Official Title:	**APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Doubleblind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ALN-TTR02 in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)**
NCT Number:	**NCT01960348**
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CLINICAL STUDY PROTOCOL
ALN-TTR02-004

APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)

Protocol Version	Version 6.0 (Incorporating Amendment 5)
Protocol Date	08 September 2015
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Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA
Sponsor Contact:	[redacted]

CONFIDENTIAL

The study will be completed according to guidelines of Good Clinical Practice. 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.

AUTHORIZED SIGNATORIES

INVESTIGATOR'S STATEMENT: I agree to conduct this study as outlined in the protocol and in accordance with the guidelines and all applicable government regulations. I have read all parts of the protocol.

Principal Investigator

Signature _____ Date _____

Name (print) _____

Sponsor

Signature [redacted] Date 08 Sept 2015

Name (print) [redacted]

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PROTOCOL SYNOPSIS

Protocol Title	APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)
Indication	Treatment of transthyretin-mediated amyloidosis (ATTR) in patients with symptomatic polyneuropathy
Protocol Number	ALN-TTR02-004
Phase of Development	3
Design	This is a multicenter, multinational, randomized, double-blind study comparing patisiran (ALN-TTR02) to placebo in ATTR patients with symptomatic Familial Amyloidotic Polyneuropathy (FAP). Consented eligible patients will be randomized to receive either 0.3 mg/kg patisiran or placebo in a 2:1 ratio (patisiran to placebo) in a blinded manner. Treatment arms will be balanced at entry for Neuropathy Impairment Score (NIS; 5-49 vs 50-130), early onset V30M (<50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous tetramer stabilizer use. Patients will receive patisiran or placebo once every 21 days for 78 weeks. Patients will have baseline efficacy assessments and efficacy assessments at 9 and 18 months. The study personnel performing these assessments will be blinded to the results of any previous assessments (e.g., Screening/Baseline, Baseline, or 9-month assessments). At the 9-month time point, if the clinical adjudication committee determines that a patient is exhibiting rapid disease progression (defined as ≥24 point increase in modified NIS+7 (mNIS+7) from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline), the patient's treating physician will provide the patient with the option of discontinuing study drug and receiving local standard of care treatment for FAP. Patients who discontinue study drug will remain on study, following a modified schedule of visits, through completion of the 18-month efficacy assessments (blinding will be maintained throughout).

	Patients who complete the 18-month efficacy assessments can elect to participate in an extension study in which patients would receive open-label administration of 0.3 mg/kg patisiran once every 21 days. A Data Monitoring Committee (DMC) will be implemented for the study and will operate under a prespecified charter.
Study Sites	This study will be conducted at multiple sites worldwide.
Investigational Drug	Patisiran (comprising a small interfering ribonucleic acid [siRNA] targeting mutant and wild-type TTR mRNA, in a lipid nanoparticle formulation for intravenous [IV] administration)
Dosage, Route of Administration and Duration of Treatment of Investigational Drug	Patients randomized to the active treatment group will receive 0.3 mg/kg patisiran once every 21 (±3) days administered as an IV infusion over 70 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. Prior to each dose of study drug, patients will receive the following premedications at least 60 minutes prior to the infusion: • Intravenous dexamethasone (10 mg) or equivalent; • Oral paracetamol/acetaminophen (500 mg) or equivalent; • Intravenous H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose); and • Intravenous H1 blocker: diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the study site). Hydroxyzine or fexofenadine 25 mg per oral suspension (PO, orally) or cetirizine 10 mg PO may be substituted for any patient who does not tolerate intravenous diphenhydramine or other intravenous H1 blocker.
Control Drug	Placebo (normal saline 0.9% for IV administration)
Dosage, Route of Administration and Duration of Treatment of Control Drug	Patients randomized to placebo will receive IV normal saline (0.9%) using the same dosing schedule and infusion rate as the active treatment group. Placebo patients will also receive the same premedication regimen as the active treatment group.
Time on Study	The duration of patient participation in this study is approximately 21 months (inclusive of a 42-day screening window and up to a 56-day post last dose study visit).
Primary Objective	The primary objective of the study is to determine the efficacy of patisiran by evaluating the difference between the patisiran and placebo groups in the change from baseline of mNIS+7 score at 18 months.

Secondary Objectives	The secondary objectives of the study are to determine the effect of patisiran on various clinical parameters by assessing the difference between patisiran and placebo in the change from baseline in the following measurements at 18 months: • Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire; • NIS-weakness (NIS-W) score; • Modified body mass index (mBMI); • Timed 10-meter walk test; • Autonomic symptoms questionnaire (Composite Autonomic Symptom Score [COMPASS-31]).

Exploratory Objectives:	The exploratory objectives of the study are:
	• To determine the difference between the patisiran and placebo groups in the change from baseline in the following measurements at 18 months:
	  • NIS+7 score;
	  • Grip strength;
	  • EuroQOL (EQ-5D) questionnaire;
	  • Level of disability (Rasch-built Overall Disability Scale [R-ODS]);
	  • Large vs small nerve fiber function including nerve conduction studies (NCS) 5 attributes (Σ5), quantitative sensory testing by body surface area including touch pressure and heat pain (QST), vibration detection threshold (VDT), heart rate response to deep breathing (HRdb), postural blood pressure;
	  • Pathologic evaluation of sensory and autonomic innervation through voluntary skin punch biopsies and analysis of intraepidermal nerve fiber density (IENFD) and sweat gland nerve fiber density (SGNFD);
	  • Assessment of ambulation through FAP stage and Polyneuropathy Disability (PND) score;
	  • Cardiac assessment through echocardiogram, troponin I, and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels;
	  • Pharmacodynamic (PD) biomarkers (TTR, retinol binding protein [RBP], vitamin A);
	• To compare the proportion of patients in the patisiran and placebo groups who meet the pre-defined criterion for rapid disease progression (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of

	2 measurements] and FAP stage progression relative to baseline) at 9 months.
Sample Size:	Approximately 200 patients will be enrolled in this study. Of those 200 patients, no more than 40 patients will have a NIS range of 101 to 130. An mNIS+7 progression rate (primary endpoint) in the placebo group of 24 ± 16 points in 18 months was estimated using natural history data from FAP patients. A sample of 154 patients provides 90% power for a 2-sided test with an 8.95 point (37.5%) mean difference between treatment groups in the primary endpoint at 2-sided alpha = 0.05. Assuming a 25% random premature discontinuation rate (due to liver transplantation or other factors), the sample size for this study is approximately 200. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim analysis.
Inclusion and Exclusion Criteria:	To be enrolled in the study, each patient must meet the following criteria at the Screening visit, except where specified: 1. Male or female of 18 to 85 years of age (inclusive); 2. Have a diagnosis of FAP with documented TTR mutation; 3. Have an NIS of 5 to 130 (inclusive) and a PND score of ≤3b (Note: This criterion must be met at the Screening/Baseline visit); 4. Have an NCS sum of the sural sensory nerve action potential (SNAP), tibial compound muscle action potential (CMAP), ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points; (Note: This criterion must be met at the Screening/Baseline visit); 5. Have a Karnofsky performance status of ≥60%; 6. Have an absolute neutrophil count (ANC) ≥1500 cells/mm^3, and a platelet count ≥50,000 cells/mm^3; 7. Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), total bilirubin within normal limits, international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed). Patients with total bilirubin ≤ 2 X ULN are 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; 8. Have a serum creatinine ≤2 × ULN;

	9. No active infection with hepatitis B or hepatitis C by serology; 10. 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 screening, throughout study participation, and for 75 days after the last dose of study drug. Highly effective methods of birth control are defined in Section 4.7; 11. Males with partners of child-bearing potential must agree to use 1 barrier method (e.g., condom) and 1 additional method (e.g., spermicide) of contraception throughout study participation and for 75 days after the last dose of study drug; males must also abstain from sperm donation after the first dose of study drug through study participation and for 75 days after the last dose of study drug; 12. Must be willing and able to comply with 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 at the time of the Screening visit: 1. Had a prior liver transplant or is planning to undergo liver transplant during the study period; 2. Has other known causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy); 3. Has known primary amyloidosis or leptomeningeal amyloidosis; 4. Has known type I diabetes; 5. Has had type II diabetes mellitus for ≥5 years; 6. Has vitamin B12 levels below the lower limit of normal (LLN); 7. Has untreated hypo- or hyperthyroidism; 8. Has had a major surgery within the past 3 months or has a major surgery planned during any point of the study period; 9. Has known human immunodeficiency virus (HIV) infection; 10. Has an active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to the first dose of study drug administration;

	11. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated; 12. Has a New York Heart Association heart failure classification >2; 13. Had acute coronary syndrome within the past 3 months; 14. Has uncontrolled cardiac arrhythmia or unstable angina; 15. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]); 16. Received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever is longer; 17. Participated in a clinical trial with antisense oligonucleotide, must have completed a 3-month wash-out prior to start of the study drug administration in this study; 18. Is currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to start of study drug administration in this study; 19. Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to start of study drug administration in this study; 20. Had a prior severe reaction to a liposomal product or a known hypersensitivity to oligonucleotides or any component of patisiran; 21. Is unable to take the required premedications; 22. Anticipated survival is less than 2 years, in the opinion of the Investigator; 23. Is considered unfit for the study by the Investigator; 24. 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/her will”).
Efficacy Assessments	Efficacy parameters will include the following (baseline evaluations will be conducted as well as evaluations at 9 and 18 months):

	• Neurologic impairment will be assessed using the mNIS+7 composite score. The mNIS+7 includes the modified NIS (weakness and reflexes), NCS Σ5, QST, as well as autonomic assessment through postural blood pressure; • Patient-reported QOL will be evaluated using the Norfolk QOL-DN and the EQ-5D. Disability will be reported by patients using the R-ODS; • Autonomic symptoms will be assessed using the COMPASS-31; • Motor function assessments to be evaluated include NIS-W, timed 10-meter walk test, and grip strength test; • PND score and FAP stage; • Nutritional status will be assessed using mBMI; • Pathologic evaluation of sensory and autonomic innervation will be evaluated by IENFD analysis and quantitation of dermal SGNFD via tandem 3 mm skin punch biopsies taken from the leg; • Neurologic impairment will also be assessed by NIS+7 (including full NIS, NCS, VDT, and HRdb); • Cardiac structure and function will be assessed through echocardiograms as well as measurement of serum levels of NT-proBNP and troponin I.
Pharmaco-dynamic Assessments	Pharmacodynamic markers assessed serially will include serum TTR, vitamin A, and RBP. Additional blood samples will be collected for exploratory biomarkers related to FAP.
Pharmacokinetic Assessments	The plasma pharmacokinetic (PK) evaluation will include, whenever possible, plasma-concentration time profiles for siRNA and the novel lipid components in patisiran: DLin-MC3-DMA and polyethylene glycol $(PEG)_{2000}$-C-DMG. The siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG concentrations will be determined for all patients at time points specified in Table 1-1, Table 1-2, and Table 1-3. Urine will be collected with void volume recorded for all patients at time points specified in Table 1-1, Table 1-2, and Table 1-3 and to determine renal clearance (CL_R) of siRNA and 4-dimethylaminodibutyric acid (the metabolite of DLin-MC3-DMA) after dosing with study drug.

Safety Assessments	Safety will be assessed throughout the study by collecting adverse events (AEs; including serious adverse events [SAEs]); clinical laboratory tests, including hematology, clinical chemistry (including liver function tests), thyroid function parameters, and urinalysis; measurement of anti-drug antibodies; electrocardiograms; vital signs; physical examination findings; and ophthalmology examinations.
Other Assessments	Disease burden and healthcare utilization will be assessed using a patient-reported pharmacoeconomics questionnaire. The investigator will periodically assess mental status as it relates to suicidal ideation and behavior by using the Columbia–Suicide Severity Rating Scale (C-SSRS) questionnaire.
Follow-Up	Patients who complete the 18-month efficacy assessments can elect to participate in an extension study in which patients would receive open-label administration of 0.3 mg/kg patisiran once every 21 days. Eligible patients who elect to participate will return for a follow-up visit 21 days after last dose of study drug. If the patient decides not to participate in the extension study, the patient will complete 2 follow-up visits at 21 and 56 days after the last dose of study drug. Each follow-up visit includes safety assessments and the 21-day follow-up also includes PD measurements.
Statistical Methods	A full statistical analysis plan (SAP) will be finalized prior to database lock. The primary analysis will compare patients administered patisiran versus those administered placebo in the modified intent-to-treat (mITT) population. Specifically, patients who are randomized and receive at least 1 dose of study drug will be included in this analysis. The primary analysis will compare change in mNIS+7 from baseline at 18 months between patisiran and placebo groups, adjusted for the stratification factors. Analysis of covariance (ANCOVA) will be used to analyze the primary endpoint. Primary endpoint data that are missing will be inferred using multiple imputations. Sensitivity analyses, including mixed model repeated measures (MMRM) analyses, will assess the robustness of the primary analysis for the mITT and per protocol (PP) populations. Type I error control for secondary endpoints will be achieved by a hierarchical ordering procedure. Briefly, endpoints will be evaluated in order to control for multiplicity. An independent interim analysis committee (IAC) will conduct a blinded interim analysis when approximately 50% of patients have completed their 9-month mNIS+7 assessments. This

	interim analysis will estimate the overall variance in the mNIS+7 score. Based on the results of the interim analysis, the committee can recommend either increasing the study sample size or making no adjustment to the sample size. PK analyses will be conducted using non-compartmental and/or compartmental evaluation. The PK parameters of siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG in plasma will be evaluated. Population PK analyses will be performed whenever possible on available siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG from sparse samples collected at various time points during the duration of the study. Inferential statistics of PD and PK/PD parameters, correlation between siRNA, DLin-MC3-DMA or PEG_{2000}C-DMG exposure versus TTR, RBP, or vitamin A, and between TTR versus RBP and vitamin A will be provided.

Table 1-1: Schedule of Assessments; Screening to 9-Month Efficacy Assessment

	Visit Type	Screening [a]	Screening/ Baseline [a]	Baseline [a]	Predosing	Dosing												9-Month Efficacy Assessment[y]	
	Study Day	Day -42 to 0			D0 Predose	D0	D21	D42	D63	D84	D105	D126	D147	D168	D189	D210	D231	D252	D253-D272	
	Study Week	NA			0	0	3	6	9	12	15	18	21	24	27	30	33	36	36-39	
Procedure	Windows	NA			0	0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA	
Informed Consent		X																		
Inclusion/Exclusion Criteria		X	X [a]																	
Medical History		X	X [b]	X [b]																
Demographics		X																		
Review Documentation of TTR Genotype		X																		
HIV Status Review		X																		
Karnofsky Performance Status		X																		
New York Heart Classification		X																		
Serology Testing [c]		X																		
Paraprotein by IFE		X																		
Vitamin B12		X																		
Efficacy Assessments																				
NIS [d] / NCS [d]		X																		
mNIS+7 [e]			X	X															X	X
NIS + 7 [f]			X	X															X	X
PND Score and FAP Stage			X [g]	X															X	
Skin Punch Biopsy (IENFD and SGNFD) [h]				X															X	
mBMI [i]				X															X	
10-meter Walk Test [j]			X [z]																X	X
Grip Strength Test [k]			X [z]																X	X
Norfolk QOL-DN; COMPASS 31 Questionnaires			X [z]																X	
EQ-5D; R-ODS Questionnaires			X [z]																X	
Echocardiogram			X [z]																X	
NT-proBNP and Troponin I				X															X	
Pharmacodynamic Assessments [l]																				
TTR Protein, Vitamin A, and RBP				X	X		X					X						X	X	
Obtain Blood Sample for Long-term Storage			X	X	X		X					X						X	X	

Table 1-1: Schedule of Assessments; Screening to 9-Month Efficacy Assessment (continued)

Procedure	Visit Type	Screening [a]	Screening/ Baseline [a]	Baseline [a]	Predosing	Dosing												9-Month Efficacy Assessment [y]
	Study Day	Day -42 to 0			D0 Predose	D0	D21	D42	D63	D84	D105	D126	D147	D168	D189	D210	D231	D252	D253-D272
	Study Week	NA			0	0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
	Windows	NA			0	0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Safety Assessments [m]																			
Physical Examination		X																X	
Weight [n]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X | X
Height		X																	
Vital Signs [o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X | X
12-Lead ECG [p]			X [z]									X							X
Serum Chemistry		X			X					X					X				
Hematology, Urinalysis		X																X	
Thyroid Function Tests		X																X	
Coagulation Studies		X																	
Anti-drug Antibody Testing [q]					X		X					X						X	
Pregnancy Test [r]		X																	
Ophthalmology Exam [s]					X													X	
Concomitant Medications		X	X	X								X							
Adverse Events												X							
Pharmacokinetic Assessments																			
Plasma PK Sampling [t]					X	X	X					X						X	
Urine PK Sampling [u]					X		X					X						X	
Other Assessments																			
Pharmacoeconomic Questionnaire					X [z]														X
C-SSRS Questionnaire			X [z]																X
Drug Administration																			
Randomization [v]					X														
Premedication Administration [w]					X		X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration [x]						X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1-1 Footnotes:

Abbreviations: COMPASS 31 = Composite Autonomic Symptom Score; EQ-5D = EuroQOL-5 Dimensions; ECG = electrocardiogram; FAP = familial amyloidotic polyneuropathy; HIV = human immunodeficiency virus; IENFD = Intraepidermal nerve fiber density; IFE = immunofixation electrophoresis; mBMI = modified body mass index; mNIS = Modified Neuropathy Impairment Score; NCS = nerve conduction studies; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PND = polyneuropathy disability; QOL-DN = Quality of Life-Diabetic Neuropathy; RBP = retinol binding protein; R-ODS = Rausch-built Overall Disability Scale; SGNFD = Sweat gland nerve fiber density; TTR = transthyretin.

a. The Screening/Baseline and Baseline visits will be performed on separate days. The Screening/Baseline visit must be performed within 21 days prior to the first dose of study drug (Day 0). The Baseline visit must be conducted at least 24 hours (approximately), but not more than 7 days, after the Screening/Baseline visit. In conjunction with the decision of the Medical Monitor(s), patients may be allowed to rescreen after a minimum of 5 days have elapsed from their last screening assessment. Note: Inclusion Criteria 3 (i.e., NIS of 5 to 130 [inclusive] and PND score ≤3b) and 4 (i.e., NCS sum of the sural sensory nerve action potential [SNAP], tibial compound muscle action potential [CMAP], ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points) must be met at the Screening/Baseline visit. All other entry criteria (inclusion and exclusion) will be assessed at the Screening visit only.
b. An interval medical history will be collected at the Screening/Baseline and Baseline visit. Only changes since the Screening visit will be collected.
c. Serologies will include hepatitis B surface antibody (HbsAb), hepatitis B surface antigen (HbsAg), and anti–hepatitis C virus antibody (anti-HCV Ab).
d. The NIS and NCS will be assessed for the likelihood of a patient meeting the NIS and NCS eligibility criteria at the Screening/Baseline visit. The documented results of previously performed NIS and NCS may be used to qualify a patient for this study if these tests were performed within 60 days prior to the date of informed consent.
e. The mNIS+7 consists of the modified NIS tool (weakness and reflexes), NCS 5 attributes (Σ5), quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), and postural blood pressure. At the 9-month efficacy assessment, 2 assessments of the mNIS+7 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).
f. 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). At the 9-month efficacy assessment, 2 assessments of the NIS+7 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).
g. At the Screening/Baseline visit, only PND score is required.
h. If the patient has provided separate informed consent for skin biopsies, 2 sets of tandem 3-mm skin punch biopsies are to be obtained (4 biopsies total). One set of biopsies will be taken from the distal lower leg, when a patient's clinical status allows, and one set from the distal thigh at each time point. Skin biopsies will be performed at a central assessment site (CAS).
i. The mBMI calculation will take place programmatically in the clinical database; the site will not perform the calculation.
j. 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 the 9-month efficacy assessment, 2 assessments of the 10-meter walk test 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.
k. 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. At the 9-month efficacy assessment, 2 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.
l. On dosing days, blood samples for PD assessments will be obtained prior to dosing and vitamin A supplementation.

Table 1-1 Footnotes (continued):

m. On dosing days, all safety assessments are performed pre-dose.
n. Weight from previous visit should be used for calculating dose. Weight must be collected pre-dose.
o. Vital signs to include: blood pressure, pulse rate, temperature, and respiratory rate. Parameters are to be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes. Vital signs must be collected pre-dose. On Day 0, vital signs will also be collected post-dose.
p. All ECGs are to be obtained in triplicate.
q. Blood samples for anti-drug antibody testing will be collected prior to study drug dosing.
r. A pregnancy test (urine- or serum-based) will be performed on all females of child-bearing potential.
s. The baseline ophthalmology examination may be performed any time after the patient is deemed eligible for participation in the study through Day 21. The 9-month ophthalmology examination will be performed between Days 231(±3) and 272 at a CAS.
t. Plasma PK samples will be collected as follows: Day 0: pre-dose (within 1 hour of planned study drug dosing) and at the end of infusion (+5 minutes). Day 21 and Day 252: pre-dose (within 1 hour of planned study drug dosing) and 30 minutes after the end of the infusion (+15 minutes). Day 126: pre-dose (within 1 hour of planned study drug dosing) and at the end of infusion (+5 minutes).
u. Urine PK samples will be collected pre-dose (within 1 hour of planned study drug dosing).
v. Randomization procedures are described in Section 4.4.1.
w. Prior to dosing, all patients will receive premedications administered at least 60 minutes prior to the start of infusion of study drug. The regimen is described in Section 5.3.1.
x. 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. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.
y. Patients who discontinue study drug due to rapid disease progression based on the 9-month efficacy assessments will continue on to the Modified Visit Schedule (See Table 1-3).
z. Assessment must be completed at a single time point during one of the specified visits, at the discretion of the investigator.

Table 1-2: Schedule of Assessments; Week 39 to Week 86 (Follow-up) / Early Withdrawal

Procedure	Visit Type	Dosing														18-Month Efficacy Assessment		End of Study[a]	Follow-up[a]	Early Withdrawal[b]		Follow-up for Patients who Discontinue Treatment but Return at 9 and/or 18 mo[c]			
	Study Day	D273	D294	D315	D336	D357	D378	D399	D420	D441	D462	D483	D504	D525	D546	D553-D560		D567	D602	NA		D253-D272		D553-D560	
	Study Week	39	42	45	48	51	54	57	60	63	66	69	72	75	78	79-80		81	86	NA		36-39		79-80	
	Windows	+3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3 D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA		±7D	±10D	2D to 7D		±10D		±10D	
Efficacy Assessments																									
mNIS+7[d]																X	X			X	X	X	X	X	X
NIS+7[e]																X	X			X	X	X	X	X	X
PND Score and FAP Stage																X				X		X		X	
Skin Punch Biopsy (IENFD and SGNFD)[f]																X				X					
mBMI[g]																X				X		X		X	
10-meterWalkTest[h]																X	X			X	X				
Grip Strength Test[i]																X	X			X	X				
Norfolk QOL-DN; EQ-5D; R-ODS Disability; COMPASS31 Questionnaires																X				X		X[j]		X[j]	
Echocardiogram																X				X					
NT-pro BNP and Troponin I																X				X					
Pharmacodynamic Assessments[k]																									
TTR Protein, Vitamin A, and RBP		X						X							X	X		X		X		X		X	
Obtain Blood Sample for Long-term Storage		X						X							X	X		X		X					

Procedure	Visit Type	Dosing														18-Month Efficacy Assessment		End of Study[a]	Follow-up[a]	Early Withdrawal[b]		Follow-up for Patients who Discontinue Treatment but Return at 9 and/or 18 mo[c]	
	Study Day	**D273**	**D294**	**D315**	**D336**	**D357**	**D378**	**D399**	**D420**	**D441**	**D462**	**D483**	**D504**	**D525**	**D546**	**D553-D560**		**D567**	**D602**	**NA**		**D253-D272**	**D553-D560**
	Study Week	**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**		**81**	**86**	**NA**		**36-39**	**79-80**
	Windows	**+3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**NA**		**±7D**	**±10D**	**2D to 7D**		**±10D**	**±10D**
Safety Assessment[l]																							
Physical Examination															X			X	X	X		X	X
Weight[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Vital Signs[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG[o]								X								X				X			
Serum Chemistry						X					X				X				X	X			
Coagulation[w]															X								
Hematology, Urinalysis															X					X			
Thyroid Function Tests															X					X			
Anti-drug Antibody Testing[p]								X							X					X			
Pregnancy Test[q]																		X	X	X			
Ophthalmology[r]															X								
Concomitant Medications		X																					
Adverse Events		X																					
Pharmacokinetic Assessments																							
Plasma Pharmacokinetic Sampling[s]								X							X					X		X	X
Urine Pharmacokinetic Sampling[t]								X							X					X			
Other Assessments																							
Pharmacoeconomic Questionnaire																X				X			

Procedure	Visit Type	Dosing														18-Month Efficacy Assessment	End of Study[a]	Follow-up[a]	Early Withdrawal[b]	Follow-up for Patients who Discontinue Treatment but Return at 9 and/or 18 mo[c]	
	Study Day	**D273**	**D294**	**D315**	**D336**	**D357**	**D378**	**D399**	**D420**	**D441**	**D462**	**D483**	**D504**	**D525**	**D546**	**D553-D560**	**D567**	**D602**	**NA**	**D253-D272**	**D553-D560**
	Study Week	**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**	**81**	**86**	**NA**	**36-39**	**79-80**
	Windows	**+3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**NA**	**±7D**	**±10D**	**2D to 7D**	**±10D**	**±10D**
C-SSRS Questionnaire																X			X		
Drug Administration																					
Premedication Administration[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Study Drug Administration[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Karnosky performance status																				X	X
NYHA class																				X	X

Table 1-2 Footnotes:

Abbreviations: COMPASS 31 = Composite Autonomic Symptom Score; C-SSRS = Columbia–Suicide Severity Rating Scale; EQ-5D = EuroQOL; ECG = electrocardiogram; FAP = familial amyloidotic polyneuropathy; IENFD = Intraepidermal nerve fiber density; mBMI = modified body mass index; mNIS = Modified Neuropathy Impairment Score; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PND = polyneuropathy disability; QOL-DN = Quality of Life-Diabetic Neuropathy; RBP = retinol binding protein; R-ODS = Rausch-built Overall Disability Scale; SGNFD = Sweat gland nerve fiber density; TTR = transthyretin.

a. If a patient enrolls in the extension study, the patient will only have to complete the 21-day follow-up assessments (EOS; Day 567) and not the 56-day follow-up assessments (Day 602). Patients who do not enroll in the extension study will need to complete both follow-up visits (Days 567 and 602).
b. The Early Withdrawal visit will take place over 2 days to allow for the repeat assessment of the mNIS+7, NIS+7, timed 10-meter walk, and grip strength test.
c. Patients who discontinue treatment may return for follow-up visits at 9 and/or 18 months.
d. The mNIS+7 consists of the modified NIS tool (weakness and reflexes), NCS Σ5, QST by body surface area including TP and HP, and postural blood pressure. Two assessments 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).
e. The NIS+7 consists of the NIS tool (weakness, sensation, and reflexes), NCS Σ5, VDT, and heart rate response to deep breathing. Two assessments 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).
f. If the patient has provided separate informed consent for skin biopsies, 2 sets of tandem 3-mm skin punch biopsies are to be obtained (4 biopsies total). One set of biopsies will be taken from the distal lower leg, when a patient's clinical status allows, and 1 set from the distal thigh at each time point.
g. The mBMI calculation will take place programmatically in the clinical database; the site will not perform the calculation.
h. 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 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.
i. Grip strength will be measured 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 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.
j. Only the Norfolk and EQ-5D are to be performed for patients who discontinue treatment and return for the 9 and 18 month visits.
k. On dosing days, blood samples for PD assessments will be obtained prior to dosing and vitamin A supplementation.
l. On dosing day, all safety assessments are performed pre-dose.
m. Weight from previous visit should be used for calculating dose. Weight must be collected pre-dose.
n. Vital signs to include: blood pressure, pulse rate, temperature, and respiratory rate. Parameters are to be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes. Vital signs must be collected pre-dose.
o. All ECGs are to be obtained in triplicate.
p. On study drug dosing days, blood samples for anti-drug antibody testing will be collected pre-dose.
q. A pregnancy test (urine- or serum-based) will be performed on all females of child-bearing potential.
r. The 18-month ophthalmology examination will be performed between Days 546(±3) and 560 at a CAS.

Table 1-2 Footnotes (continued):

s. Plasma PK samples will be collected as follows: Day 399: pre-dose (within 1 hour of planned study drug dosing) and at the end of infusion (+5 minutes). Day 546: pre-dose (within 1 hour of planned study drug dosing) and 30 minutes after the end of the infusion (+15 minutes). Early Withdrawal: any time within the visit window.

t. Urine PK samples will be collected as follows: Day 399 and Day 546: pre-dose (within 1 hour of planned study drug dosing). Early Withdrawal: any time within the visit window.

u. Prior to dosing, all patients will receive premedications administered at least 60 minutes prior to the start of infusion of study drug. The regimen is described in Section 5.3.1.

v. 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. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.

w. INR assessment only, which is to be used for qualification for Study TTR02-006.

Table 1-3: Modified Schedule of Assessments for Patients who Discontinue Study Drug for Rapid Disease Progression; Week 39 to End of Study

Procedure	Visit Type	Dosing					18-Month Efficacy Assessment		End of Study	Early Withdrawal [a]	
	Study Day	D273 [b]	D294	D378	D462	D546	D553-D560		D567	NA	
	Study Week	39	42	54	66	78	79-80		81	NA	
	Windows	+3D	±3D	±3D	±3D	±3D	NA		±7D	2D to 7D	
Consultation on treatment options [c]		X									
Efficacy Assessments											
mNIS+7 [d]							X	X		X	X
NIS + 7 [e]							X	X		X	X
PND Score and FAP Stage							X			X	
Skin Punch Biopsy (IENFD and SGNFD) [f]							X			X	
mBMI [g]							X			X	
10-meter Walk Test [h]							X	X		X	X
Grip Strength Test [i]							X	X		X	X
Norfolk QOL-DN; EQ-5D; R-ODS Disability; COMPASS 31 Questionnaires							X			X	
Echocardiogram							X			X	
NT-proBNP and Troponin I							X			X	
PD Assessments											
TTR Protein, Vitamin A, and RBP			X			X			X	X	
Obtain Blood Sample for Long-term Storage			X			X			X	X	

Table 1-3: Modified Schedule of Assessments for Patients who Discontinue Study Drug for Rapid Disease Progression; Week 39 to End of Study (continued)

	Visit Type	Dosing					18-Month Efficacy Assessment		End of Study	Early Withdrawal [a]	
	Study Day	D273 [b]	D294	D378	D462	D546	D553-D560		D567	NA	
	Study Week	39	42	54	66	78	79-80		81	NA	
Procedure	Windows	+3D	±3D	±3D	±3D	±3D	NA		±7D	2D to 7D	
Safety Assessments											
Physical Examination			X			X			X	X	
Weight						X	X	X	X	X	X
Vital Signs [j]		X	X			X	X	X	X	X	X
12-Lead ECG [k]							X			X	
Serum Chemistry			X			X				X	
Coagulation [r]						X					
Hematology, Urinalysis						X					
Thyroid Function Tests						X				X	
Anti-drug Antibody Testing						X				X	
Pregnancy Test [l]			X			X				X	
Concomitant Medications [m]		X									
Adverse Events [n]		X									
Study-procedure-related Adverse Events [o]				X							
PK Assessments											
Plasma PK Sampling			X			X					
Urine PK Sampling			X			X					
Other Assessments											
Pharmacoeconomic Questionnaire						X				X	
C-SSRS Questionnaire							X			X	
Collect Data on Subsequent FAP Treatment Regimens			X	X[p]	X[p]	X			X	X	
Phone Contact to Obtain Health Status Update [q]				X	X						

Table 1-3 Footnotes:

Abbreviations: COMPASS 31 = Composite Autonomic Symptom Score; C-SSRS = Columbia–Suicide Severity Rating Scale; EQ-5D = EuroQOL; ECG = electrocardiogram; FAP = familial amyloidotic polyneuropathy; IENFD = Intraepidermal nerve fiber density; mNIS = Modified Neuropathy Impairment Score; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PND = polyneuropathy disability; QOL-DN = Quality of Life-Diabetic Neuropathy; RBP = retinol binding protein; R-ODS = Rausch-built Overall Disability Scale; SGNFD = Sweat gland nerve fiber density; TTR = transthyretin.

a. The Early Withdrawal visit will be conducted for any patient who discontinues from the study after the Day 273 visit (e.g., from Day 274 onward). This visit will take place over 2 days (at least 24 hours [approximately], but not more than 7 days apart) to allow for the repeat assessment of the mNIS+7, NIS+7, timed 10-meter walk, and grip strength test.

b. Patients who discontinue study drug and also decide to discontinue from the study at the time of this visit will not have any additional visits after the Day 273 assessments are completed.

c. The patient will consult with the Investigator on a subsequent plan of care, which may include receiving therapy for FAP as per the local standard of care.

d The mNIS+7 consists of the modified NIS tool (weakness and reflexes), NCS Σ5, QST by body surface area including TP and HP, and postural blood pressure. Two assessments 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).

e. The NIS+7 consists of the NIS tool (weakness, sensation, and reflexes), NCS Σ5, VDT, and heart rate response to deep breathing. Two assessments 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. Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed once at each assessment (e.g., the weakness component should not be performed more than once on any given day).

f. If the patient has provided separate informed consent for skin biopsies, 2 sets of tandem 3-mm skin punch biopsies are to be obtained (4 biopsies total). One set of biopsies will be taken from the distal lower leg, when a patient's clinical status allows, and 1 set from the distal thigh at each time point.

g. The mBMI calculation will take place programmatically in the clinical database; the site will not perform the calculation.

h. 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 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.

i. Grip strength will be measured 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 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.

j. Vital signs to include: blood pressure, pulse rate, temperature, and respiratory rate. Parameters are to be measured in the supine position using an automated instrument after the patient has rested comfortably for 10 minutes.

k. All ECGs are to be obtained in triplicate.

l. A pregnancy test (urine- or serum-based) will be performed on all females of child-bearing potential.

m. Concomitant medications/treatments will be collected through Day 294 (Week 42) only. Data on subsequent FAP treatment regimens will be collected separately.

n. Adverse events will be collected through Day 294 (Week 42) only. See Section 8.5 for SAE reporting periods.

o. Following the Day 294 (Week 42) visit, only adverse events that are considered related to the study procedures will be collected (e.g., skin biopsies, venipunctures).

p. At these time points, data will be collected through phone contact.

q. Study personnel will contact patients by phone to query for general health status and information on subsequent FAP treatment regimens.

r. INR assessment only, which is to be used for qualification visit for Study TTR02-006.

ABBREVIATIONS

Abbreviation	Definition
Σ5	5 attributes
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATTR	Transthyretin-mediated amyloidosis
BUN	Blood urea nitrogen
CAS	Central Assessment Site
CC	Complete case
CFR	Code of Federal Regulations
CL_R	Renal clearance
CMAP	Compound muscle action potential
COMPASS-31	Composite Autonomic Symptom Score
CRF	Case Report Form
CRO	Contract research organization
C-SSRS	Columbia–Suicide Severity Rating Scale
DEHP	di(2-ethylhexyl)phthalate
DLin-MC3-DMA	1,2-Dilinoleyloxy-N,N-dimethylpropylamine
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EQ-5D	EuroQOL
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme linked immunosorbent assay
ERG	Electroretinography
EU	European Union
FAC	Familial amyloidotic cardiomyopathy
FAP	Familial amyloidotic polyneuropathy
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
H1/H2 blocker	Histamine H1/H2 receptor antagonist

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HP	Heat pain
HPLC	High performance liquid chromatography
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
IFE	Immunofixation electrophoresis
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRS	Interactive response system
IV	Intravenous(ly)
LLN	Lower limit of normal
LOCF	Last observation carried forward
LNP	Lipid nanoparticles
mBMI	Modified body mass index
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MMRM	Mixed model repeated measures
mNIS	Modified Neuropathy Impairment Score
mRNA	Messenger ribonucleic acid
NIS	Neuropathy Impairment Score
NCS	Nerve conduction studies
NOAEL	No observed adverse effect limit
Norfolk QOL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NSAID	Nonsteroidal anti-inflammatory
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
OTC	Over-the-counter
PCS	Patient Care Site
PD	Pharmacodynamic
PEG_{2000}-C-DMG	3-N-[(ω-methoxy poly(ethylene glycol)2000) carbamoyl]-1,2-dimyristyloxy-propylamine

Abbreviation	Definition
PI	Principal Investigator
PK	Pharmacokinetic(s)
PND	Polyneuropathy disability
PO	Per os (orally)
PP	Per protocol
PVC	Polyvinyl chloride
PT	Prothrombin time
QST	Quantitative sensory testing
QTc	QT interval corrected for heart rate
RBC	Red blood cell
RBP	Retinol binding protein
RNAi	RNA interference
R-ODS	Rausch-built Overall Disability Scale
SAE	Serious adverse event
SGNFD	Sweat gland nerve fiber density
siRNA	Small interfering ribonucleic acid
SNAP	Sensory nerve action potential
SUSAR	Suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TP	Touch pressure
TSH	Thyroid stimulating hormone
TTR	Transthyretin
TUDCA	Tauroursodeoxycholic acid
ULN	Upper limit of normal
US/USA	United States
USP/EP	United States Pharmacopeia/European Pharmacopoeia
V30M	Val30Met
VDT	Vibration detection threshold
WBC	White blood cell
WHO	World Health Organization
WT	Wild type

1 INTRODUCTION

1.1 Background and Rationale

1.1.1 Disease Overview

Transthyretin-mediated amyloidosis (ATTR) is an inherited, autosomal dominant, systemic disease caused by a mutation in the transthyretin (TTR) gene.[1] Transthyretin is a tetrameric 127 amino acid protein that is secreted predominantly (>95%) by hepatocytes, with a smaller fraction produced by the choroid plexus and retina.[2] Physiologically, TTR is a major serum carrier for retinol binding protein (RBP) and a minor carrier of thyroxine (T4). Mutations in the TTR protein lead to destabilization of the tetrameric form and dissociation into dimers and monomers; misfolding of mutated monomers from the α-helical to the β-pleated sheet structure results in tissue deposition of amyloid fibrils.[3] Amyloid deposits typically contain both mutant and wild-type (WT) TTR. 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. ATTR is a progressive disease associated with severe morbidity, with a life expectancy limited to 5 to 15 years from symptom onset.[4] There are over 100 reported TTR mutations which are associated with 2 clinical syndromes: familial amyloidotic polyneuropathy (FAP) and familial amyloidotic cardiomyopathy (FAC).[5,6,7]

"Patisiran" (the International Nonproprietary Name [INN] name for the drug product previously referred to as ALN-TTR02) is being developed for the treatment of ATTR patients with symptomatic FAP.

The estimated worldwide prevalence of FAP is 5,000 to 10,000, with the majority of cases in Portugal, Sweden, France, Japan, Brazil, and the United States.[8,9] The most common causative mutation of FAP is TTR Val30Met (V30M), with the onset of symptoms typically occurring between 30 and 55 years of age.[10] Amyloid deposition occurs largely in the peripheral nerves, starting as a nerve length-dependent sensory polyneuropathy in the feet causing numbness and pain and progressing to painful dysesthesias. Disabling motor neuropathy follows, characterized by leg weakness and eventual inability to walk. Autonomic neuropathy is another common feature of the disease, resulting in severe gastrointestinal pathology (including diarrhea or constipation and malabsorption, leading to severe malnutrition), orthostatic hypotension, and bladder dysfunction with recurring urinary tract infections.[11,12,13,14] For several mutations, cardiac pathology also occurs due to amyloid infiltration of the sinus node, atrioventricular conduction system, and infiltration of the myocardium.[15,16] Involvement of the conduction system can lead to sudden death due to dysrhythmias, and myocardial infiltration can lead to diastolic dysfunction and right-sided heart failure.[17] The cardiomyopathy proceeds inexorably, leading to death typically within 10 years.[18]

There are multiple lines of evidence demonstrating that reduction of circulating TTR improves outcomes in patients with ATTR. Because the liver is the primary source of WT and mutant TTR, orthotopic liver transplantation has been used since 1990 in an attempt to treat FAP,[19] and is the current standard of care in patients who are eligible for transplant (patients with minimal neuropathy symptoms and no cardiac involvement).

When liver transplantation is performed early in the course of the disease, it can stabilize and slow the course of neuropathic disease in patients with FAP due to V30M, but is less effective in patients with other TTR mutations.[20] However, it is less effective in patients with more advanced disease, especially those with heart involvement, due to the continued production and deposition of WT TTR in tissues with pre-existing amyloid.[21,22,23]

It is estimated that approximately two-thirds of FAP patients are not transplant-eligible. Furthermore, liver transplant poses risks from the surgical procedure and from life-threatening complications due to graft rejection or infections. The 1-year mortality rate post-transplant is 10%.[24]

Nonsurgical options that are used for the treatment of FAP (depending on geographic location) include tafamidis (Vyndaqel®) and diflunisal. Tafamidis is a small molecule TTR stabilizer that binds to the thyroxine binding sites of the TTR tetramer, thus preventing its dissociation to monomers and potentially preventing fibril formation. While tafamidis is approved in the European Union (EU) for the treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment, it is not considered the standard of care throughout the EU and it has not been approved for use outside the EU.[25]

Diflunisal is a generic, nonsteroidal anti-inflammatory drug (NSAID) that is also a tetramer stabilizer and binds to TTR in a similar manner as tafamidis. A multinational, placebo-controlled Phase 3 study in patients with all stages of FAP was recently completed; however, the results have not been released. Due to the restricted use of liver transplantation and tafamidis in patients with early stage of disease, and the non-standard use of diflunisal among practitioners, there remains an unmet medical need for a potent and effective therapy for FAP that will have an impact on patients across a broad range of neurologic impairment, regardless of their mutation (V30M or non-V30M).

1.1.2 RNA Interference

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by "small interfering ribonucleic acids" (siRNAs).[26] Typically, synthetic siRNAs are 19 to 23 base pair double-stranded oligonucleotides in a staggered duplex with a 2-nucleotide overhang at one or both of the 3' ends. Such siRNAs can be designed to target an endogenous or virally-expressed gene. When introduced into cells, the net effect of an RNAi-based pharmacological approach is the binding of the siRNA to its complementary messenger ribonucleic acid (mRNA) sequence, cleavage of this target mRNA, and suppression of the target protein.[27] The ability to selectively and potently degrade the mRNA encoding the TTR protein using an siRNA offers a potent and specific approach for the treatment of ATTR.

Unformulated siRNAs, and those without chemical modification, are rapidly degraded and eliminated upon systemic administration, and thus do not achieve significant tissue distribution.[28] As a result, various formulations are used to target siRNA distribution to tissues, and to facilitate their uptake into the relevant cell type. One approach that has been used successfully *in vivo*, including in rodents, non-human primates, and humans, employs IV delivery of siRNAs in lipid nanoparticles (LNPs).[29,30,31,32] These LNPs, with

their small size (<100 nm) and low surface charge, can pass through the fenestrated vascular endothelium of the liver. Endocytosis of the intact LNPs, followed by fusion with the endosomal membrane and release of the siRNA into the cytoplasm, results in the siRNA engaging the endogenous RNAi machinery described above leading to targeted degradation of the mRNA, and a consequent reduction in target protein levels. [33,34]

1.1.3 PATISIRAN

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.[35] This TTR siRNA has a target region within the 3'UTR region of TTR gene to ensure and confirm homology with WT TTR as well as all reported TTR mutations. Following LNP-mediated delivery to the liver, patisiran targets TTR mRNA for degradation, resulting in the potent and sustained reduction of mutant and WT TTR protein via the RNAi mechanism.

Since circulating TTR is almost exclusively synthesized in the liver, the IV administration of patisiran is postulated to reduce the level of precursors that lead to amyloid fibril deposition, resulting in clinical benefit to patients with FAP.

1.1.4 Therapeutic Hypothesis

Patisiran is a novel investigational agent intended for the treatment of FAP, a serious and life-threatening orphan disease. The therapeutic hypothesis that systemic amyloidoses can be managed by reduction in circulating levels of amyloidogenic protein has been validated in other acquired (e.g., immunoglobulin light chain systemic [AL], or amyloid A [AA]) and hereditary (e.g. Fibrinogen A α-chain, ApoA1) amyloidosis. The experience from these systemic amyloidotic disorders,[36,37,38,39] as well as the liver transplant data in FAP, suggest that lowering of the circulating amyloidogenic protein by at least 50% is required to impact the clinical course of the disease, with reductions in protein beyond 50% providing further incremental improvements in outcomes. It is therefore postulated that the >80% suppression in *both* WT and mutant TTR observed upon administration of 0.3 mg/kg patisiran once every 21 days will result in clinical benefit in FAP patients with mild to moderate polyneuropathy. This hypothesis is further supported by evidence from tafamidis suggesting that reduction in free TTR monomer can slow neuropathy progression in early-stage V30M patients with FAP.[10]

1.2 Summary of Patisiran Nonclinical Data

[redacted]

Further information can be found in the patisiran (ALN-TTR02) IB.

1.3 Summary of Clinical Data with Patisiran

A Phase 1 multicenter, randomized, placebo-controlled, single-blind, single-ascending dose clinical study of patisiran in healthy volunteers was completed in the UK. Patisiran was administered as a single 60-minute IV infusion to healthy volunteers at doses of 0.01 to 0.05 mg/kg. Patients were premedicated with dexamethasone, H1 and H2 blockers, and paracetamol/acetaminophen prior to dosing to minimize the risk of infusion-related reactions (IRRs). Significant pharmacology in terms of TTR protein lowering (>80% reduction from pretreatment baseline) was observed at doses ≥0.15 mg/kg. Transthyretin levels showed evidence of recovery beginning at around Day 21 to 28, returning to baseline by Day 70.

An open-label, Phase 2, multiple-ascending dose study of patisiran in ATTR patients with FAP (Study ALN-TTR02-002) to determine the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a 60-70 minute IV infusion of patisiran administered once every 3 or 4 weeks for 2 doses has completed enrollment (N=29). Preliminary data show >80% TTR knockdown with 0.3 mg/kg after the first and second doses ($p<0.001$), with better sustained suppression of >80% observed throughout the dosing interval with the once every 3 week dosing schedule compared with once every 4 weeks. In V30M patients, both mutant and wild-type TTR were suppressed to the same extent. Multiple doses of patisiran have been generally safe and well-tolerated, including 0.3 mg/kg administered once every 3 or 4 weeks with either a 60-minute infusion and original premedication regimen (total of 28 mg dexamethasone or equivalent, administered the night before and morning of infusion) or a 70-minute step-wise infusion (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minutes for the remainder of the infusion) and a simplified premedication regimen (total of 10 mg dexamethasone or equivalent, administered at least 60 minutes prior to infusion).

Patients completing Study ALN-TTR02-002 are eligible to enroll into a Phase 2, open-label, extension study (ALN-TTR02-003) designed to evaluate the safety and tolerability of long-term patisiran dosing administered to patients with FAP; additional information will be evaluated including PK, PD, and clinical activity. Patients will receive 0.3 mg/kg patisiran once every 21 days for approximately 2 years. Data from this study of March 13, 2015 demonstrate a sustained mean serum TTR knockdown of approximately 80%, with mean nadir up to 88% between doses, for approximately 16 months in patients receiving patisiran 0.3 mg/kg once every 3 weeks (n=20). Neuropathy impairment scores were stable through 12 months with mean change in mNIS+7 and NIS of -2.5 and +0.4 points, respectively.

Further details on these clinical studies can be found in the patisiran (ALN-TTR02) IB.

1.4 Study Design Rationale

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter, multinational study of patisiran in FAP patients. The patients proposed for this study are reflective of the FAP population encountered by clinicians in various different countries worldwide, including patients with a range of neuropathy severity and broad spectrum of TTR mutations. Disease progression will be assessed by neurological measures and functional tests; therefore, the range of baseline neuropathy severity (NIS of 5-130) is selected such that the lower end is advanced enough to show significant progression in the placebo group, while the upper end is not so advanced as to preclude detection of change as a result of a ceiling effect of neuropathy measures or to be confounded by other comorbidities.

The inclusion of placebo as a control allows for a rigorous analysis of the treatment effect of patisiran. However, given the 18-month duration of the study, those patients who have evidence of rapid disease progression at 9 months (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline) will be given the option of discontinuing study drug and receiving local standard of care treatment for their FAP. Such patients will be asked to follow a modified study visit schedule and return for their 18-month efficacy assessment (blinding will be maintained throughout). It is expected that fewer than 5% of patients involved in the ALN-TTR02-004 study will meet the definition of rapid disease progression at 9 months.

Given the orphan nature of the disease and the significant, progressive morbidities associated with FAP, randomization to patisiran or placebo will be performed in a 2:1 ratio (patisiran:placebo) to increase the probability that patients will receive active drug. Treatment groups will be balanced at entry for NIS (5-49 vs 50-130), early onset V30M (<50 years of age at onset) vs all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous tetramer stabilizer use.

The primary endpoint for this study is the change from baseline at 18 months in a composite measure of neurologic impairment termed modified NIS+7 (mNIS+7), which includes a clinical exam-based assessment of neurologic impairment (NIS) combined with electrophysiologic measures of small and large nerve fiber function (NCS and QST),

and measurement of autonomic function (postural blood pressure). The utility of various neuropathy endpoints in demonstrating a treatment effect in randomized, controlled clinical trials in patients with FAP has been established through Phase 3 studies using the small molecule TTR tetramer stabilizers tafamidis and diflunisal. For these studies, the primary efficacy endpoint utilized variations of NIS (NIS-Lower Limbs in the case of tafamidis and NIS+7 for diflunisal). Composite endpoints, such as NIS+7, have been found to be more sensitive in detecting abnormalities in patients with generalized peripheral neuropathy, such as diabetic polyneuropathy and chronic idiopathic demyelinating polyneuropathy, and the reproducibility of composite scores has been shown to be greater than for individual tests. The use of mNIS+7 in this study is expected to increase the sensitivity and reproducibility of the measurement of neuropathy progression in a heterogeneous group of FAP patients presenting with a broad spectrum of disease severity and TTR mutations.

The 18-month endpoint was selected based on the expected rate of neuropathy progression in patients with FAP, derived from a global natural history dataset of 283 patients from Alnylam collaborators in the USA, Portugal, France, and Italy. From these data, it is estimated that a patient's mNIS+7 score will have increased by approximately 24 points in the placebo group after 18 months, thereby providing adequate disease progression for the detection of a treatment effect in the patisiran group.

1.5 Dose Selection and Dosing Schedule Rationale

Given the fundamental role of TTR in the pathogenesis of the disease and the data from liver transplantation in FAP, it is postulated that the optimal dose and schedule for patisiran is one that will result in the greatest level of sustained TTR suppression with an acceptable safety profile. Based on the data to date from the nonclinical and clinical studies with patisiran, >80% maintained suppression of circulating TTR is consistently achieved at the 0.3 mg/kg dose administered once every 3 weeks, and this dose was generally well tolerated. Patisiran will be administered every 21 days as a 70-minute IV infusion (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minute for the remainder of the infusion) with a premedication regimen consisting of IV dexamethasone and H1/H2 blockers along with oral paracetamol/acetaminophen given at least 60 minutes prior to each infusion.

The chronic toxicology studies in rodents (6-month duration) and monkeys (9-month duration), in which animals safely tolerated 14 doses of patisiran at ≥0.3 mg/kg once every 2 or 3 weeks (rats or monkeys, respectively), also supports long-term dosing in FAP patients at 0.3 mg/kg once every 21 days.

1.6 Risk-Benefit Assessment

Patisiran is a novel investigational agent intended for the treatment of FAP, a serious and life-threatening orphan disease with limited treatment options. The therapeutic hypothesis that systemic amyloidoses can be managed by reducing circulating levels of amyloidogenic protein has been established in other acquired and hereditary amyloidoses. The experience from these systemic amyloidotic disorders, as well as the liver transplant data in FAP, suggest that lowering of the circulating amyloidogenic protein could impact the clinical course of the disease. Based on nonclinical and clinical data that showed suppression in

levels of WT and mutant TTR upon administration of 0.3 mg/kg patisiran once every 21 days, it is possible that long term treatment with patisiran may have a clinical benefit in FAP patients with mild to moderate polyneuropathy and that further study is warranted.

In completed and ongoing clinical studies (ALN-TTR02-001, ALN-TTR02-002 and ALN-TTR02-003), single and multiple doses of patisiran have been generally well tolerated. Potential risks of patisiran include the following:

- Infusion-Related Reactions

  Infusion-related reactions (IRRs) can occur with systemic administration of certain biological agents such as liposomes or monoclonal antibodies. In order to reduce the potential for an IRR with patisiran, all patients in this study will be premedicated prior to dosing with patisiran or placebo. The step-wise infusion regimen over approximately 70 minutes (starting with a slower infusion rate of approximately 1 mL/minute for the first 15 minutes before increasing to 3 mL/minute for the remainder of the infusion), may further reduce the risk of an IRR.

- Liver function test abnormalities

  In preclinical studies, patisiran-related increased serum liver markers and histopathology in the liver were observed at dosages > 0.1 mg/kg in rats and > 1.0 mg/kg in monkeys. In general, all of the findings were not observed or were observed at lower severity at the end of the 60-90 day dose free period, indicating that the toxicities were reversible. In clinical studies to date, there have been no clinically significant changes in liver function tests in either the single-dose or multiple-dose studies. Patients in the study are monitored for liver function via serial laboratory assessments.

- Vitamin A Lowering

  The suppression of serum levels of TTR and RBP is expected to result in the lowering of circulating vitamin A levels. Preclinical and clinical data have shown that the lowering of circulating vitamin A associated with suppression of RBP does not result in severe vitamin A deficiency. Furthermore, there are individuals with RBP/TTR mutations who have life-long low levels of circulating vitamin A and are essentially in good health, suggesting that there are compensatory transport mechanisms for vitamin A that are yet undescribed.[40] This has also been confirmed in TTR knockout mice, which do not exhibit any manifestations of vitamin A deficiency, with vitamin A uptake by most tissues continuing in the absence of RBP.[41] Provided there is adequate vitamin A in the diet, tissue stores of vitamin A should not be affected by the lowering of TTR and RBP. However, as the vitamin A content of the diet may vary between different countries and different individuals within a country, all patients on the study will be asked to take a daily supplement containing the recommended daily allowance of vitamin A. Patients should have started vitamin A supplementation by the time they start his/her first dose of patisiran or placebo.

- Osteoporosis

  Patients with FAP may be at risk for osteoporosis.[42] In addition, as part of the premedication regimen administered prior to patisiran dosing every three weeks, FAP

patients participating in this study are given glucocorticoids, a drug known to have the potential to reduce bone mineralization. If there are no medical contraindications, and per investigator judgment and local standard of care, study participants should, if appropriate, receive therapy for the prevention and early treatment of osteoporosis such as: calcium and vitamin D supplementation, bisphosphonates, calcitonin, parathyroid hormone, estrogen agonist/antagonist or combination therapies.

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

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to determine the efficacy of patisiran (ALN-TTR02) by evaluating the difference between the patisiran and placebo groups in the change from baseline of mNIS+7 score at 18 months.

2.2 Secondary Objectives

The secondary objectives of the study are to determine the effect of patisiran on various clinical parameters by assessing the difference between patisiran and placebo in the change from baseline in the following measurements at 18 months:

- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire;
- NIS-weakness (NIS-W) score;
- Modified body mass index (mBMI);
- Timed 10-meter walk test;
- Autonomic symptoms questionnaire (Composite Autonomic Symptom Score [COMPASS-31]).

2.3 Exploratory Objectives

The exploratory objectives of the study are:

- To determine the difference between the patisiran and placebo groups in the change from baseline in the following measurements at 18 months:
  - NIS+7 score;
  - Grip strength;
  - EuroQOL (EQ-5D) questionnaire;
  - Level of disability (Rasch-built Overall Disability Scale [R-ODS]);
  - Large vs small nerve fiber function including nerve conduction studies (NCS) 5 attributes (Σ5), quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), vibration detection threshold (VDT), heart rate response to deep breathing (HRdb), postural blood pressure;
  - Pathologic evaluation of sensory and autonomic innervation through voluntary skin punch biopsies and analysis of intraepidermal nerve fiber density (IENFD) and sweat gland nerve fiber density (SGNFD);
  - Assessment of ambulation through FAP stage and Polyneuropathy Disability (PND) score;
  - Cardiac assessment through echocardiogram, troponin I, and N terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels;
  - Pharmacodynamic (PD) biomarkers (TTR, RBP, vitamin A);

- To compare the proportion of patients in the patisiran and placebo groups who meet the pre-defined criterion for rapid disease progression (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline) at 9 months.

3 STUDY PLAN

3.1 Overall Design

This is a multicenter, multinational, randomized, double-blind, placebo-controlled, Phase 3 study designed to demonstrate the clinical efficacy of patisiran (ALN-TTR02) and to establish the safety of chronic dosing in adult patients with FAP. A schematic of the study design is presented in Figure 1.

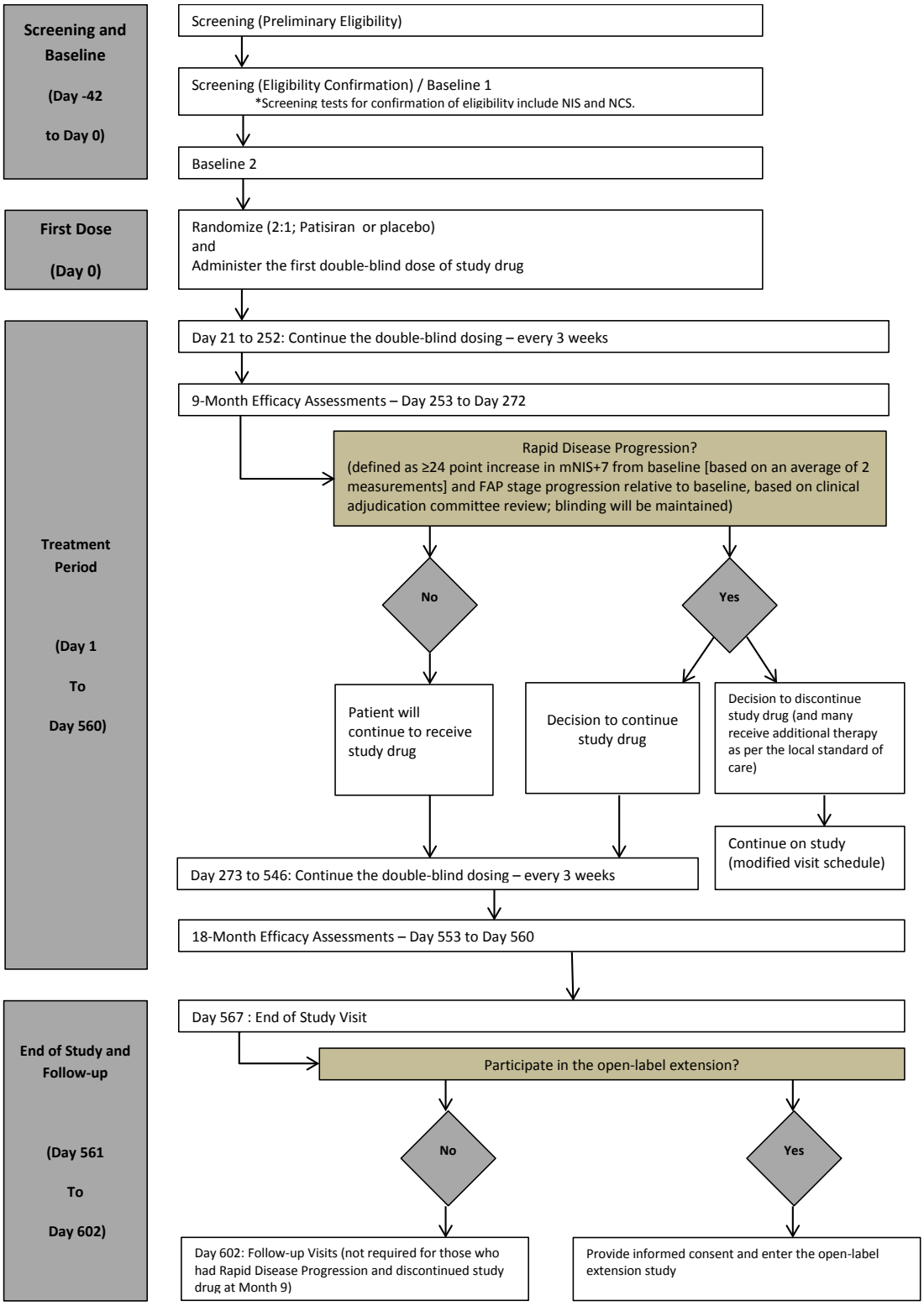
The duration of patient participation in this study is approximately 21 months. Patients will be screened within 42 days prior to administration of study drug. Consented eligible patients will be randomized to receive either patisiran or placebo (2:1 ratio, patisiran to placebo) once every 21 days for 78 weeks. Treatment groups will be balanced at entry for NIS (5-49 vs 50-130), early onset V30M (<50 years of age at onset) vs all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous tetramer stabilizer use.

Prior to dosing, patients will receive premedications in order to reduce the risk of experiencing an IRR. The premedications will be administered at least 60 minutes prior to the start of infusion of study drug. Blinded study drug will be administered as a 70-minute IV infusion (approximately 1 mL/minute for the first 15-minutes followed by approximately 3 mL/minute for the remainder of the infusion). In addition to returning to the site for dosing of study drug once every 21 days, patients will also return for out-patient visits at 9 and 18 months for efficacy assessments (see Section 6 for details). The study personnel performing these assessments will be blinded to the results of any previous assessments (e.g., Screening/Baseline, Baseline, or 9-month assessments).

At the 9-month time point, if the clinical adjudication committee determines that a patient is exhibiting rapid disease progression (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline, see Section 4.6), the patient's treating physician will provide the patient with the option of discontinuing study drug and receiving local standard of care treatment for FAP. Patients who discontinue study drug will remain on study through completion of the 18-month efficacy assessments, following a modified visit schedule as shown in Table 1-3 and described in Section 6.4. Blinding will be maintained throughout. Patients who complete the 18-month efficacy assessments can elect to participate in an extension study in which patients will receive open-label administration of 0.3 mg/kg patisiran once every 21 days.

A Data Monitoring Committee (DMC) will be implemented for the study and will operate under a prespecified charter.

Figure 1: Study Schematic



3.2 Efficacy Assessments

Efficacy parameters will include the following (baseline evaluations will be conducted as well as evaluations at 9 and 18 months):

- Neurologic impairment will be assessed using the mNIS+7 composite score. The mNIS+7 includes the modified NIS (weakness and reflexes), NCS Σ5, QST, as well as autonomic assessment through postural blood pressure;
- Patient-reported QOL will be evaluated using the Norfolk QOL-DN and the EQ-5D. Disability will be reported by patients using the R-ODS;
- Autonomic symptoms will be assessed using the COMPASS-31;
- Motor function assessments to be evaluated include NIS-W, timed 10-meter walk test, and grip strength test;
- PND score and FAP stage;
- Nutritional status will be assessed using mBMI;
- Pathologic evaluation of sensory and autonomic innervation will be evaluated by IENFD analysis and quantitation of SGNFD via tandem 3 mm skin punch biopsies taken from the leg;
- Neurologic impairment will also be assessed by NIS+7 (including full NIS, NCS, VDT, and HRdb);
- Cardiac structure and function will be assessed through echocardiograms as well as measurement of serum levels of NT-proBNP and troponin I.

3.3 Safety Assessments

Safety will be assessed throughout the study by collecting adverse events (AEs; including serious adverse events [SAEs]); clinical laboratory tests, including hematology, clinical chemistry (including liver function tests), thyroid function parameters, and urinalysis; measurement of anti-drug antibodies; electrocardiograms; vital signs; physical examination findings; and ophthalmology examinations.

3.4 Pharmacodynamic Assessments

Pharmacodynamic markers assessed serially will include serum TTR, vitamin A, and RBP. Additional blood samples will be collected for exploratory biomarkers related to FAP.

3.5 Pharmacokinetic Assessments

The plasma PK evaluation will include, whenever possible, plasma-concentration time profiles for siRNA and the novel lipid components in patisiran: DLin-MC3-DMA and polyethylene glycol $(PEG)_{2000}$-C-DMG. The siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG concentration will be determined for all patients at time points specified in Table 1-1, Table 1-2, and Table 1-3.

Urine will be collected with void volume recorded for all patients at time points specified in Table 1-1, Table 1-2, and Table 1-3 and to determine renal clearance (CL_R) of siRNA

and 4-dimethylaminodibutyric acid (the metabolite of DLin-MC3-DMA) after dosing with study drug.

3.6 Other Assessments

Disease burden and healthcare utilization will be assessed using a patient-reported pharmacoeconomics questionnaire. The investigator will periodically assess mental status as it relates to suicidal ideation and behavior by using the Columbia–Suicide Severity Rating Scale (C-SSRS) questionnaire.

4 PATIENT POPULATION

4.1 Eligibility of Patients

Approximately 200 patients are expected to be enrolled at multiple centers worldwide. All centers will be selected on the basis of their experience in the treatment of patients with FAP.

4.2 Inclusion Criteria

To be enrolled in the study, each patient must meet the following criteria at the Screening visit, except where specified:

1. Male or female of 18 to 85 years of age (inclusive);
2. Have a diagnosis of FAP with documented TTR mutation;
3. Have an NIS of 5 to 130 (inclusive) and a PND score of ≤3b (Note: This criterion must be met at the Screening/Baseline visit);
4. Have an NCS sum of the sural sensory nerve action potential (SNAP), tibial compound muscle action potential (CMAP), ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points (Note: This criterion must be met at the Screening/Baseline visit);
5. Have a Karnofsky performance status of ≥60%;
6. Have an absolute neutrophil count (ANC) ≥1500 cells/mm^3, and a platelet count ≥50,000 cells/mm^3;
7. Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), total bilirubin within normal limits, international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed). Patients with total bilirubin ≤ 2 × ULN are 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;
8. Have a serum creatinine ≤2 × ULN;
9. No active infection with hepatitis B or hepatitis C by serology;
10. 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 screening, throughout study participation, and for 75 days after the last dose of study drug. Highly effective methods of birth control are defined in Section 4.7;
11. Males with partners of child-bearing potential, must agree to use 1 barrier method (e.g., condom) and 1 additional method (e.g., spermicide) of contraception throughout study participation and for 75 days after the last dose of study drug; males must also abstain from sperm donation after the first dose of study drug through study participation and for 75 days after the last dose of study drug;

12. Must be willing and able to comply with protocol-required visit schedule and visit requirements and provide written informed consent.

4.3 Exclusion Criteria

A patient will be excluded if they meet any of the following criteria at the time of Screening visit:

1. Had a prior liver transplant or is planning to undergo liver transplant during the study period;
2. Has other known causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, monoclonal gammopathy, etc.);
3. Has known primary amyloidosis or leptomeningeal amyloidosis;
4. Has known type I diabetes;
5. Has had type II diabetes mellitus for ≥5 years;
6. Has vitamin B12 levels below the lower limit of normal (LLN);
7. Has untreated hypo- or hyperthyroidism;
8. Has had a major surgery within the past 3 months or has a major surgery planned during any point of the study period;
9. Has known human immunodeficiency virus (HIV) infection;
10. Has an active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to the first dose of study drug administration;
11. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated;
12. Has a New York Heart Association heart failure classification >2;
13. Had acute coronary syndrome within the past 3 months;
14. Has uncontrolled cardiac arrhythmia or unstable angina;
15 Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer]);
16. Received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever is longer;
17. Participated in a clinical trial with antisense oligonucleotide, must have completed a 3-month wash-out prior to start of the study drug administration in this study;
18. Is currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid (TUDCA); if previously on any of these agents, must have completed a 14-day wash-out prior to start of study drug administration in this study;

19. Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to start of study drug administration in this study;
20. Had a prior severe reaction to a liposomal product or a known hypersensitivity to oligonucleotides or any component of patisiran (ALN-TTR02);
21. Is unable to take the required premedications;
22. Anticipated survival is less than 2 years, in the opinion of the Investigator;
23. Is considered unfit for the study by the Investigator.
24. 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/her will").

4.4 Assignment to Treatment Group/Patient Number

4.4.1 Randomization Procedures

Patients will be randomly assigned in a 2:1 ratio to receive either 0.3 mg/kg patisiran or placebo (normal saline 0.9%).

Patients will be randomized via an interactive response system (IRS). Either designated unblinded site personnel or the pharmacist may request randomization for the patient, but only the pharmacist or unblinded personnel will be allowed to receive the treatment code. The treatment code will be delivered to the unblinded personnel and the pharmacist will use the necessary number of vials for that patient based on their weight.

Treatment arms will be balanced at entry for NIS (5-49 vs 50-130), early onset V30M (<50 years of age at onset) vs all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs no previous tetramer stabilizer use.

4.4.2 Patient Numbering

At enrollment, each patient will be uniquely identified in the study by a combination of his/her center number and screening number. The center number will be assigned by the Sponsor. Upon signing the informed consent form, the patient will be assigned a screening number by the IRS. The Investigator or his/her delegate will contact the IRS (via phone or web) after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The patient will be randomized via the IRS, assigned a patient number and a study treatment. A combination of the center number, screening 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.

4.4.3 Blinding Procedure

Only the pharmacist and designated site personnel who dispense or administer study drug will be unblinded to the study treatment. All other site personnel will be blinded to the treatment. Study personnel performing assessments related to the efficacy endpoints will be different from the Investigator and other personnel managing the patient, and all of these study personnel will be blinded to any clinical laboratory results that could

potentially unblind them (e.g., TTR levels, vitamin A levels, thyroid function tests). In addition, the study personnel performing assessments related to the efficacy endpoints will also be blinded to the results of any previous assessments (e.g., Screening/Baseline, Baseline, or 9-month assessments).

All patients will be blinded to treatment and will receive an IV infusion once every 21 days using identical volumes for placebo and patisiran. The tubing and the lines will be covered so that it will not be possible to detect a difference in active versus placebo drug.

Furthermore, unblinded source documentation containing all descriptions of pharmacy preparations and infusions or distribution of study drug or randomization data will be stored separate from all other study data/records and from other pharmacy staff not participating on the study.

Unblinding is only to occur in the case of patient emergencies or when necessary from a regulatory reporting perspective (e.g., Suspected Unexpected Serious Adverse Reactions [SUSAR] occurring in the EU), and at the conclusion of the study.

Patients who discontinue study drug at 9 months due to rapid disease progression will remain blinded throughout the study.

4.4.4 Breaking the Blind

In the event that the Investigator requests to know a patient's study treatment assignment, the Investigator will first contact the CRO Medical Monitor to discuss the need for unblinding. In case of an emergency, the treatment allocation for each patient will be available from the unblinded site personnel, pharmacist, or the IRS system.

If a patient becomes pregnant or seriously ill during the study, the blind should be broken only if knowledge of the treatment administered will affect treatment options available to the patient. Before breaking the blind, the PI or Sub-investigator should attempt to contact the CRO Medical Monitor. If the Medical Monitor is immediately unreachable, the PI or Sub-investigator should break the blind as necessary using the code breaking information provided and contact the Medical Monitor as soon as possible. A record should be kept of when the blind was broken, who broke it, and why.

4.5 Early Patient Discontinuation or Withdrawal

Patients are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care.

There are 3 ways for a patient to discontinue treatment and/or withdraw from the study:

1) The patient or investigator decides to discontinue study treatment, but the patient agrees to remain in the study and undergo follow-up assessments (as described in Section 6.3).
2) The patient experiences protocol-defined rapid disease progression at Month 9 and elects to discontinue study treatment but remain in the study and return for protocol-specified visits, including follow-up assessment at Month 18 (as described in Section 4.6).
3) The patient decides to no longer participate in the study and withdraws consent.

A patient will be considered to have completed the study if the patient does not withdraw consent from the study and completes protocol-specified procedures up through the 18-month efficacy assessment visit.

4.5.1 Reasons for Treatment Discontinuation or Withdrawal

The Investigator may discontinue treatment or 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 5.8);
- Requests to discontinue treatment or be withdrawn from the study;
- Is found to be considerably noncompliant with the protocol-required patisiran dosing visits.

A patient may discontinue treatment or be withdrawn from the study if, in the Investigator's opinion, they are unable to continue. The Investigator will also withdraw the patient from the study upon the request of Alnylam, including if Alnylam terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with Alnylam before discontinuing treatment.

In general, patients who discontinue treatment will be encouraged to remain on the study to complete study assessments, particularly the Month 9 and Month 18 assessments, so that their experience is captured in the final analyses. However, a patient may withdraw consent to participate in the study at any time.

Missing an occasional dose of study drug will not necessarily result in the patient being withdrawn from the study. However, if a patient misses 2 consecutive doses of study drug, the Investigator at the site and the Medical Monitor will determine whether treatment should be discontinued.

4.5.2 Handling of Withdrawals or Patients who Discontinue from Treatment

In the event a patient discontinues treatment, withdraws, or is withdrawn from the study, the CRO Medical Monitor must be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator for protocol-specified safety follow-up procedures.

If a patient discontinues treatment, withdraws, or is withdrawn from the study, the primary reason for discontinuation must be recorded in the appropriate section of the CRF and all efforts will be made to complete and report the observations as thoroughly as possible.

If a patient withdraws or is withdrawn from the study, the site staff is to encourage the patient to complete the Early Withdrawal visit. Patients who withdraw or are withdrawn from the study, or patients who remain on the study and permanently discontinue study treatment for reasons other than rapid disease progression at Month 9 (see Section 4.6),

will not be eligible to participate in the planned extension study in which patients will receive open-label administration of 0.3 mg/kg patisiran once every 21 days.

4.5.3 Replacements

No replacements will be allowed for patients who withdraw early from the study.

4.6 Discontinuation Due to Rapid Disease Progression

At the 9-month time point, if the clinical adjudication committee determines that a patient is exhibiting rapid disease progression (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline), the patient's treating physician will provide the patient with the option of discontinuing study drug and receiving local standard of care treatment for FAP.

Patients who discontinue due to rapid disease progression will remain on study through completion of the 18-month efficacy assessments (blinding will be maintained throughout), following a modified visit schedule as shown in Table 1-3. Patients who complete the 18-month efficacy assessments can elect to participate in an extension study in which patients will receive open-label administration of 0.3 mg/kg patisiran once every 21 days. Patients who discontinue study drug due to rapid disease progression and also decide to withdraw from the study will not have any additional visits after the Day 273 assessments are completed and will not be eligible to participate in the planned extension study.

4.7 Pregnancy and Breastfeeding Restrictions / Contraception Requirements

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 screening, throughout study participation, and for 75 days after the last dose of study drug. Highly effective methods of birth control result in a low failure rate (i.e., less than 1% per year)[43]. 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Patients should be instructed to use two different forms of effective contraception from the list above. Examples of two 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.

Males (including men who have had vasectomies) with partners of child-bearing potential, must agree to use 1 barrier method (e.g., condom) and 1 additional method (e.g., spermicidal foam, gel, film, cream, or suppository) of contraception throughout study participation and for 75 days (i.e., a whole spermatogenic cycle) after the last dose of study drug. Males must also abstain from sperm donation after the first dose of study drug through study participation and for 75 days after last dose of study drug.

Pregnancy reporting guidelines are provided in Section 8.12.

5 STUDY MEDICATION

5.1 Presentation of Study Drug

Patisiran (ALN-TTR02) Solution for Injection is an RNAi therapeutic consisting of an siRNA targeting TTR mRNA formulated in a LNP. The patisiran drug product is a sterile formulation of TTR siRNA with lipid excipients (DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline. Patisiran Solution for Injection contains 2 mg/mL of TTR siRNA drug substance.

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.

The control drug for this study will be a placebo (normal saline 0.9% for IV administration). Control drug will be provided by a central supplier.

5.2 Preparation of Study Drug

Each investigational site will be responsible for IV preparation and labeling, according to separate handling instructions, and allocating treatments to the patients.

The pharmacist or unblinded study personnel will prepare the study drug under aseptic conditions. The total amount to be infused into each patient at each dosing visit will be 200 mL. To maintain the blind, all IV infusion bags and lines will have amber-colored covers added prior to leaving the pharmacy.

Additional study drug preparation details are provided in the patisiran (ALN-TTR02) Pharmacy Manual.

5.2.1 Preparation of Patisiran

The amount (in mg) of patisiran to be administered will be determined based on the patient's body weight (kg). For each dose administered, the weight obtained during the previous visit will be used to calculate the dose of study drug. In the event that the weight obtained on the previous dosing day is not available, the weight obtained predose on the 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.

Sterile normal saline (0.9% NaCl) will be added to a sterile infusion bag, and the calculated volume of patisiran will be withdrawn from the vials and injected into the infusion bag.

5.2.2 Preparation of Placebo

Normal saline (0.9% NaCl), provided by a central supplier, will be infused into patients randomized into the control group. Depending on the availability, saline may need to be withdrawn from a larger bag or additional saline may need to be added to a sterile infusion bag to ensure the 200 mL volume.

5.3 Drug Administration

5.3.1 Premedication

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

- Intravenous dexamethasone (10 mg) or equivalent;
- Oral paracetamol/acetaminophen (500 mg) or equivalent;
- Intravenous H2 blocker (e.g., 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 or fexofenadine 25 mg per os (PO, orally) or cetirizine 10 mg PO may be substituted for any patient who does not tolerate IV diphenhydramine or other IV H1 blocker.

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 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 below 10 mg 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 intravenous dexamethasone or equivalent is used as the steroid premedication, then proceed to Section 5.9.

Further details (including a table of equivalent premedications) can be found in the patisiran (ALN-TTR02) Pharmacy Manual.

5.3.2 Study Drug Administration

Patients who are randomized into the active treatment group will receive 0.3 mg/kg patisiran once every 21 days (± 3 days). Patients who are randomized into the control group will receive placebo (normal saline 0.9%) once every 21 days (± 3 days).

The body weight that was obtained during the previous visit must be used to calculate the dose of study drug. In the event that the body weight obtained on the previous dosing day is not available, the body weight obtained pre-dose on the dosing day can be used for the dose calculation. Patients who weigh 105 kg or more will receive patisiran dosing based on an assumption of a body weight of 104 kg.

Study drug (either patisiran or placebo) will be administered under the supervision of the unblinded site personnel, as a 70-minute IV infusion (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minute for the remainder of the infusion). The study drug will be administered via a controlled infusion device with an extension set containing a 1.2 micron filter supplied by Alnylam or designee. Infusion products must not contain polyvinyl chloride, di(2-ethylhexyl)phthalate (PVC, DEHP). As described in Section 4.4.3, the tubing and the lines will be covered so that it will not be possible to detect a difference in active versus placebo drug.

- 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 study drug administration will not be resumed until the case is discussed with the medical monitor (see Section 5.9).
- If the infusion time for a patient was extended due to an IRR, that modified infusion duration should be continued throughout the duration of the study for that particular patient. Returning the patient's infusion duration to 70 minutes will require a discussion with the medical monitor.
- For the first 3 infusions of study drug 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 study drug within the dosing window (±3 days), the dose will be considered missed and not administered.

Additional details can be found in the patisiran (ALN-TTR02) Pharmacy Manual.

In addition, patients will receive an oral daily supplemental dose of the recommended daily allowance of vitamin A.

5.4 Storage of Study Drug

All study drug must be stored in a secure, temperature controlled location and may be dispensed only by a staff member specifically authorized by the Investigator or by a

pharmacist, as appropriate. All study drug 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 Alnylam and use of the study drug halted until authorization for its continued use has been given by Alnylam or designee.

No special procedures for the safe handling of patisiran are required. An unblinded Alnylam Monitor or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

No study product(s) may be administered to any person not enrolled in the study.

Additional preparation details are provided in the patisiran (ALN-TTR02) Pharmacy Manual.

5.5 Labeling and Packaging of Study Drug

All packaging and labeling as well as the preparation of patisiran and placebo 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.

Study drug 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.

5.6 Measurement of Patient Compliance

Treatment compliance with study drug administration is dependent on the proper preparation and administration of IV infusions by unblinded study site personnel as well as attendance by the patient to the clinic. Treatment compliance with study drug administration will be verified by unblinded study staff observation. A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the PI, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue on the study.

Patients failing to complete the 18-month efficacy assessment visit will not be eligible to receive patisiran on the open-label extension study.

5.7 Study Drug Accountability

The Investigator will maintain accurate records of receipt and the condition of all study drugs 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 study drug 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 unblinded Alnylam Monitor or designee that will not have a role in any other aspect of managing the study. Remaining study drug (all used, partially used, and unused vials) will be returned to Alnylam or its specified designee/depot or destroyed at the site according to applicable regulations.

Study drug must not be used for any purpose other than the present study. Study drug which has been dispensed for a patient and returned unused must not be redispensed.

Further instructions about study drug accountability are detailed in the patisiran (ALN-TTR02) Pharmacy Manual.

5.8 Concomitant Medication / Treatment

Use of the following medications/treatments is prohibited during study participation (with the exclusion of patients who have rapid disease progression and discontinue study drug after the 9-month efficacy assessments):

- Any investigational agent other than patisiran;
- Tafamidis (use prior to screening permitted);
- Diflunisal (use prior to screening permitted);
- Doxycycline/TUDCA (use prior to screening permitted);
- 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 (e.g., asthma, rheumatoid arthritis, etc.), 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.

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.

Investigator should review over-the-counter (OTC) and or herbal preparations to ensure that these are not potentially disease modifying.

Use of all concomitant medications and treatments will be recorded on the patient's CRF through the time points shown in Table 1-1, Table 1-2, and Table 1-3. This will include all prescription drugs, herbal preparations, OTC medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the CRF.

Any concomitant medication or treatment that is required for the patient's welfare may be given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication or treatment are recorded on the CRF, and coded using an internationally recognized and accepted coding dictionary.

5.9 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 study drug 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 study drug 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 study drug 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 study drug. 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.
- Study drug 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.

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. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments. 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 STUDY VISITS

The duration of a patient's participation in this study is approximately 21 months (inclusive of a 42-day screening period and up to a 56-day post last dose study visit).

Screening evaluations are to be performed within 42 days before receiving the first dose of study drug, as indicated in Table 1-1. Patients determined to be eligible based on Screening assessments will receive blinded study drug IV infusion of either patisiran (ALN-TTR02) or placebo once every 21 days. Patients will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.

In order to decrease the variability in the efficacy assessment testing, there will be a limited number of sites within any one territory that conduct efficacy assessments at Screening/Baseline, Baseline, 9-month, and 18-month visits (referred to as "Central Assessment Sites [CAS]"); these sites can also screen, dose, and manage patients. There will also be sites that screen, dose, and manage the patients ("Patient Care Sites [PCS])", while sending the patients to the nearest CAS for their Screening/Baseline, Baseline, 9- and 18-month efficacy assessments.

Prior to starting the study and screening patients in the protocol, the CAS and PCS will create a delegation of responsibilities document that clearly details which site is responsible for which tests and safety parameters to ensure adherence to the protocol. This document will become part of the study site specific documentation.

All patients who discontinue from the study early will return to the study site for their Early Withdrawal assessments.

6.1 Screening, Screening/Baseline, and Baseline Visits (Days –42 to Day 0)

Screening evaluations will be conducted over 3 or more visits (Screening, Screening/Baseline, and Baseline). All screening visits must occur within 42 days of the first dose of study drug (Day 0). Table 1-1 provides an overview of the schedule of events required at each screening visit.

Prior to screening activities, the patient will sign and date an informed consent form (ICF) and receive a copy of the signed ICF. No study procedures should be performed prior to informed consent being obtained. The Investigator or another person authorized by the Investigator will also sign and date the informed consent prior to giving a copy to the patient. The ICF will be filed in the patient's medical record.

In conjunction with the decision of the Medical Monitor(s), patients may be allowed to rescreen after a minimum of 5 days have elapsed from their last screening assessment.

6.1.1 Screening

The following activities must be performed during the Screening visit as part of the initial review of patient eligibility:

- Assess study eligibility using the inclusion and exclusion criteria;
- Obtain medical history information, including inquiry into HIV status;
- Obtain demographic information;

- Determine Karnofsky Performance Status (see Appendix 1);
- Determine New York Heart Association classification of heart failure (see Appendix 2);
- Collect and review documentation for TTR genotype;
- Perform a physical examination;
- Measure weight;
- Measure height;
- Measure vital signs;
- Collect blood samples for clinical laboratory tests, including:
    - Paraprotein (assessed by immunofixation electrophoresis [IFE]);
    - Vitamin B_{12};
    - Serology;
    - Hematology;
    - Serum chemistries;
    - Coagulation studies;
    - Thyroid function tests.
- Collect urine sample for urinalysis;
- Perform a pregnancy test (for females of child-bearing potential only);
- Obtain information on concomitant medications;
- Perform NIS and NCS. Note: The documented results of previously performed NIS and NCS may be used to qualify a patient for this study if these tests were performed within 60 days prior to the date of informed consent. These studies may be completed as per local protocol.

6.1.2 Screening/Baseline Visit

Patients who meet all of the Screening criteria (including NIS and NCS assessments) will complete the screening process during 2 subsequent visits (which will be conducted at CAS for patients screened at PCS): a Screening/Baseline visit and a Baseline visit.

The Screening/Baseline visit must be performed within 21 days prior to the first dose of study drug (Day 0).

The following assessments must be performed during the Screening/Baseline visit:

- Perform the following efficacy assessments:
    - mNIS+7*;
    - NIS+7*;

      *Note: Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed only once.

- PND score;

- Collect blood sample for long-term frozen storage of serum to permit testing of additional proteins related to FAP;
- Measure vital signs;
- Measure weight;
- Obtain information on concomitant medications;
- Obtain an interval medical history;
- Confirm that NIS, PND, and NCS results meet study eligibility requirements. Inclusion Criteria 3 (i.e., NIS of 5 to 130 [inclusive] and PND score of ≤3b) and 4 (i.e., NCS sum of the sural SNAP, tibial CMAP, ulnar SNAP, ulnar CMAP, and peroneal CMAP of ≥2 points).

Note: The following assessments may be performed at a single time point during either the Screening/Baseline visit or as noted below, at the discretion of the investigator.

At the Screening/Baseline or Baseline visit:

- Perform a 12-lead ECG;
- Complete the Norfolk QOL-DN, and COMPASS-31 questionnaires;
- Complete the C-SSRS questionnaire;

At any time after the patient is deemed eligible for participation in the study, but before the first administration of study drug:

- Perform a timed 10-meter walk test.

At any time after the patient is deemed eligible for participation in the study through the Day 0 visit:

- Perform a grip strength test;
- Perform an echocardiogram;
- Complete the EQ-5D and R-ODS questionnaires;

At any time after the patient is deemed eligible for participation in the study through the Day 21 visit:

- Perform an ophthalmology exam;
- Complete the pharmacoeconomics questionnaire.

6.1.3 Baseline Visit

The Baseline visit will occur at least 24 hours (approximately), but no greater than 7 days, from the Screening/Baseline visit. The following activities should be performed during the Baseline visit:

- Perform a 12-lead ECG (if not completed at the Screening/Baseline visit);
- Measure vital signs;

- Measure weight;
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Obtain information on concomitant medications;
- Perform the following efficacy assessments:
    - mNIS+7*;
    - NIS+7*;

      *Note: Components that are shared between the mNIS+7 and NIS+7 (including NIS and NCS) will be performed only once.
    - PND score (see Appendix 5);
    - FAP stage (see Appendix 6);
    - If the patient has provided separate informed consent for the skin biopsies, obtain 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total; 1 set from the distal lower leg, when a patient's clinical status allows, and 1 set from the distal thigh). Skin biopsies will be performed at a CAS;
    - mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
    - Collect blood samples for NT-proBNP and troponin I;
    - Norfolk QOL-DN (if not completed at the Screening/Baseline visit);
    - COMPASS-31 (if not completed at the Screening/Baseline visit).
- Complete the C-SSRS questionnaire (if not completed at the Screening/Baseline visit);
- Obtain an interval medical history.

The following activities may also be completed at the Baseline visit if not completed at the Screening/Baseline visit, as described in Section 6.1.2:

- Timed 10-meter walk test;
- Grip strength test;
- Echocardiogram;
- EQ-5D and R-ODS questionnaires;
- Ophthalmology examination at a CAS;
- Pharmacoeconomics questionnaire.

6.2 Treatment Visits

Patients who are determined to be eligible for the study will be enrolled on Day 0.

On all study visit days, patients should take their vitamin A supplement after completing the blood draws.

Prior to dosing, all patients will receive premedications in order to reduce the risk of experiencing an IRR as described in Section 5.3.1.

6.2.1 Day 0

6.2.1.1 Pre-dose on Day 0

On Day 0, patients will undergo the following procedures prior to study drug administration:

- Measure weight;
- Measure vital signs;
- Timed 10-meter walk test (if not completed at the Screening/Baseline or Baseline visits);
- Collect blood samples for clinical laboratory tests, including:
    - Serum chemistries;
    - Anti-drug antibody testing.
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Collect blood sample for plasma PK assessment within 1 hour of planned study drug dosing start;
- Collect urine sample for PK assessment within 1 hour of planned study drug dosing start;
- Obtain information on concomitant medications;
- Randomize the patient (See Section 4.4.1);
- Administer premedications at least 60-minutes prior to the start of administration of study drug (see Section 5.3.1);
- Document any AEs.

The following activities are to be completed on Day 0 pre- or post-dosing if not completed at the Screening/Baseline or Baseline visits, as described in Section 6.1.2:

- Grip strength test;
- Echocardiogram;
- EQ-5D and R-ODS questionnaires.

6.2.1.2 Administration of Study Drug on Day 0

As described in Section 5.3.2, after completion of all pre-dose evaluations and procedures, study drug will be administered by a controlled infusion device as a 70-minute IV infusion (approximately 1 mL/minute for the first 15 minutes followed by approximately 3 mL/minute for the remainder of the infusion) or at a more prolonged infusion rate (up to 3 hours) if required due to prior IRR. 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.

The infusion time may be extended up to 3 hours in the event of a mild or moderate IRR. Study drug administration will not be resumed for any patient following a severe infusion reaction until the case is discussed with the Medical Monitor.

Suggested guidelines for management of IRRs are provided in Section 5.9.

6.2.1.3 Post-dose on Day 0

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. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments:

- Measure vital signs;
- Collect a PK sample at the end of infusion (+5 minutes);
- Obtain information on concomitant medications;
- Document any AEs.

The following activities may also be completed on Day 0 if not completed at the Screening/Baseline or Baseline visits, as described in Section 6.1.2:

- Ophthalmology examination at a CAS;
- Pharmacoeconomics questionnaire.

6.2.2 Routine Study Visits

The procedures described below are to be performed for all routine study visits (from Day 21 through Day 546), with the exception of the 9-month and 18-month efficacy assessments (occurring on Days 253-272 and Days 553-560, respectively). All visits have a window of "±3 days" except for the Day 273 visit which has a window of "+3 days" to allow adequate time for the assessment of the patient's 9-month mNIS+7 and FAP stage testing, which will determine if the patient met the criteria for Rapid Disease Progression.

Patients will undergo the following procedures before study drug dosing:

- At all dosing visits, administer premedications at least 60 minutes prior to the start of administration of study drug (see Section 5.3.1);
- At all dosing visits, measure weight;
- At all dosing visits, measure vital signs;

- On Days 252 and 546, perform a physical examination;
- On Days 126 and 399, perform a 12-lead ECG;
- On Days 21, 126, 252, 273, 399, and 546, collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- On Days 84, 189, 357, 462, and 546, collect blood samples for serum chemistry tests;
- On Day 546, collect blood sample for INR;
- On Days 21, 126, 252, 399, and 546, collect a blood sample for anti-drug antibody assessment;
- On Days 252 and 546, collect blood samples for clinical laboratory tests, including:
    - Hematology;
    - Thyroid function tests.
- On Days 252 and 546, collect urine sample for urinalysis;
- On Days 21, 126, 252, 399, and 546, collect a plasma PK sample pre-dose (within 1 hour of planned study drug dosing);
- On Days 21, 126, 252, 399, and 546, collect a urine PK sample pre-dose (within 1 hour of planned dosing start);
- Perform ophthalmology examinations on Day 21 (if baseline examination was not completed prior to the Day 21 visit), once between Days 231(±3) and 272 at a CAS, and once between Days 546(±3) and 560 at a CAS;
- Complete the pharmacoeconomics questionnaire on Day 21, if not completed prior to the Day 21 visit;
- At all dosing visits, obtain information on concomitant medications;
- At all dosing visits, document any AEs.

Following the completion of all required pre-dose activities and assessments, administer the study drug at all dosing visits, as described in Section 6.2.1.2.

Following dosing, collect plasma PK samples as follows:

- On Days 126 and 399, collect a plasma PK sample at the end of the infusion (+5 minutes);
- On Days 21, 252, and 546, collect a plasma PK sample 30 minutes after the end of the infusion (+15 minutes).

6.2.3 Efficacy Assessment Visits (9 Months and 18 Months)

Efficacy assessment will be performed on all patients at approximately 9 and 18 months (Days 253-272 and 553-560, respectively). Patients will not receive any study drug on these days.

As described in Section 4.6, in consultation with the Investigator on Day 273 (+3 days), patients who meet the criteria for Rapid Disease Progression based on the 9-month efficacy assessments may continue study drug dosing or discontinue study drug dosing. Patients who discontinue study drug dosing may receive additional therapy for FAP, as per the local standard of care. These patients will remain on the study and follow the modified schedule of assessments shown in Table 1-3 and described in Section 6.4. Blinding will be maintained throughout.

The 9- and 18-month efficacy assessment visits will take place over 2 days.

- Perform the following efficacy assessments:
    - mNIS+7*;
    - NIS+7*;
    - Timed 10-meter walk test*;
    - Grip strength test*;

    *Note: For the mNIS+7, NIS+7, timed 10-meter walk test, and grip strength test, an independent assessment will be performed on each day. Each site will make every effort to have these assessments performed by the same Investigator. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater than 7 days apart. For the mNIS+7 and NIS+7, components that are shared (including NIS and NCS) will be performed only once on each assessment day.

    - PND score (see Appendix 5);
    - FAP stage (see Appendix 6);
    - If the patient has provided separate informed consent for the skin biopsies, obtain 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total); 1 set from the distal lower leg when a patient's clinical status allows, and 1 set from the distal thigh. Skin biopsies will be performed at a CAS;
    - mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
    - Echocardiogram;
    - Collect blood samples for NT-proBNP and troponin I;
    - Norfolk QOL-DN;
    - EQ-5D;
    - R-ODS;
    - COMPASS-31.
- Measure weight on both efficacy assessment days;
- Measure vital signs on both efficacy assessment days;

- Complete the C-SSRS questionnaire;
- Complete the pharmacoeconomics questionnaire;
- Perform a 12-lead ECG;
- Collect blood samples for:
    - TTR protein, RBP, and vitamin A;
    - Additional aliquots of serum for long-term frozen storage, to permit testing of additional proteins related to FAP.
- Perform an ophthalmology examination (2 exams with 1 being completed between Days 231(±3) and 272 at a CAS, and 1 completed between Days 546(±3) and 560 at a CAS);
- Obtain information on concomitant medications;
- Document any AEs.

6.2.4 Follow-Up Visits

Patients will return to the study site for 2 follow-up visits, 21 days and 56 days after receiving their last dose of study drug. If a patient enrolls in the extension study, they will only have to complete the 21-day follow-up assessments (End of Study [EOS]; Day 567) and not the 56-day follow-up assessments (Day 602). Patients who do not enroll in the extension study will need to complete both follow-up visits (EOS [Day 567] and Day 602).

6.2.4.1 Twenty-One-Day Follow-up Visit (End of Study)

The following procedures will be performed at the 21-Day Follow-up visit (EOS; Day 567).

- Perform a physical examination;
- Measure weight;
- Measure vital signs;
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Perform a pregnancy test (for females of child-bearing potential only);
- Obtain information on concomitant medications;
- Document any AEs.

6.2.4.2 Fifty-Six-Day Follow-up Visit

This visit will only be conducted for patients who do not enroll in the extension study.

The following procedures will be performed at the 56-Day Follow-up visit (Day 602):

- Perform a physical examination;

- Measure vital signs;
- Collect blood sample for serum chemistry testing;
- Perform a pregnancy test (only for females of child-bearing potential);
- Obtain concomitant medications information;
- Document any AEs.

6.3 Early Withdrawal Visit and Follow-up Visits for Patients who Permanently Discontinue Study Treatment

6.3.1 Early Withdrawal Visit

For patients who withdraw early from the study, every effort will be made to have them return to the study site to have the following procedures performed. These visits will take place over 2 days.

- Perform the following efficacy assessments:
    - mNIS+7*;
    - NIS+7*;
    - Timed 10-meter walk test*;
    - Grip strength test*.

    *Note: For the mNIS+7, NIS+7, timed 10-meter walk test, and grip strength test, an independent assessment will be performed on each day. Each site will make every effort to have these assessments performed by the same Investigator. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater than 7 days apart. For the mNIS+7 and NIS+7, components that are shared (including NIS and NCS) will be performed only once on each assessment day.

    - PND score (see Appendix 5);
    - FAP stage (see Appendix 6);
    - If the patient has provided separate informed consent for the skin biopsies, obtain 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total); 1 set from the distal lower leg when a patient's clinical status allows, and 1 set from the distal thigh;
    - mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
    - Echocardiogram;
    - Collect blood samples for NT-proBNP and troponin I;
    - Norfolk QOL-DN;
    - EQ-5D;

- R-ODS;
- COMPASS-31.

- Complete the pharmacoeconomics and C-SSRS questionnaires.
- Measure weight on both efficacy assessment days.
- Measure vital signs on both efficacy assessment days.
- Perform a physical examination.
- Collect a 12-lead ECG.
- Collect blood samples for clinical laboratory tests, including:
  - Hematology;
  - Serum chemistries;
  - Thyroid function tests;
  - Anti-drug antibody testing.
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP.
- Collect urine sample for urinalysis.
- Perform a pregnancy test (only for females of child-bearing potential).
- Collect a blood sample for plasma PK assessment;
- Collect a urine sample for PK assessment;
- Obtain information on concomitant medications;
- Document any AEs.

6.3.2 Follow-up Visits for Patients who Permanently Discontinue Study Treatment

Patients who permanently discontinue study treatment at any time after their first dose of study drug (due to decision made by treating physician or by the patient) may consent to return for follow-up visits at Months 9 and/or 18. If the patient discontinues study treatment >24 weeks prior to the Month 9 evaluation visit, the patient will complete follow-up visits at 9 and 18 months; if the patient discontinues study treatment after the Month 9 evaluation visit and >24 weeks before the Month 18 evaluation visit, the patient will complete a follow-up visit at 18 months.

These visits will take place over 2 days (at least 24 hours [approximately], but not more than 7 days apart). The following procedures will be performed:

- Perform the following efficacy assessments:
  - mNIS+7*;
  - NIS+7*;

*Note: For the mNIS+7 and NIS+7, an independent assessment will be performed on each day. Each site will make every effort to have these assessments performed by the same Investigator. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater than 7 days apart. For the mNIS+7 and NIS+7, components that are shared (including NIS and NCS) will be performed only once on each assessment day.

- PND score (see Appendix 5);
- FAP stage (see Appendix 6);
- mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
- Norfolk QOL-DN;
- EQ-5D

- Perform a physical examination;
- Measure weight on both efficacy assessment days;
- Measure vital signs on both efficacy assessment days;
- Collect blood sample for serum TTR protein, RBP, and vitamin A.
- Determine Karnofsky Performance Status (see Appendix 1);
- Determine New York Heart Association classification of heart failure (see Appendix 2);
- Collect a blood sample for plasma PK assessment;
- Collect data on subsequent FAP treatment regimens.

6.4 Modified Visit Schedule for Patients who Discontinue Study Drug for Rapid Disease Progression at Month 9

As described in Section 4.6, in consultation with the Investigator, patients who meet the criteria for Rapid Disease Progression based on the 9-month efficacy assessments may continue study drug dosing or discontinue study drug dosing. Patients who discontinue study drug dosing may receive additional therapy for FAP, as per the local standard of care. These patients will remain on the study and follow a modified visit schedule as shown in Table 1-3 and described in detail below. Blinding will be maintained throughout.

6.4.1 Modified Day 273

The following procedures will be performed on Day 273 (+3 days):

- Consult with the patient on a subsequent plan of care, which may include receiving therapy for FAP as per the local standard of care;
- Measure vital signs;

- Collect information on concomitant medications;
- Document any AEs.

Patients who discontinue treatment and also decide to discontinue from the study at the time of this visit will not have any additional visits after the Day 273 assessments are completed.

6.4.2 Modified Day 294

The following procedures will be performed:

- Perform a physical examination;
- Measure vital signs;
- Collect blood sample for serum chemistry testing;
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Collect a blood sample for plasma PK assessment;
- Collect a urine sample for PK assessment;
- Perform a pregnancy test (only for females of child-bearing potential);
- Obtain concomitant medications information (this will be the final collection of concomitant medications);
- Document any AEs (following this visit, only AEs that are considered related to study procedures will be collected);
- Collect data on subsequent FAP treatment regimens.

6.4.3 Modified Day 378 and Day 462

Study personnel will contact the patient by phone to query for general health status and data on subsequent FAP treatment regimens.

6.4.4 Modified Day 546

The following procedures will be performed:

- Perform a physical examination;
- Measure weight;
- Measure vital signs;
- Collect blood samples for clinical laboratory tests, including:
    - Hematology;
    - Serum chemistries and INR;
    - Thyroid function tests;
    - Anti-drug antibody testing.

- Collect urine sample for urinalysis;
- Perform a pregnancy test (only for females of child-bearing potential);
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Collect a blood sample for plasma PK assessment;
- Collect a urine sample for PK assessment;
- Complete the pharmacoeconomics questionnaire;
- Document any study-procedure-related AEs;
- Collect data on subsequent FAP treatment regimens.

6.4.5 Modified 18-Month Efficacy Assessment Visit

This visit will take place over 2 days. The following procedures will be performed:

- Perform the following efficacy assessments:
    - mNIS+7*;
    - NIS+7*;
    - Timed 10-meter walk test*;
    - Grip strength test*;

    *Note: For the mNIS+7, NIS+7, timed 10-meter walk test, and grip strength test, an independent assessment will be performed on each day. Each site will make every effort to have these assessments performed by the same Investigator. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater than 7 days apart. For the mNIS+7 and NIS+7, components that are shared (including NIS and NCS) will be performed only once on each assessment day.

    - PND score (see Appendix 5);
    - FAP stage (see Appendix 6);
    - If the patient has provided separate informed consent for the skin biopsies, obtain 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total); 1 set from the distal lower leg when a patient's clinical status allows, and 1 set from the distal thigh;
    - mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
    - Echocardiogram;
    - Collect blood samples for NT-proBNP and troponin I;
    - Norfolk QOL-DN;

- EQ-5D;
- R-ODS;
- COMPASS-31.

- Measure weight on both efficacy assessment days;
- Measure vital signs on both efficacy assessment days;
- Collect a 12-lead ECG;
- Complete the C-SSRS questionnaire;
- Document any study-procedure-related AEs.

6.4.6 Modified Twenty-One-Day Follow-up Visit (End of Study)

The following procedures will be performed:

- Perform a physical examination;
- Measure weight;
- Measure vital signs;
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Document any study-procedure-related AEs;
- Collect data on subsequent FAP treatment regimens.

6.4.7 Modified Early Withdrawal Visit

If the patient on the modified visit schedule discontinues from the study any time after the Day 273 assessments are completed (i.e., Day 274 onward), every effort will be made to have the patient return to the study site for the Modified Early Withdrawal visit. This visit will take place over 2 days (at least 24 hours [approximately], but not more than 7 days apart). The following procedures will be performed:

- Perform the following efficacy assessments:
  - mNIS+7*;
  - NIS+7*;
  - Timed 10-meter walk test*;
  - Grip strength test*;

  *Note: For the mNIS+7, NIS+7, timed 10-meter walk test, and grip strength test, an independent assessment will be performed on each day. Each site will make every effort to have these assessments performed by the same Investigator. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater than 7 days apart. For the mNIS+7 and NIS+7, components that are shared (including NIS and NCS) will be performed only once on each assessment day.

- PND score (see Appendix 5);
- FAP stage (see Appendix 6);
- If the patient has provided separate informed consent for the skin biopsies, obtain 2 sets of tandem 3-mm skin punch biopsies (4 biopsies total); 1 set from the distal lower leg when a patient's clinical status allows, and 1 set from the distal thigh;
- mBMI (Note: The site will only measure the patient's weight. Using this weight, mBMI will be calculated programmatically in the clinical database; the site will not perform the calculation.);
- Echocardiogram;
- Collect blood samples for NT-proBNP and troponin I;
- Norfolk QOL-DN;
- EQ-5D;
- R-ODS;
- COMPASS-31.

- Complete the pharmacoeconomics and C-SSRS questionnaires;
- Perform a physical examination;
- Measure weight on both efficacy assessment days;
- Measure vital signs on both efficacy assessment days;
- Collect a 12-lead ECG;
- Collect blood sample for serum TTR protein, RBP, and vitamin A. Additionally, aliquots of serum samples will be taken for long-term frozen storage, to permit testing of additional proteins related to FAP;
- Collect blood samples for clinical laboratory tests, including:
  - Serum chemistries;
  - Thyroid function tests;
  - Anti-drug antibody testing.
- Perform a pregnancy test (only for females of child-bearing potential);
- Document any study-procedure-related AEs;
- Collect data on subsequent FAP treatment regimens.

6.5 Unscheduled Visits

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

7 STUDY ASSESSMENTS

7.1 Demographic Data and Medical History

At the Screening visit, patient demographic data and a complete medical history will be obtained, including review of documentation of TTR genotype. At the Screening/Baseline visit and Baseline visit, an interval medical history will be obtained, capturing only changes since the Screening visit.

At the Screening visit, HIV status will be obtained. The Investigator will assess the patient according to the Karnofsky Scale (see Appendix 1) and the New York Heart Association Classification of Heart Failure (see Appendix 2).

7.2 Efficacy Assessments

Efficacy assessments will occur at Screening/Baseline, Baseline, 9 months, 18 months, and Early Withdrawal (if applicable). A central neurologic testing core facility will review the 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 also be responsible for processing and analyzing skin punch biopsy samples.

The study personnel performing assessments related to the efficacy endpoints will be blinded to the results of any previous assessments (e.g., Screening/Baseline, Baseline, or 9-month assessments).

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

7.2.1 Modified Neurological Impairment Score +7

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

- Clinical exam-based neurologic impairment score (NIS-weakness and reflexes);
- Electrophysiologic measures of small and large nerve fiber function (+7) including:
  - NCS Σ5;
  - QST by body surface area including TP and HP.
- Autonomic function (postural blood pressure).

A summary of the scoring of the components of the mNIS+7 is provided in Appendix 4.

At each time point, 2 independent assessments will be performed. Each site will make every effort to have these assessments performed by the same blinded study personnel, who will be different from the Investigator and other personnel managing the patient. Assessments are to be performed at least 24 hours (approximately) apart from each other but no greater 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.

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

7.2.2 Neurological Impairment Score +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;
  - VDT.
- HRdb.

A summary of the scoring of the components of the NIS+7 is provided in Appendix 4.

At each time point, 2 independent assessments will be performed in the same manner as described above for mNIS+7. Every effort will be made to use the same devices for NCS and VDT for a patient throughout the duration of the study.

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

7.2.3 Familial Amyloidotic Polyneuropathy Stage and Polyneuropathy Disability Score

Changes in ambulation will be evaluated through the PND score and FAP stage (see Appendix 5 and Appendix 6, respectively).[44,45]

7.2.4 Intraepidermal Nerve Fiber Density and Sweat Gland Nerve Fiber Density

Quantification of nerve fibers in skin will be assessed via IENFD and SGNFD. Patients who have provided additional voluntary consent for skin biopsy will undergo tandem 3mm skin punch biopsies for IENFD and SGNFD assessment. At each time point, 1 set of biopsies will be taken from the distal lower leg, when a patient's clinical status allows, and 1 set from the distal thigh (4 biopsies total).

A repeat baseline biopsy may be performed if the initial sample is not of sufficient quality.

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

7.2.5 Modified Body Mass Index

Sites will measure body weight at the time points specified in Table 1-1, Table 1-2, and Table 1-3. Using that data, the mBMI will be calculated (BMI × albumin). This calculation will take place programmatically in the clinical database; the sites will not perform the calculation.

7.2.6 Timed Ten-meter Walk Test

To perform the timed 10-meter walk, 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 the 9-month, 18-month, and Early Withdrawal visits, the assessments will be conducted on 2 days, at least 24 hours (approximately), but not more than 7 days apart.

7.2.7 Grip Strength Test

Hand grip strength will 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 on the same day for each time point.

Every effort will be made to use the same dynamometer for a patient throughout the duration of the study.

At the 9-month, 18-month, and Early Withdrawal visits, the assessments will be conducted on 2 days, at least 24 hours (approximately), but not more than 7 days apart.

7.2.8 Composite Autonomic Symptom Score

To evaluate changes in autonomic symptoms, patients will complete the COMPASS-31 questionnaire. The questionnaire consists of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, secretomotor, gastrointestinal, bladder, and pupillomotor).[46]

7.2.9 Norfolk Quality of Life - Diabetic Neuropathy Questionnaire

Quality of life will be assessed through the Norfolk 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.[47]

7.2.10 EuroQoL Quality of Life Questionnaire

Quality of life will be assessed through the use of the EQ-5D, a standardized 5-question instrument for use as a measure of health outcomes.[48]

7.2.11 Rasch-built Overall Disability Scale

An assessment of the disability each patient experiences will be assessed through the R-ODS.[49] The R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

7.2.12 Echocardiogram and Biomarkers of Cardiac Function

Cardiac structure and function will be assessed through echocardiograms as well as measurement of serum levels of the cardiac biomarkers NT-proBNP and troponin I.

Echocardiograms will be performed at the time points specified in Table 1-1, Table 1-2, and Table 1-3 and interpreted at a central echocardiography core lab. 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 at the time points specified in Table 1-1, Table 1-2, and Table 1-3. Details on sample collection, processing, and storage will be provided in a Study Laboratory Manual.

7.3 Pharmacodynamic Assessments

Pharmacodynamic sample collection, processing, and storage guidelines will be provided in a Study Laboratory Manual.

7.3.1 Transthyretin

Blood for serum TTR levels will be collected at the Baseline visit and prior to the administration of study drug at the time points specified in Table 1-1, Table 1-2, and Table 1-3.

Serum TTR will be assessed using both ELISA (enzyme linked immunosorbent assay) and turbidimetric assays.

7.3.2 Retinol Binding Protein

Blood for serum RBP levels will be collected at the Baseline visit and prior to the administration of study drug at the time points specified in Table 1-1, Table 1-2, and Table 1-3.

Serum RBP will be quantified using nephelometry.

7.3.3 Vitamin A

Blood for serum vitamin A levels will be collected at the Baseline visit and prior to the administration of study drug at the time points specified in Table 1-1, Table 1-2, and Table 1-3. Supplemental vitamin A will be taken at the time points specified in Table 1-1, Table 1-2, and Table 1-3.

7.3.4 Exploratory Biomarkers

To explore the expression of hepatocyte derived proteins to further characterize the biological effects of siRNA and/ or to explore possible metabolite profiling of patisiran (ALN-TTR02), serum and plasma samples will be collected at the time points specified in Table 1-1, Table 1-2, and Table 1-3.

Details on biomarker sample collection, processing, and storage will be provided in a Laboratory Manual.

Biological samples for biomarker research and possible metabolic profiling can be retained on behalf of Alnylam for a maximum of 15 years following the last patient's last visit in the study.

7.4 Pharmacokinetic Evaluations

Details on PK sample collection, processing, and storage will be provided in a Laboratory Manual. Plasma and urine samples will be evaluated using a validated ATTO-Probe-HPLC (high performance liquid chromatography) assay to determine siRNA concentration and by LC/MS/MS for DLin-MC3-DMA and PEG_{2000}-C-DMG concentrations.

7.4.1 Plasma Pharmacokinetics

Plasma samples will be collected at the time points shown in Table 1-1, Table 1-2, and Table 1-3 for assessment of siRNA, DLin-MC3-DMA and PEG_{2000}-C-DMG. PK parameters, including population PK will be analyzed, whenever possible as outlined in Section 9.2.6.

7.4.2 Urine Pharmacokinetics

Urine samples and urine volume void will be obtained at specified time points as specified in Table 1-1, Table 1-2, and Table 1-3. Renal clearance (CL_R) will be determined whenever possible for siRNA and 4-dimethylaminobuttyric acid, metabolite of DLin-MC3-DMA, excreted in the urine. PK parameters will be analyzed, whenever possible, as outlined in Section 9.2.6.

7.5 Safety Assessments

All safety assessment measures will be recorded in the patient's medical record and CRF.

7.5.1 Physical Examination

A complete physical examination (including general appearance; head, ears, eyes, nose, and throat [HEENT]; cardiovascular; dermatologic; abdominal; genito-urinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological) is to be at the study visits listed in Table 1-1, Table 1-2, and Table 1-3.

7.5.2 Body Weight and Height

Body weight will be measured at the study visits listed in Table 1-1, Table 1-2, and Table 1-3. The rules for using body weight to calculate dose are described in Section 5.3.2.

Height will only be measured at Screening.

7.5.3 Vital Signs

Vital signs will be measured at the time points specified in Table 1-1, Table 1-2, and Table 1-3. Vital signs include systolic/diastolic blood pressure, pulse rate, respiratory rate, and 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 or Fahrenheit. 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 added at the discretion of the Investigator.

7.5.4 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained in triplicate at each time point listed in Table 1-1, Table 1-2, and Table 1-3 and read locally by a cardiologist or qualified physician. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/s.

The following electrophysiologic parameters will be assessed: rhythm, ventricular rate, PR interval, QRS duration, and QT interval. If the ECG machine does not calculate the

heart rate corrected QT interval (QTc), either Bazett's and/or Fridericia's formula will be used to calculate the QTc.

For any clinically significant abnormal results, the Investigator must contact the CRO Medical Monitor to discuss continued participation of the patient in the study (e.g., ischemic ECG changes, wave/interval changes, or arrhythmia).

7.5.5 Clinical Laboratory Tests

Blood samples for clinical laboratory testing will be collected prior to study drug dosing at the time points listed in Table 1-1, Table 1-2, and Table 1-3. 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 study drug administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality.

The following clinical laboratory parameters are to be determined:

Hematology	
• Hematocrit	• Neutrophils, absolute and %
• Hemoglobin	• Lymphocytes, absolute and %
• Red blood cell (RBC) count	• Monocytes, absolute and %
• White blood cell (WBC) count	• Eosinophils, absolute and %
• Mean corpuscular volume	• Basophils, absolute and %
• Mean corpuscular hemoglobin	• Platelet count
• Mean corpuscular hemoglobin concentration	
Serum Chemistries	
• Aspartate transaminase (AST)	• Alkaline phosphatase
• Alanine transaminase (ALT)	• Bilirubin (total and direct)
• Sodium	• Glucose
• Potassium	• Phosphate
• Blood urea nitrogen (BUN)	• Albumin
• Creatinine	• Calcium

Coagulation Studies
• Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) • International Normalized Ratio (INR)
Thyroid Function Tests
• Thyroid stimulating hormone (TSH) • Thyroxine (Free T4) • Triiodothyronine (Free T3)
Anti-drug Antibodies
• Anti-PEG antibodies
Urinalysis
• Visual inspection for color and appearance • pH • Specific gravity • Ketones • Protein • Glucose • Leukocytes • Bilirubin • Nitrite • Urobilinogen • Microscopic inspection of sediment
Serology
• Hepatitis B surface antibody (HbsAb) • Hepatitis B surface antigen (HbsAg) • Anti–hepatitis C virus antibody (anti-HCVAb)
Cardiac Biomarkers
• N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) • Troponin I
Other
• β-human chorionic gonadotropin (women of child-bearing potential only; may be a urine- or serum-based test)
• Vitamin B12
• Paraprotein by IFE

7.5.5.1 Pregnancy Test

The pregnancy test may be urine- or serum-based, at the discretion of the Investigator. The test will only be performed for women of child-bearing potential. The timing of the tests is specified in Table 1-1, Table 1-2, and Table 1-3; additional testing may be done any time pregnancy is suspected. The results must be known prior to administration of

study drug. Patients who are pregnant are not eligible for study participation. Patients who become pregnant while on study will be followed until the pregnancy outcome is known (see Section 8.12).

7.5.6 Ophthalmology Examination

The timing of the ophthalmology examinations is specified in Section 6.2.2 and in Table 1-1 and Table 1-2. These examinations will be performed at a CAS and will include assessment of visual acuity, slit-lamp evaluation, intraocular pressure, dilated indirect ophthalmoscopy, color fundus photography, visual field, and electroretinography (ERG). Visual acuity should be evaluated at the beginning of each specified visit in the study (i.e., prior to slit-lamp examination). Manifest refraction will be performed at each specified visit prior to 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. ERG evaluations will be centrally read.

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

7.5.7 Adverse Events and Study-Procedure-Related Adverse Events

Adverse events will be assessed and recorded at the time points specified in Table 1-1, Table 1-2, and Table 1-3.

As shown in Table 1-3, only study-procedure-related AEs (e.g., skin-biopsy-related AE, venipuncture-related AE) will be collected after Day 294 for patients who meet the criteria for Rapid Disease Progression at Month 9 and receive their last dose of study drug on Day 252 but remain on the study.

Section 8 provides assessment and reporting guidelines.

7.5.8 Concomitant Medications and Treatments

Use of all concomitant medications and treatments will be recorded on the patient's CRF through the time points shown in Table 1-1, Table 1-2, and Table 1-3. This will include all prescription drugs, herbal preparations, OTC medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the CRF. Section 5.8 provides guidelines on concomitant medications and treatments.

7.6 Other Assessments

7.6.1 Pharmacoeconomics Questionnaire

The burden of disease and healthcare utilization will be assessed using a patient-reported, 21-question pharmacoeconomics questionnaire. This assessment will be performed at a CAS.

7.6.2 Suicidality Questionnaire

The Columbia–Suicide Severity Rating Scale (C-SSRS) will be used to assess patient's mental status as it relates to suicidal ideation and behavior.[50] This questionnaire will be administered to the patient by trained study personnel.

7.6.3 Phone Contact for Health Status Update and FAP Treatment

Patients following the Modified Schedule of Assessments will be called on the telephone by study personnel at the time points specified in Table 1-3. Patients will be asked about their general health status and any treatments they may have received for FAP.

8 REPORTING ADVERSE EVENTS

8.1 Adverse Event Definition

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.

All IRRs will be recorded as AEs.

For patients who meet the criteria for rapid disease progression at Month 9 and receive their last dose of study drug on Day 252 but remain on the study, AEs will be followed through Day 294. Following Day 294, only study-procedure-related AEs will be collected (e.g., skin-biopsy-related AE, venipuncture-related AE).

8.2 Serious Adverse Event Definition

An 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 (e.g., such events include allergic bronchospasm, blood dyscrasias or convulsions, or the development of drug dependency or abuse).

8.3 Eliciting Adverse Event Information

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, ECG changes, or other findings.

8.4 Adverse Event Reporting

The Investigator is responsible for reporting all AEs that are observed or reported after the first dose of study drug regardless of their relationship to study drug through until the end of the reporting periods defined in Section 8.5. For patients who meet the criteria for Rapid Disease Progression at Month 9 and receive their last dose of study drug on Day 252 but remain on the study, AEs will be followed through Day 294. Following Day 294, only study-procedure-related AEs will be collected (e.g., skin-biopsy-related AE, venipuncture-related AE).

Any medical condition that is present when a patient is screened 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 until the end of the reporting periods defined in Section 8.5 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 at 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.

8.5 Adverse Event Reporting Period

AEs and SAEs will be reported according to the following timeframes:

- For patients who complete the study, AEs will be assessed through the End of Study visit on Day 567 or the Follow-up visit on Day 602 (depending whether or not the patient plans to roll over to the open-label extension study). All AEs that occur after the start of study drug administration on Day 0 must be reported in detail on the appropriate CRF page and followed to satisfactory resolution, or through the end of study visit on Day 567 or Day 602 (depending whether or not the patient plans to roll over to the open label extension study) after the last dose of study drug administration. SAEs will be followed through the end of study visit on Day 567 or Day 602 (depending whether or not the patient plans to roll over to the open label extension study), or until satisfactory resolution, or until the SAE is considered by the Investigator to be chronic or the patient is stable, whichever occurs first.
- For patients who meet the criteria for Rapid Disease Progression at Month 9 and receive their last dose of study drug on Day 252 but remain on the study, AEs will be followed through Day 294. Following Day 294, only study-procedure-related AEs will be collected (e.g., skin-biopsy-related AE, venipuncture-related AE). SAEs will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable.

- 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.

8.6 Assessment of Causality

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.

8.7 Assessment of Severity

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).

8.8 Action Taken for Adverse Event

Action taken in regards to study drug will be defined as:

- None;
- Infusion interrupted and restarted at a later time;
- Infusion stopped and was not restarted at a later time;
- Infusion cycle delayed.

8.9 Outcome of Adverse Event

Outcome will be defined as:

- Resolved (with or without sequelae);
- Ongoing;
- Lost to follow-up.

8.10 Coding of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA®) will be used to code AEs.

8.11 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 8.2) 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 study drug.

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 to study drug.

SAE reporting will be via electronic data capture (EDC).

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] or call the [redacted] SAE hotline (phone number will be provided in the Study Manual), and fax the completed back-up paper SAE form to [redacted] (fax number will be provided in the Study Manual) within

24 hours of awareness. When the EDC system becomes available, the SAE information must be entered into the EDC system within 24 hours of the system becoming available. [redacted] Safety personnel will be available for SAE reporting on a 24-hour basis. Incoming reports will be reviewed during normal business hours.

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 (e.g., patient discharge summary or autopsy reports) to [redacted] 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 relationship to study drug, 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 independent ethics committee (IEC) or Institutional Review Board (IRB) when required by national regulations.

Alnylam 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 Alnylam 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 Alnylam or its representative has first knowledge of them.

The Investigator may be informed by Alnylam 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 Alnylam as part of the TMF on study completion.

8.12 Pregnancy Reporting

A female patient with a positive pregnancy test at Screening is ineligible for 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 study drug, 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. 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 (i.e., 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.

9 STATISTICAL METHODS

9.1 Sample Size

Approximately 200 patients will be enrolled in this study. Of those 200 patients, no more than 40 patients will have a NIS range of 101 to 130. An mNIS+7progression rate (primary endpoint) in the placebo group of 24 ± 16 points in 18 months was estimated using natural history data from FAP patients. A sample of 154 patients provides 90% power for a 2-sided test with an 8.95 point (37.5%) mean difference between treatment groups in the primary endpoint at 2-sided alpha = 0.05. Assuming a 25% random premature discontinuation rate (due to liver transplantation or other factors), the sample size for this study is approximately 200. Additional patients may be enrolled based on a recommendation to increase the sample size in the interim analysis.

9.2 Statistical Methodology

A full statistical analysis plan will be finalized prior to database lock.

9.2.1 Populations to be Analyzed

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

- Modified ITT (mITT) population: All patients who were randomized and received at least 1 dose of study drug;
- Per protocol (PP) population: All patients who completed the 18-month efficacy assessment visit and did not have any major protocol violations;
- Safety population: All patients who received at least 1 dose of study drug (analyzed as treated, not as randomized).

The primary population for efficacy analyses will be the mITT population; key efficacy results will also be analyzed secondarily for the PP population. For efficacy analyses, patients will be grouped according to the treatment to which they were randomized. The primary population for safety analysis will be the safety population. Patients will be grouped according to treatment received for summaries of safety.

9.2.2 Baseline Evaluations

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

9.2.3 Efficacy Analyses

9.2.3.1 Primary Efficacy Endpoint

The primary analysis will compare change in mNIS+7 from baseline between treatment groups of the mITT population. An analysis of covariance (ANCOVA) model, with baseline mNIS+7 value and age as continuous covariates and genotype (V30M vs Non-V30M), prior tetramer stabilizer (tafamidis or diflunisal) use (Yes vs No), and treatment group (patisiran [ALN-TTR02] vs Placebo) as factors will be employed to analyze the primary mNIS+7 endpoint. The mNIS+7 change from baseline will be assessed at 78 weeks. Primary endpoint data that are missing will be inferred using multiple

imputation (MI) (see Section 9.2.10). Analyses will be conducted using PROC MI and PROC MIANALYZE in SAS 9.2 (or later). The efficacy of patisiran will have been established if the estimate of the parameter associated with treatment variable demonstrates that patisiran improves mNIS+7 relative to placebo with a p-value (2-sided) less than or equal to 0.05, based on the MI methodology.

Sensitivity analyses will assess the robustness of the primary analysis in the mITT and PP populations for different methods of handling missing data, including mixed model repeated measures (MMRM), complete cases (CC), and last observation carried forward (LOCF).

9.2.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed using methods similar to those employed for the primary analysis, e.g. ANCOVA with multiple imputations, as appropriate.

Type I error control for secondary endpoints will be achieved by a hierarchical ordering procedure. Endpoints will be tested in the following prespecified hierarchy:

- Norfolk QOL-DN questionnaire;
- NIS-W score;
- mBMI;
- Timed 10-meter walk test;
- COMPASS-31.

If and only if a comparison is significant at $p<0.05$, the next endpoint in the hierarchy may be tested.

9.2.3.3 Exploratory Efficacy Endpoints

Continuous exploratory efficacy variables, including those closely related to the mNIS+7 primary endpoint, may be compared using methods similar to those employed for the primary analysis, e.g. ANCOVA with multiple imputations, as appropriate. Binary secondary endpoints will be assessed by the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors.

9.2.4 Safety Analyses

A summary of study drug exposure, 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 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. 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.

Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Details of any abnormalities will be included in patient listings.

9.2.5 Pharmacodynamics

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. Similar analyses will be performed for the secondary PD biomarkers (RBP and vitamin A).

9.2.6 Pharmacokinetics

Pharmacokinetic analyses will be conducted using non-compartmental and/or compartmental evaluation. Whenever possible, the PK parameters of siRNA, DLin-MC3-DMA, and PEG_{2000}-DMG (lipid) in sparse plasma samples collected from all patients. PK parameters will be calculated using a validated version of WinNonlin® Enterprise (Version 5.2 or higher) with NCA Model 200.

Population PK analyses, will be performed whenever possible, on available siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG from sparse plasma samples obtained from all patients during the duration of the study using Phoenix NLME (Version 1.1 or later). Summary tables and figures and inferential statistics will be generated with Phoenix NLME (Version 1.1 or later) or similar software.

Pharmacokinetic/PD analysis will be conducted whenever possible, of sparse plasma samples collected during the study period. The analysis will include, but not limited to, the determination of the relationship between exposure to siRNA, DLin-MC3-DMA, and PEG_{2000}-C-DMG and the extent of suppression of TTR, RBP, and vitamin A and their correlation will be evaluated. Correlation between TTR versus RBP and vitamin A will also be performed. The strength of the relationship will be assessed using statistical estimators. As part of the PK/PD analysis, additional PD baseline analysis on serum TTR, RBP, and vitamin A may be conducted to include the PD data obtained post-PD recovery period. The PD and PK/PD analysis will be performed with WinNonLin or Phoenix NLME (Version 1.1 or later) or similar software. The PD and PK/PD parameters summary tables and figures and inferential statistics will be generated and will not be limited to descriptive statistics.

9.2.7 Summary of Efficacy Assessments

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 (e.g., the NIS weakness and reflex scores, the NCS Σ5, and QST values). The NIS+7 score, including its components (e.g. full NIS, HRdb, VDT) will also be summarized.

Patient reported quality of life and disability will be assessed by summary statistics for the Norfolk QOL-DN, EQ-5D, 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), and ambulation (FAP stage and PND score). Descriptive statistics will also be provided for proportions of patients in each group that meet the rapid progression definition at 9 months and those that meet the responder criterion at 18 months.

9.2.8 Other Assessments

The observed values and changes from baseline in burden of disease and healthcare utilization will be evaluated and summarized using descriptive statistics. Data on suicidality will be summarized by treatment group using descriptive statistics.

9.2.9 Interim Analysis

Because the sample size estimates are based on limited data for variance and disease progression, it is intended that an interim analysis will be conducted by an independent committee when approximately 50% of patients have completed their 9-month mNIS+7 assessment. This interim analysis will be blinded and will only estimate the overall variance observed in the primary endpoint. Since the interim analysis examines only the pooled variance of all patients in a blinded fashion, it does not require an adjustment to the overall alpha level for the test of the primary endpoint. Based on the results of the interim analysis, the committee can recommend either increasing the study size or making no adjustment to the sample size. Details regarding the Interim Analysis Committee are provided in Section 10.3.3.

9.2.10 Missing Data

Patients who discontinue due to rapid disease progression will have their 78-week mNIS+7 change from baseline value imputed using a stepwise regression approach for identification of explanatory variables (e.g., demographics, stratifying variables, and baseline/9-month mNIS+7 data when available); treatment assignment will not be included in the imputation. Imputed datasets will then be analyzed as complete cases via the ANCOVA model specified for the primary analysis, and then combined to produce inferential results. Further details on imputations and sensitivity analyses will be included in the SAP that will be finalized before database lock.

10 STUDY MANAGEMENT

The Investigator is accountable for the conduct of the study. If any responsibilities are delegated, the Investigator should maintain a list of appropriately qualified staff to whom he/she has delegated specified significant trial related duties.

10.1 Data Handling and Quality Assurance

10.1.1 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.

Alnylam 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 Alnylam 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 Alnylam. A copy of the CRF will remain in the Investigator's files.

10.1.2 Monitoring

The clinical monitor, as a representative of Alnylam, has an obligation to follow the study closely. In doing so, the monitor will visit the Investigators and sites periodically as well as 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 Alnylam or its designee for compliance with applicable government regulations in respect to Good Clinical Practice (GCP) and current standard operating procedures.

10.1.3 Inspections

The Investigator will permit trial-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 Alnylam 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 Alnylam, representatives from Alnylam, or regulatory agencies access to all study records.

10.2 Regulatory Guidelines

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 Health Organization (WHO)

Declaration of Helsinki, the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), and all other applicable medical privacy laws and regulations.

10.2.1 Institutional Review Board/Independent Ethics Committee

National regulations and 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, ICFs, advertisements to be used for patient recruitment, 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 (e.g., 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.

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

10.2.2 Regulatory Authorities

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

10.2.3 Modification of the Protocol

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by Alnylam 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 prior to patients being enrolled under the amended protocol.

10.2.4 Informed Consent Form

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

Alnylam 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 Alnylam 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 Alnylam. Revisions to the ICF required during the study must be agreed upon, and a copy of the revised ICF provided to Alnylam.

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 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.

10.2.5 Study Reporting Requirements

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 Alnylam 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.

10.2.6 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.

10.3 Study Committees

10.3.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be involved in the conduct of this study. The DMC has the responsibility for monitoring the progress of the clinical study and the safety of the study participants. The DMC will perform periodic reviews of data and study conduct during the course of the clinical trial, as defined in the DMC Charter for this clinical trial. The membership of the DMC and reporting structure are defined in the DMC Charter.

10.3.2 Clinical Adjudication Committee

An independent clinical adjudication committee will perform a blinded adjudication of the results of those patients who have clinical evidence of rapid disease progression (defined as ≥24 point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP stage progression relative to baseline) at 9 months. Each review will follow procedures detailed in the committee's charter.

10.3.3 Interim Analysis Committee

An Interim Analysis Committee (IAC), comprised of 2 statisticians (1 blinded and 1 unblinded) independent of the conduct of the study, will be responsible for the

implementation of the interim analysis and for the calculations and recommendations surrounding whether an adjustment to the sample size is warranted, and if so, the appropriate adjustment, based on the study's primary endpoint data from the interim analysis. The Sponsor, the CROs, and all other parties conducting the study will remain blinded to all interim analyses until study completion. The IAC will follow the procedure outlined in the committee's charter.

10.4 Ancillary Research

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

10.5 Study Record Retention

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 Curriculum Vitae (CVs) 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 Alnylam in writing and giving Alnylam the opportunity to store the records for a longer period of time at Alnylam's expense.

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

10.6 Discontinuation of the Study by Alnylam

Alnylam reserves the right to discontinue the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, the study may be discontinued at that site. Should the study be terminated and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to Alnylam or its representative, and the Investigators, IEC/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.

10.7 Study Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6 and 21 CFR by providing at least the following essential documents:

- An original signed Investigator agreement page of the protocol and any amendments;
- An IEC/IRB and Alnylam approved ICF;
- IEC/IRB approval of the protocol, and any amendments;
- Completed and signed FDA form 1572;
- Curriculum vitae for the Investigator signed and dated by the Investigator indicating that it is current;
- Financial disclosure information (if applicable);

- Other documents which the Investigator should provide before study start include:
    - Curriculum vitae for all Sub-investigators; these should be signed and dated by the Sub-investigators indicating that they are current;
    - Financial disclosure information for all Sub-investigators (if applicable);
    - Advertisements for patient recruitment and any other written information to be given to patients, family members or legal guardians and IEC/IRB approval of any advertisements and any other written information;
    - IEC/IRB composition: If the Investigator or any of the Sub-investigators is a member of the IEC/IRB, assurance that he/she refrained from voting should be provided;
    - Laboratory accreditation and reference ranges for any laboratory values for local laboratories.

10.8 Confidentiality

The Investigator must ensure that the patients' anonymity will be maintained. On the CRFs or other documents submitted to Alnylam 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 Alnylam or designees, the names (except for initials) will be obliterated and the assigned patient number added to the document. Documents not for submission to Alnylam (e.g. signed ICFs) should be maintained by the Investigator in strict confidence.

Following the principles of the Good Clinical Practice, 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 Alnylam, thereby allowing no unwarranted access to the information. When reporting results for interim safety assessment, the interim analysis, and at the end of the study, the code will be shared per standard operating procedures with the responsible member of the Biostatistical and Data Management Departments of the CRO. The numbering code will also be held for samples in storage until marketing approval of patisiran (ALN-TTR02) 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. Alnylam must approve any transfer of information not directly involved in the study.

10.9 Publications/Reports

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 Alnylam at least 30 days prior to its submission.

No submission of a manuscript may be made until the results from all of the study sites have been received and analyzed by Alnylam, 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 Alnylam confirms receipt of the manuscript 30 days prior to submission.

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12 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 (e.g., IV fluids, nonsteroidal anti-inflammatory [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 SNAP/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.

ALN-TTR02-004
APOLLO Global Protocol Amendment Summary
Version 4.0 – 30 January 2017

Protocol Version No.	Date	Summary of Changes
1.0 (Original)	15 August 2013	N/A

2.0	18 October 2013	• Secondary endpoints reordered and methods of analysis were modified
		  ○ EuroQOL questionnaire was made an exploratory endpoint
		  ○ Removal of the analysis by families
		• Clarification that study personnel performing the efficacy assessments will remain blinded to the results of any previous assessment until the study has been completed
		• Change of the schedule of assessments in tables 1-1,1-2, and 1-3 and Sections 6.1.1, 6.1.2, and 6.1.3
		• Inclusion criteria modified to allow an INR of ≤3 only for patients on warfarin
		• Definition of "highly effective birth control" was clarified in Section 4.7
		• Premedication regimen was modified to reflect those used in earlier trials of ALN-TTR02
		• Addition that either Bazett's or Friderica's correction may be used in the case that an ECG machine does not calculate QTc
		• Description of the pharmacoeconomics questionnaire was corrected to reflect the inclusion of 21, rather than 16, questions

3.0	21 March 2014	• Additional clarification that entry criteria, besides Inclusion Criteria #3 [Have a NIS of 10 to 100 (inclusive)] and #4 [[redacted]], will be assessed at the Screening Visit only • Inclusion Criterion #1 [Male or female of 18 to 80 years of age (inclusive)] modified to allow for enrollment of subjects up to 85 years of age (inclusive) • Lower limit of the Neuropathy Impairment Score (NIS) from 10 to 5 in Inclusion Criterion #3 [Have a NIS of 10 to 100 (inclusive)] • Inclusion Criterion #4 [redacted] • Inclusion Criterion #6 [Have an absolute neutrophil count (ANC) ≥1500 cells/mm³, a platelet count ≥100,000 cells/mm³, and hemoglobin ≥10 g/dL (or ≥100 g/L)] modified from a platelet count of ≥ 100,000 cells/mm^3 to ≥50000 cells/mm^3 • Inclusion Criterion #7 [Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), total bilirubin within normal limits, albumin >3 g/dL (or >30 g/L), international normalized ratio (INR) ≤1.2 (patients on warfarin with an INR of ≤3 will be allowed)] modified to increase INR value from ≤3 to ≤3.5 • Exclusion Criterion #1 [Has vitamin A levels below the lower limit of normal (LLN)] was clarified to exclude patients with vitamin A levels consistent with vitamin A deficiency (ie, <20µg/dL) • Exclusion Criterion #18 was removed ([Participated in a clinical trial with an antisense oligonucleotide for more than 3 months; if in a clinical trial with antisense oligonucleotide for ≤3 months, must have completed a 3‑month wash-out prior to start of study drug administration in this study] • Diflusinal was removed from Exclusion Criterion #19 [Is currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to start of study drug administration in this study] and added as new Exclusion Criterion #20 [Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to start of study drug administration in this study] to clarify that a 3-day washout period prior to start of study drug for this particular agent is sufficient for that agent

Protocol Version No.	Date	Summary of Changes
4.0	24 April 2014	• The screening window was expanded from 28 days to 42 days to make it less restrictive for traveling patients. • *Corrected typographical errors identified in the SOA in version 3.0*
5.0	04 August 2014	• Inclusion Criterion #3 [Have an NIS of 5 to 100 (inclusive) (Note: This criterion must be met at the Screening/Baseline Visit)] changed to the upper limit NIS from 100 to 130 and added requirement for a Polyneuropathy Disability (PND) score of ≤3b. • Inclusion Criterion #7 [Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), total bilirubin within normal limits, albumin >3 g/dL (or >30 g/L), international normalized ratio (INR) ≤1.2 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)] modified to remove albumin criterion and to increase INR criterion from ≤1.2 to ≤2.0 • Inclusion Criterion #8 [Have a serum creatinine ≤1.5 × ULN] modified from serum creatinine ≤1.5 to ≤2 × ULN • Inclusion Criterion #9 [Have negative serology for hepatitis B virus (HBV) and hepatitis C virus (HCV] clarified to exclude only patients with an active hepatitis B or hepatitis C infection • Inclusion Criterion #10 [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 screening, throughout study participation, and for 1 month after last dose of study drug. Highly effective methods of birth control are defined in Section 4.7] modified to extend the period from 1 month to 75 days after last dose of study drug for WOCBP • Inclusion Criterion #11 [Males with partners of child-bearing potential, must agree to use 1 barrier method (e.g., condom) and 1 additional method (e.g., spermicide) of contraception throughout study participation and for 1 month after the last dose of study drug; males must also abstain from sperm donation after the first dose of study drug through study participation and for 1 month after last dose of study drug] modified to extend the period that males with partners of child-bearing potential must use 1 barrier method and 1 additional method of contraception from 1 month to 75 days after the last dose of study drug • Exclusion Criterion #1 [Has vitamin A levels consistent with vitamin A deficiency (<20 µg/dL)] removed • Exclusion Criterion #16 [Has a known history of alcohol abuse or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer])] clarified to patients with a history of alcohol abuse within the past 2 years or daily heavy alcohol consumption • Exclusion Criterion #17 [Participated in a clinical trial with antisense oligonucleotide, must have completed a 3-month wash-out prior to start of the study drug administration in this study] added to exclude patients who participated in a clinical trial with antisense oligonucleotide unless there is a 3 month wash-out period • Exclusion Criterion #24 [Is under legal protection] modified to define “under legal protection” • The protocol has been modified to permit select changes to the premedication regimen for an individual having difficulty tolerating the premedication regimen only after consultation with the study medical monitors. • The sample size was modified to limit the number of patients with a Neuropathy Impairment Score (NIS) in the range of 101 to 130 to no more than 40 of the 200 planned patients to prevent overenrolling patients with more severe impairment.

Protocol Version No.	Date	Summary of Changes
6.0	08 September 2015	• Implemented a reduced dose of dexamethasone for the protocol-specified premedication regimen • Included that specified patients who are intolerant of 10 mg IV dexamethasone or equivalent on the day of infusion may be considered for further step-wise reduction in dexamethasone or equivalent after consultation with the medical monitor • The risk benefit assessment has been updated to reflect liver function test abnormalities and risk for osteoporosis • Because patients may be at risk for osteoporosis, it has been added that, if appropriate, study participants should receive therapy for the prevention and early treatment of osteoporosis • Inclusion #4 [redacted] Note: This criterion must be met at the Screening/Baseline visit)] added ulnar SNAP and ulnar CAP measurements to the qualifying NCS • Inclusion #7 [Have aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤2.5 × the upper limit of normal (ULN), total bilirubin within normal limits, international normalized ratio (INR) ≤2.0 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)] changed to permit patients with a total bilirubin level elevation to ≤ 2 x upper limit of normal to enroll • Exclusion #14 [Has uncontrolled clinically significant cardiac arrhythmia or unstable angina] changed to include clarification that patients with any uncontrolled cardiac arrhythmia or unstable angina are not permitted to enroll in the study • Included the option for patients to permanently discontinue study treatment and remain on-study • Provided clarification about local personnel responsible for reading ECGs to include that ECGs will be read locally by a cardiologist or qualified physician