dynamometer and testing for the study. When performing the test, patients will stand, holding the dynamometer in their dominant hand, with their arm parallel to the body without squeezing the arm against the body. Tests will be performed in triplicate for each assessment. Two assessments of the grip strength test are to be conducted on separate days (1 assessment on each

day). The second (repeat) assessment must be conducted at least 24 hours (approximately) but not more than 7 days after the first assessment.

Every effort will be made to use the same dynamometer for a patient on both assessment days.

8.1.8. Composite Autonomic Symptom Score

To evaluate changes in autonomic symptoms, patients will complete the Composite Autonomic Symptom Score (COMPASS 31) questionnaire. The questionnaire consists of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, secretomotor, gastrointestinal, bladder, and pupillomotor).

8.1.9. Norfolk Quality of Life - Diabetic Neuropathy Questionnaire

Quality of life will be assessed through the Norfolk Quality of Life - Diabetic Neuropathy (QOL-DN) questionnaire, a standardized 47-item patient-reported outcomes measure that is sensitive to the different features of diabetic neuropathy (DN)-small fiber, large fiber, and autonomic nerve function.

Patients who are entering this study from a protocol that does not include the Norfolk QOL-DN questionnaire (eg, ALN-TTR02-003) will not complete this assessment.

8.1.10. EuroQoL Quality of Life Questionnaire

Quality of life will also be assessed through the use of the EuroQOL (EQ-5D) questionnaire, a standardized 5 question instrument for use as a measure of health outcomes.

8.1.11. Rasch-built Overall Disability Scale

An annual assessment of the disability each patient experiences will be assessed through the Rasch-built Overall Disability Scale (R-ODS) at the time points specified in Table 1. The R-ODS is a questionnaire completed by the patient that consists of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

8.1.12. Pharmacoeconomics Questionnaire

The burden of disease and healthcare utilization will be assessed using a patient-reported pharmacoeconomics questionnaire. This assessment will be performed at the location of the patient's scheduled visit.

8.1.13. Echocardiogram and Biomarkers of Cardiac Function

Cardiac structure and function will be assessed annually through echocardiograms and measurement of serum levels of the cardiac biomarkers N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin I at the time points specified in Table 1.

Echocardiograms will be performed and interpreted at a central echocardiography core laboratory. Patients entering this study from Study ALN-TTR02-003 who were not previously participating in the cardiac subgroup study will also be required to have an echocardiogram performed before dosing on Day 0. Image acquisition, storage, and transfer guidelines will be provided in a Study Manual.

Blood samples will be drawn to measure levels of NT-proBNP and troponin I. Details on sample collection, processing, and storage will be provided in a Study Laboratory Manual.

8.1.14. Blood Sample for Long-term Storage

To permit exploratory investigations and the application of novel approaches to bioanalysis that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action and/or efficacy of patisiran, blood samples will be collected for long-term storage. These samples will be securely stored in a central biorepository for up to 10 years following the last patient last visit in this clinical study. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

All study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples. Those who do not wish to contribute specimens to the biorepository will be asked to sign an "opt out" form. Moreover, patients who subsequently decide to withdraw consent for the utilization of such stored samples will be able to do so, with the understanding that any data arising from samples already analyzed will be the property of Alnylam Pharmaceuticals.

8.1.15. Blood Sample for Genetic Testing

Where local regulations permit and subject to discretionary approval from each center's IRB/IEC as well as patient consent, a blood sample will be collected at the timepoint specified in Table 1 to analyze DNA sequences within genes relevant to the mode of action and response to patisiran.

Details regarding the collection, processing, storage, and shipping of the samples can be found in the Laboratory Manual.

The sample collected will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient, last visit), or as local regulations allow. After 10 years have elapsed, the samples will be destroyed.

8.2. Pharmacodynamic Parameters

8.2.1. Transthyretin

Blood for serum TTR levels will be collected at scheduled time points specified in Table 1 before the administration of patisiran. Serum TTR will be assessed using enzyme linked immunosorbent assay (ELISA).

8.2.2. Vitamin A

Blood for serum vitamin A levels will be collected at scheduled visits specified in Table 1 before the administration of vitamin A.

8.3. Anti-drug Antibodies

Serum samples for anti-drug antibodies (ADA) will be collected as specified in Table 1.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

All safety assessment measures will be recorded in the patient's medical record and CRF. Refer to Table 1 for the timing of each safety assessment.

9.1.1. Demographic and Medical History

Patient demographic data will be obtained from the parent study.

The Investigator will assess all patients according to the Karnofsky Scale (see Appendix 1) and the New York Heart Association Classification of Heart Failure (NYHA; see Appendix 2).

For all patients, a complete medical history will be obtained, including TTR genotype. Any AEs from the parent study that are ongoing on Day 0 will be considered as part of the medical history.

9.1.2. Vital Signs

Vital signs will be measured pre-dose on all dosing days. Vital signs include systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature, and will be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes. Each patient's blood pressure should be taken using the same arm. Temperature will be recorded in Celsius. Heart rate will be counted for a full minute and recorded in beats per minute. Respirations will be counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital signs may be obtained at the discretion of the Investigator.

9.1.3. Weight and Height

Body weight will be measured on all dosing days if possible to inform the next infusion dosing calculation. The rules for using body weight to calculate dose are described in Section 6.3.

Height will be measured only if it was not obtained in the parent study.

9.1.4. Physical Examination

A physical examination will be performed by a physician before dosing at scheduled time points. The physical examinations may include the examination of the following: general appearance; head, ears, eyes, nose, and throat; cardiovascular; dermatologic; abdominal; genito-urinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological.

9.1.5. Laboratory Assessments

Blood samples for clinical laboratory testing will be collected before patisiran dosing at the time points listed in Table 1. All samples will be sent to a central laboratory for analysis. Details on sample collection, processing, and shipping will be provided in a Laboratory Manual.

In the event of an unexplained clinically relevant abnormal laboratory test occurring after patisiran administration, the test should be repeated and followed up until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality.

9.1.5.1. Hematology

Blood samples will be collected for evaluation of the following hematology parameters:

- Hematocrit
- Hemoglobin
- Red blood cell (RBC) count
- White blood cell (WBC) count
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Neutrophils, absolute and %
- Lymphocytes, absolute and %
- Monocytes, absolute and %
- Eosinophils, absolute and %
- Basophils, absolute and %
- Platelet count

9.1.5.2. Blood Chemistry

Blood samples will be collected for evaluation of the following chemistry parameters:

- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Sodium
- Potassium
- Blood urea nitrogen (BUN)
- Creatinine
- Thyroid stimulating hormone (TSH)
- Alkaline phosphatase
- Bilirubin (total and direct)
- Glucose
- Phosphate
- Albumin
- Calcium
- Chloride
- Bicarbonate

9.1.5.3. Urinalysis

Urine samples will be collected for evaluation of the following urinalysis parameters:

- Visual inspection for color and appearance
- pH
- Specific gravity
- Ketones
- Protein
- Glucose
- Leukocytes
- Bilirubin
- Nitrite
- Urobilinogen
- Microscopic inspection of sediment

9.1.5.4. Coagulation

A sample for INR assessment will be collected. The INR result taken from the ALN-TTR02-004 Day 546 sample may be used for ALN-TTR02-006 qualification at Day 0.

9.1.5.5. Pregnancy Screen

Urine pregnancy tests are to be performed for all women of child-bearing potential. The timing of the tests is specified in Table 1; additional testing may be done any time following country-specific regulations, and if pregnancy is suspected.

9.1.6. Ophthalmology Examination

Ophthalmology examinations will include assessment of visual acuity, visual fields, and slit-lamp evaluation. Visual acuity should be evaluated at the beginning of each specified visit in the study (ie, prior to slit-lamp examination). Manifest refraction will be performed at each specified visit before visual acuity testing and will be used to obtain a correction for visual acuity evaluations. Visual acuity testing should be done with best (most recent) correction.

An electroretinogram (ERG) is a test to evaluate the retinal response to light. It is done to determine if there is damage to rods and cones. ERG testing should be performed if visual changes raise the suspicion for this sort of retinal disease and if clinically indicated.

Further details regarding the ophthalmology examinations will be provided in the Study Reference Manual.

9.1.7. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess each patient's mental status as it relates to suicidal ideation and behavior. If a patient's C-SSRS raises concern of suicidal ideation or behavior, the Investigator must ensure prompt and appropriate mental health interventions in accordance with standard of care.

9.2. Adverse Events and Serious Adverse Events

9.2.1. Definition of Adverse Events

9.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Disease progression (including worsening of neuropathy impairment) will not be considered an AE. However, all SAEs (as defined in Section 9.2.1.2, Serious Adverse Event) should be captured, even though the events may be considered disease progression and are treated following standard of care procedures.

All IRRs will be recorded as AEs.

9.2.1.2. Serious Adverse Event

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred; it does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- An important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above (eg, such events include allergic bronchospasm, blood dyscrasias or convulsions, or the development of drug dependency or abuse)

9.3. Relationship to Study Drug

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

Definitely Related:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.
Possibly Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.
Unlikely Related:	A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
Not Related:	A clinical event, including laboratory test abnormality, that has no temporal relationship to the medication or has more likely alternative etiology.

9.4. Recording Adverse Events

The patient should be asked about medically relevant changes in his/her health since the last visit. The patient should also be asked if he/she has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and OTC).

In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, or other findings.

Adverse events are to be graded according to the categories detailed below.

Mild: Mild events are those which are easily tolerated with no disruption of normal daily activity.

Moderate: Moderate events are those which cause sufficient discomfort to interfere with daily activity.

Severe: Severe events are those which incapacitate and prevent usual activity.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

9.5. Reporting Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported after the first dose of patisiran regardless of their relationship to patisiran administration through the end of the study.

Any medical condition that is present when the patient enters this extension study and does not deteriorate should not be reported as an AE. However, if it does deteriorate at any time during the study, it should be reported as an AE.

All AEs must be fully recorded in the site's source records and in the patients' CRF, whether or not they are considered to be drug-related. Each AE should be described in detail: onset time and date, description of event, severity, relationship to investigational product, action taken, and outcome (including time and date of resolution, if applicable).

Adverse events should be followed through the end of study visit or until recovery to the normal state has been achieved, whichever occurs first. In the event of a patient not returning to the clinical unit, the outcome of this event will be recorded as lost to follow-up.

For patients who withdraw from the study early, ongoing AEs will be followed until resolution or 28 days from last dose, whichever occurs first. SAEs will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable.

9.5.1. Serious Adverse Event Reporting

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the above seriousness criteria (Section 9.2.1.2) must be

reported immediately to the CRO, always within 24 hours from the time that site personnel first learn of the event. All SAEs must be reported regardless of the relationship to patisiran.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of causality

Serious AE reporting will be via electronic data capture (EDC).

To report the SAE, complete the SAE form electronically in the EDC system for the study. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at [redacted] or call the Medpace SAE hotline listed below (country-specific phone number will be provided in the Study Manual), and fax the completed back-up paper SAE form to Medpace (country-specific fax number will be provided in the Study Manual) within 24 hours of awareness. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. When the EDC system becomes available, the SAE information must be entered into the EDC system within 24 hours of the system becoming available. Medpace Safety personnel will be available for SAE reporting on a 24 hour basis. Incoming reports will be reviewed during normal business hours.

Medpace SAE hotline USA:
Telephone: [redacted], ext. [redacted] or [redacted] ext [redacted]
Facsimile: [redacted] or [redacted]

Medpace SAE hotline Europe:
Telephone: [redacted]
Facsimile: [redacted]

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Safety personnel via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of causality, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

The Investigator will be responsible for reporting all SAEs to the local IEC or IRB when required by national regulations.

The Sponsor or its representative will be responsible for the reporting of all relevant events to the concerned regulatory authorities according to all applicable regulations.

In Europe, in accordance with the Directive 2001/20/EC, the Competent Authorities and the Ethics Committees in the concerned Member States will be notified of fatal and life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) as soon as possible but no later than 7 calendar days after the Sponsor or its representative has first knowledge of the minimum criteria for expedited reporting. Non-fatal and non-life-threatening SUSARs should be reported no later than 15 calendar days after the Sponsor or its representative has first knowledge of them.

The Investigator may be informed by the Sponsor or its representative of SAEs from other Investigators or clinical studies which may have relevance to this clinical study. These SAEs should also be reported promptly to the IEC/IRB that approved the study. All SAE reports should be transmitted to the IEC/IRB with a cover letter or transmittal form, and a copy of that transmittal should be maintained in the Investigator's files and forwarded to the Sponsor as part of the trial master file on study completion.

9.5.2. Pregnancy Reporting

A female patient must have a negative pregnancy test within 14 days before the first dose of patisiran on this study. If a female patient is found to be pregnant during the course of the study or during the first month after receiving the last dose of patisiran, the Investigator should report the pregnancy to the CRO within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. Treatment with patisiran will be discontinued in any patient who is found to be pregnant during the study. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), then the Investigator should follow the procedures for reporting an SAE outlined above.

Pregnancy occurring in the partner of a patient participating in the study should also be reported to the Investigator, who will then report this to the CRO and follow to outcome as described above.

10. STATISTICS

10.1. Sample Size

This is an open-label extension study enrolling patients who have previously completed a patisiran study; the size of the study is not determined via power analysis of particular hypotheses tests.

10.2. Statistical Methodology

Statistical analyses will be primarily descriptive in nature.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

All data will be provided in by-patient listings.

10.2.1. Populations to be Analyzed

The following patient populations (ie, analysis sets) may be evaluated and used for presentation of the data:

- Full Analysis Set: All patients who were enrolled will be included in the full analysis set. The full analysis set will be the primary set for the analysis of efficacy data.
- Safety Analysis Set: All patients in the full analysis set who received patisiran. The safety analysis set will be used for the analysis of safety assessments.

10.2.2. Baseline Evaluations

Demographic information and baseline disease characteristic data collected in the parent study will be summarized. Data to be tabulated will include sex, age, and race, as well as disease-specific information.

10.2.3. Efficacy Analyses

Associations between PD (serum TTR) and efficacy data will be explored via correlation.

Summary statistics of observed values and changes from baseline will be provided for the mNIS +7 composite score. Summaries will also be provided for the components of the composite score (ie, the NIS weakness and reflex scores, the Σ5 NCS, and QST values). The NIS+7 score (including full NIS, NCS, VDT, and HRdb), and full NIS will be summarized also.

Patient reported quality of life and disease burden will be assessed by summary statistics for the EQ5D and R-ODS. Summary statistics will be provided for observed values and changes from baseline. Patient reported autonomic neuropathy symptoms will be assessed by descriptive statistics for the COMPASS 31.

Descriptive statistics will also be provided for observed values and changes from baseline in motor function (10-meter walk test and test of grip strength), nutritional status (mBMI), sensory

and autonomic innervation (IENFD and SGNFD), VDT, and ambulation (FAP stage and PND score).

Summary tables and graphical displays of observed values and changes from baseline in serum TTR will be used to assess the durability of suppression over the course of the study.

Descriptive statistics will be provided for actual values and changes from baseline in serum levels of troponin I and NT-proBNP. Results of echocardiograms will be summarized.

10.2.4. Safety Analyses

A summary of exposure to patisiran, including the durations of the infusions and doses, and the proportions of patients with modifications in the durations of infusions will be produced.

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment emergent AEs, treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, and discontinuations due to AEs, and AEs by severity. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Laboratory shift tables from baseline to worst values will be presented.

10.2.5. Healthcare Utilization Assessments

A listing of healthcare utilization data will be presented.

10.2.6. Interim Analysis

Interim data examinations may be performed, but these will be of a descriptive nature and will not involve any formal hypothesis testing.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

The Clinical Monitor, as a representative of the Sponsor, has an obligation to follow the study closely. In doing so, the Monitor will visit the Investigators and sites periodically and maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation and discussion of the conduct of the study with the Investigator and staff.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulations in respect to Good Clinical Practice (GCP) and current standard operating procedures.

11.2. Audits and Inspections

The Investigator and the site will permit study-related monitoring, audits and review by the IEC or IRB and/or Regulatory Authorities, providing direct access to source data/documents. The study may be subject to audit by the Sponsor or its representatives or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to the required patient records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives from the Sponsor, or regulatory agencies access to all study records.

11.3. Institutional Review Board

The Investigator must obtain IRB or IEC approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Study personnel are expected to adhere to the following practices, governed by GCP and all applicable regulatory requirements. To ensure these practices are in place, the Sponsor may conduct a quality assurance audit.

The Investigator will submit reports of SAEs as outlined in this protocol. In addition, the Investigator agrees to submit progress reports to his/her IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Deviations from the protocol necessary to protect patient safety should be reported to the CRO within 24 hours of knowledge of the event.

Any communications from regulatory agencies in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the CRO.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol.

Regulatory authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report according to national and any local regulations.

13. ETHICS

13.1. Ethics Review

National regulations and International Conference on Harmonization (ICH) require that approval be obtained from an IRB or an IEC prior to participation of patients in research studies. Prior to the study onset, the protocol, any protocol amendments, informed consent forms (ICFs), and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB or IEC.

All IRB and IEC approvals must be dated and contain IRB/IEC Chairman or designee authorization and must identify the IRB/IEC (eg, name and address), the clinical protocol by title and/or protocol number, and the date of approval or favorable opinion was granted for the clinical research.

The Investigator should not start any study procedure with the patient until documentation of the approval by the IEC/IRB and written notification of the approval from the head of the study site to the Investigator and Alnylam Pharmaceuticals, Inc.

No drug will be released to the site to dose a patient until written IRB/IEC authorization has been received by the Sponsor or designee.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB or IEC. The Investigator must supply the Sponsor with written documentation of the approval of the continued clinical research.

The Investigator will make all attempts to ensure that the IRB or IEC is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

13.2. Ethical Conduct of the Study

This study will be performed in accordance with the clinical trial agreement, the protocol, all applicable government laws, regulations, and guidances where the study is being conducted including policies with foundations in the World Medical Association Declaration of Helsinki, the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in the US, and all other applicable medical privacy laws and regulations.

13.2.1. Financial Disclosure Reporting Obligations

Each Investigator (including Principal and any Sub Investigators) directly involved in the treatment or evaluation of study patients is required to provide financial disclosure information according to all applicable legal requirements. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of one year after the completion of the study.

13.3. Written Informed Consent

Written informed consent in compliance with 21 Code of Federal Regulations (CFR) § 50 and ICH will be obtained from each patient before undergoing any protocol-specific tests or procedures that are not part of routine care.

The Sponsor or the CRO designee will provide an ICF template to the Investigator for use in developing a site-specific ICF. Prior to submission of the site-specific ICF to the IRB or IEC, the site-specific ICF must be reviewed and approved by the Sponsor or designee. Any changes requested by the IRB or IEC must also be agreed upon. The final IRB/IEC approved ICF must be provided to the Sponsor. Revisions to the ICF required during the study must be agreed upon, and a copy of the revised ICF provided to the Sponsor.

At the time of recruitment, each prospective patient (or legal guardian) will be given a full explanation of the study and be allowed to read the ICF. Once the Investigator is assured that the patient/legal guardian understands the commitments of participating in the study, the patient/legal guardian will be asked to sign and date the ICF. A copy of the fully signed and dated ICF will be given to the patient. The original ICF will be maintained in the patient's medical record at the site. All active patients will sign an updated ICF if revisions are made to the ICF during the course of the study.

Prior to dosing in this study, the patient will sign and date the ICF and receive a copy of the signed ICF. No study procedures should be performed before informed consent is obtained. The Investigator or another person authorized by the Investigator will also sign and date the informed consent before giving a copy to the patient. The ICF will be filed in the patient's medical record.

13.4. Compensation for Health Damages

A copy of the certificate of insurance as a measure to compensation for health damages will be submitted to the IRB/IEC if required per local regulations.

14. DATA HANDLING AND RECORD KEEPING

14.1. Case Report Forms

The Investigator and designees agree to maintain accurate CRFs and source documentation as part of these case histories. Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial.

The Sponsor will supply CRFs for each patient. Case report forms must be completed only by persons designated by the Investigator. Corrections must be made so as not to obliterate original data and must be identified and dated by the person who made the correction. All data entered into the CRF must also be available in the source documents. The Investigator will allow designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the CRFs.

Each completed CRF must be reviewed and signed by the Investigator or designee in a timely manner. The completed CRF will be the records maintained by the Sponsor. A copy of the CRF will remain in the Investigator's files.

14.2. Confidentiality

The Investigator must ensure that the patients' anonymity will be maintained. On the CRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number and initials. If patient names are included on copies of documents submitted to the Sponsor or designees, the names (except for initials) will be obliterated and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

Following the principles of the GCP, if local regulations specify a patient's number and initials will be used to identify the patient on their study records. Laboratory samples may be labeled with an independent numbering code, and the label will not contain any other personal identification information. The numbering code associated with these labels will be held by the study CRO and the Sponsor, thereby allowing no unwarranted access to the information. The numbering code will also be held for samples in storage until marketing approval of patisiran in the countries where this study was conducted, or until clinical development of patisiran is halted. Throughout sample collection, storage (limited, staff only access area containing locked sample storage, and limited access sample tracking) and processing, the samples will only be handled by appropriate personnel per the laboratory's standard operating procedures.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

14.3. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

14.4. Retention of Records

Essential documents should be retained for the period of time required by applicable local law. The essential documents include the signed and dated final protocol, signed and dated amendments(s), if applicable, signed and dated curricula vitae of the Investigators, copies of the completed CRFs, signed ICFs, IEC/IRB approval and all related correspondence, financial agreements, regulatory approval, drug accountability, study correspondence, and patient identification codes. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

If a patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before the withdrawal of consent, and may obtain and use information from public databases.

15. PUBLICATION POLICY

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. A copy of the manuscript must be provided and confirmed received at the Sponsor at least 30 days before its submission.

No submission of a manuscript may be made until the results from all of the clinical sites have been received and analyzed by the Sponsor, or the study has been terminated at all centers. A separate, individual publication of the results of the study will be delayed until initial publication of the results of the multicenter study, or a decision not to publish is made. If an initial draft is not produced within 18 months of completion of the study at all centers, or the timeframe for publication is not satisfactory, the Investigator may disclose the results after providing a copy and the Sponsor confirms receipt of the manuscript 30 days before submission.

Research ancillary to this main protocol may not be performed by individual sites without prior discussion and approval by the Sponsor.

16. LIST OF REFERENCES

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17. APPENDICES

Appendix 1: Karnofsky Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 2: New York Heart Association Classification of Heart Failure

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

Appendix 3: Categorization of Infusion-Related Reactions

Signs and symptoms of an infusion-related reaction (IRR) usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, urticaria (hives, welts, wheals), vomiting.

Categorization of IRRs is as follows:

Categorization	**Description**
Mild	Mild reaction: infusion may be continued; if intervention is indicated it is minimal and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Moderate reaction: requires treatment including more intensive therapy (eg, IV fluids, nonsteroidal anti-inflammatory drug [NSAIDs]) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	More than moderate reaction: not rapidly responsive to medication or to interruption of infusion; and/ or prolonged (treatment is indicated for >24 hours); recurrence of severe symptoms following initial improvement.

Appendix 4: Neuropathy Scores and Their Components

Assessment Tool	Total Points	Components (points)

NIS+7	270	• Neurologic exam of lower limbs, upper limbs and cranial nerves (NIS[a])
		  • Weakness (192)
		  • Sensation (32)
		  • Reflexes (20)
		• Nerve conduction studies ∑5 (18.6)[a]
		  • Sural SNAP, tibial motor n. distal latency, peroneal CMAP/motor n. conduction velocity/motor n. distal latency
		• Vibration detection threshold (3.7)
		• Heart rate response to deep breathing (3.7)

Modified NIS+7	304	• Neurologic exam of lower limbs, upper limbs and cranial nerves (mNIS[a])
		  • Weakness (192)
		  • Reflexes (20)
		• Nerve conduction studies ∑5 (10)[a]
		  • Ulnar CMAP and SNAP, sural SNAP, tibial CMAP, peroneal CMAP
		• Quantitative sensory testing: QST-BSA_{TP+HP5} (80)
		• Postural blood pressure (2)

a Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment.

Appendix 5: Polyneuropathy Disability Score

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of one stick or crutch. Walking with the help of two sticks or crutches.
IV	Confined to a wheelchair or bedridden.

Appendix 6: Familial Amyloidotic Polyneuropathy Stage

Stage	Description
0	No symptoms
I	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Assistance with ambulation required, mostly moderate impairment progression to the lower limbs, upper limbs, and trunk.
III	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs.