REVUSIRAN

ALN-TTRSC-005

AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REVUSIRAN IN PATIENTS WITH TRANSTHYRETIN-MEDIATED FAMILIAL AMYLOIDOTIC POLYNEUROPATHY WITH DISEASE PROGRESSION POST-ORTHOTOPIC LIVER TRANSPLANT

Original Protocol:	12 June 2015
Protocol Amendment 1 (Sweden):	19 August 2015
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EUDRACT Number:	2015-002603-29
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Sponsor Contact:	[redacted] Senior Vice President, Clinical Development

Signature

Date

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.

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTRSC-005 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

STUDY SYNOPSIS

Name of Sponsor: Alnylam Pharmaceuticals, Inc.

Name of Investigational Product: Revusiran (ALN-TTRSC)

Name of Active Ingredient: ALN- 51547

Title of Study: An Open-label Study to Evaluate the Efficacy and Safety of Revusiran in Patients with Transthyretin-mediated Familial Amyloidotic Polyneuropathy with Disease Progression Post-Orthotopic Liver Transplant

Study center(s): It is anticipated that approximately 5 clinical study centers will participate in this study.

Objectives:

Primary:

- Assess the efficacy of revusiran in patients with Transthyretin (TTR) -mediated Familial Amyloidotic Polyneuropathy (FAP) with disease progression post-orthotopic liver transplant (OLT) by evaluating the reduction in serum TTR level compared to baseline

Secondary:

- Evaluate the safety and tolerability of revusiran when administered to TTR-mediated FAP patients with disease progression post-OLT
- Characterize the pharmacokinetics (PK) of revusiran
- Describe the effect of revusiran on neurologic impairment

Exploratory:

- Evaluate the effect of revusiran on various clinical activity parameters including quality of life, disease stage, modified body mass index (mBMI), and cardiac function

Methodology:

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, and PK of subcutaneously administered revusiran in patients with FAP with disease progression post-OLT.

Eligible, consenting patients will receive 5 daily doses of revusiran (Days 0 through 4) and a dose at Day 7, followed by once weekly doses for the duration of the study.

Visits will be held at the clinical study center for Screening, Screening/Baseline, and Baseline, and Daily Dosing (Days 0 through 4) as well as each month for the first 3 months, and approximately every 3 months through Month 18 (or Early Termination), and at the End of Study (approximately 28 days after last dose). The remaining study visits may be conducted at the clinical study center or in the patient's home.

The primary objective of the study will be evaluated by the collection of serum samples for the measurement of total TTR levels. After screening and baseline measurements, TTR will be assessed on a monthly basis for 3 months, approximately every 3 months, thereafter, and at ET.

Adverse events will be collected throughout the treatment period and at the End of Study visit.

An independent Data Monitoring Committee will be implemented for the study and will operate under a prespecified charter.

Number of Patients (planned): Approximately 12 patients will be enrolled in the study

Diagnosis and eligibility criteria:

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Male or female ≥18 years of age
2. Diagnosis of FAP with documented TTR mutation
3. Received an OLT ≥12 months before the date of informed consent
4. An increase in polyneuropathy disability (PND) score (eg, a PND change from 1 to 2 or 3a to 3b) compared to a preliver transplant assessment OR increase in PND score between any 2 assessments postliver transplant, which in the opinion of the Investigator is due to underlying FAP progression
5. On stable immunosuppressive regimen with ≤10 mg/day of prednisone for at least 3 months before the date of informed consent
6. Neurological impairment score (NIS) of 5 to 130 (inclusive)
7. Polyneuropathy Disability score of ≤3b
8. Karnofsky Performance Status ≥60%
9. No liver allograft rejection episodes (chronic, acute, or subacute) in the past 6 months before the date of informed consent
10. Normal liver function, including aspartate transaminase, alanine transaminase, and total bilirubin (≤ upper limit of normal), unless elevation in total bilirubin is due to Gilbert's Syndrome based on central laboratory evaluation
11. Adequate renal function demonstrated by estimated glomerular filtration rate ≥45 mL/min/1.73 m^2 (calculated by a central laboratory using the Modification of Diet in Renal Disease formula)
12. Women of child-bearing potential must have a negative pregnancy test, cannot be breastfeeding, and use 1 highly effective method of contraception in combination with a barrier method throughout study participation, and for 28 days after last dose of study drug
13. Males with partners of child-bearing potential, must agree to use a condom, accompanied with spermicidal foam, gel, film, cream, or suppository, except in countries where spermicide is not available for use in combination with condom, throughout study participation and for 28 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 28 days after the last dose of study drug
14. Patient, or patient's legal representative, is able and willing to provide written informed consent and the patient is willing to comply with the study requirements

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Untreated hypo- or hyperthyroidism
2. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed before the first dose of study drug administration

3. Active infection with hepatitis B or hepatitis C (based on serology)
4. Known human immunodeficiency virus infection
5. New York Heart Association (NYHA) classification of >2
6. Known leptomeningeal amyloidosis
7. Other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease)
8. Known type I diabetes
9. Type II diabetes mellitus for ≥5 years from the time of informed consent
10. Vitamin B12 levels below the lower limit of normal
11. Current, heavy alcohol use, defined as regular consumption of greater than 2 to 3 units/day for women and 3 to 4 units/day for men (a unit of alcohol equals 1 glass of wine [125 mL], 1 measure of spirits, or ½ pint of beer), or a known history of alcohol abuse within the last 2 years from the time of informed consent
12. Received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the study drug, whichever is longer
13. Currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day washout before start of study drug administration in this study
14. Malignancy within the last 2 years from the time of informed consent, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
15. History of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc)
16. History of intolerance to subcutaneous (SC) injection
17. Other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation

Investigational product, dosage, and mode of administration:

Revusiran is comprised of a small interfering RNA targeting mutant and wild-type TTR messenger ribonucleic acid with a covalently-attached triantennary GalNAc ligand formulated in water for injection.

Beginning on Day 0, patients will receive 5 daily SC doses of 500 mg of revusiran administered as 2 injections. The same dose will be administered at Day 7 and then weekly from Week 2 through 18 months. Study drug will be administered at the clinical study center on Days 0 through 4 by qualified clinical study center staff under the supervision of the Investigator or designee. After Day 4, study drug may be administered at home by a healthcare professional trained in the administration of study drug or at the clinical study center. At the discretion of the Investigator, after the Month 6 dosing visit, patients/caregivers may be trained by the Investigator or qualified clinical study center staff in the administration of the study drug, according to the protocol dosing requirements.

Duration of treatment: The time on study for each patient is approximately 21 months (inclusive of a 42-day screening period and a follow-up visit 28 days after the last dose of study drug). The duration of treatment is 18 months.

Reference therapy, dosage, and mode of administration: N/A

Efficacy and Clinical Activity Endpoints:

Primary Endpoint

The primary endpoint is the percent reduction from baseline in serum TTR level at 6 months.

Secondary Endpoints

The secondary endpoints of the study are the change from baseline over 18 months for the following:

- Serum TTR
- Modified (m)NIS+7
- Norfolk Quality of Life-Diabetic Neuropathy questionnaire
- PND Score

Pharmacokinetic Assessments:

Blood samples will be obtained for the assessment of plasma levels of revusiran. Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of revusiran.

Safety Assessments

The safety of revusiran will be evaluated by:

- Adverse events (AEs), including liver allograft rejection
- Vital sign measurements
- Clinical laboratory Evaluations
- 12-lead electrocardiogram (ECG)
- Physical examinations
- Ophthalmology examinations
- Concomitant medications, including immunosuppressive agent monitoring

Exploratory Endpoints:

The exploratory endpoints of the study are to assess the change from baseline over 18 months for the following:

- mBMI
- FAP Stage
- NIS
- Grip Strength Test
- NYHA classification
- Karnofsky Performance Status
- Echocardiogram (ECHO) parameters
- Cardiac biomarkers
- EuroQoL questionnaire in 5-dimensions (EQ-5D)

- Composite Autonomic Symptom Score (COMPASS) 31 questionnaire
- Columbia Suicide Severity Rating Scale Questionnaire
- Pharmacoeconomics questionnaire
- Optional exploratory residual liver tissue evaluation

Statistical methods:

The primary population used to evaluate efficacy will be the Evaluable Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses.

The primary endpoint is the percent reduction from baseline in serum TTR level at 6 months. The primary efficacy analysis will be a 2-sided 95% confidence interval (CI) for the mean of the primary endpoint. A t-test, in which the null hypothesis of no reduction is compared against the alternative hypothesis of a change, will also be performed.

For secondary endpoints with continuous parameters, measurements will be summarized using descriptive statistics. For secondary endpoints with categorical parameters, frequencies and percentages will be presented. The mean change (for continuous variables) from baseline to 18 months with the associated 80% and 95% CIs will also be presented. For categorical variables, frequencies and percentages will be presented. To understand the effect of revusiran from baseline, the frequency and percentage of patients at each of the category shifts from baseline at 18 months will be summarized.

The exploratory endpoints will be analyzed in a similar fashion as the secondary endpoints.

Adverse event summaries will include tabulations of all treatment-emergent AEs, treatment-related AEs, serious AEs, discontinuations due to AEs, and AEs graded according to maximum severity and will be primarily descriptive in nature. Clinical laboratory data, vital signs data, and ECG interval data will also be presented as both actual values and changes from baseline relative to each on-study evaluation.

For categorical safety variables, summary tabulations of the frequency and percentage of patients will be presented. For continuous safety variables, the mean, median, standard deviation, minimum, and maximum values will be presented.

Table 1: Schedule of Assessments

Procedure	Month	Screening	Screening[a]/ Baseline	Baseline[a]	Predose[d]	Daily Dosing					Weekly Dosing (After D7±1, study drug will be administered weekly ±2 days)																Early Termination[b]	EOS
	Days/Weeks	D-42 to D -1			D0	D0	D1	D2	D3	D4	D7/W1	W2	M1	W4-6	M2	W8-11	M3	W13-25	M6	W27-38	M9	W40-51	M12	W53-65	M15	W67-77	M18		M19
													W3		W7		W12		W26		W39		W52		W66		W78		W82
	Visit Window (Days)[c]					NA					±1D	±2D	±7D	±2D	±7D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D		±7D
Clinical Procedures and Assessments																													
Informed Consent		X																											
Inclusion/Exclusion Criteria[d]		X	X	X	X																								
Medical History[e]		X	X	X																									
Demographics		X																											
HIV Status Review		X																											
Physical Examination		X											X				X		X		X		X		X		X	X	X
Body Weight		X			X														X				X				X	X	X
Height		X																											
Vital Signs[f]		X			X	X	X	X	X	X			X		X		X		X		X		X		X		X	X	X
PND score		X	X																X				X				X	X	
NYHA Classification		X	X																X				X				X		
Karnofsky Performance Status		X																	X				X				X		
FAP Stage			X																X				X				X	X	
Study Drug Administration[g]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
mBMI			X																X				X				X	X	

Procedure	Month	Screening	Screening[a] / Baseline	Baseline[a]	Predose[d]	Daily Dosing					Weekly Dosing (After D7±1, study drug will be administered weekly ±2 days)																Early Termination[b]	EOS
											D7/W1	W2	M1	W4-6	M2	W8-11	M3	W13-25	M6	W27-38	M9	W40-51	M12	W53-65	M15	W67-77	M18		M19
	Days/Weeks	D-42 to D -1			D0	D0	D1	D2	D3	D4	W3		W7		W12		W26		W39		W52		W66		W78			W82
	Visit Window (Days)[c]					NA					±1D	±2D	±7D	±2D	±7D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D		±7D
Prior and Concomitant Medications[h]		X	X	X	X		X																					
Adverse Events		ONGOING THROUGHOUT THE DURATION OF THE STUDY																										
Laboratory Assessments																												
Serum Chemistry, including LFTs		X	X[a]		X[d]					X	X	X	X		X		X	X[w]	X		X		X		X		X	X	X
Hematology and Urinalysis		X			X														X				X					X	X
Pregnancy Test[i]		X			X									X		X	X	X		X		X	X	X		X	X	X	X
HBsAg, HBsAb, and HCVAb		X																											
Coagulation Assessments[j]		X			X								X		X		X	X[w]	X				X					X	X
TSH		X																					X					X	X
Antidrug Antibodies[k]					X								X						X				X				X	X	
TTR Protein[l]			X	X	X								X		X		X	X[m]	X		X		X	X[n]	X		X	X	
Blood samples for long-term storage[o]			X	X	X								X		X		X		X		X		X		X		X	X	
Vitamin A					X														X				X				X	X	
Vitamin B12		X																											
Blood samples for plasma PK analysis[p]					X	X							X						X				X						

Procedure	Month	Screening	Screening[a] / Baseline	Baseline[a]	Predose[d]	Daily Dosing					Weekly Dosing (After D7±1, study drug will be administered weekly ±2 days)																	Early Termination[b]	EOS
											D7/W1	W2	M1	W4-6	M2	W8-11	M3	W13-25	M6	W27-38	M9	W40-51	M12	W53-65	M15	W67-77	M18		M19
	Days/Weeks	D-42 to D -1			D0	D0	D1	D2	D3	D4	W3		W7		W12		W26		W39		W52		W66		W78			W82
	Visit Window (Days)[c]					NA					±1D	±2D	±7D	±2D	±7D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D		±7D
NT-proBNP, BNP, and Troponin T and I					X												X		X		X		X		X		X		
Immunosuppressive agent monitoring[q]					X												X		X										
Cardiac, Ophthalmologic, and Neurological Assessments																													
NIS[r]		X	X	X															X				X				X	X	
mNIS+7[s]			X	X															X				X				X	X	
Grip Strength Test[s]			X	X															X				X				X	X	
ECHO with Doppler[t]			X																X				X				X	X	
Ophthalmology Exam		X																					X					X	X
12-Lead ECG[u]		X																	X				X					X	X
Questionnaires																													
Norfolk QOL-DN			X																X				X				X	X	
EQ-5D Questionnaire			X[v]																X				X				X	X	
COMPASS 31 Questionnaire			X[v]																X				X				X	X	
Pharmacoeconomics Questionnaire			X																X				X				X	X	
Columbia Suicide Severity Questionnaire			X																X				X				X		

Abbreviations: aPTT=activated partial thromboplastin time; BNP=brain natriuretic peptide; COMPASS=Composite Autonomic Symptom Score; D=day; ECG=electrocardiogram; ECHO=echocardiogram; EOS=End of Study; EQ-5D= EuroQol 5 dimensions questionnaire; FAP=familial amyloidotic polyneuropathy; HBsAg=hepatitis B surface antigen;

Procedure	Month	Screening	Screening[a]/ Baseline	Baseline[a]	Predose[d]	Daily Dosing					Weekly Dosing (After D7±1, study drug will be administered weekly ±2 days)																	Early Termination[b]	EOS
											D7/W1	W2	M1	W4-6	M2	W8-11	M3	W13-25	M6	W27-38	M9	W40-51	M12	W53-65	M15	W67-77	M18		M19
	Days/Weeks	D-42 to D -1			D0	D0	D1	D2	D3	D4			W3		W7		W12		W26		W39		W52		W66		W78		W82
	Visit Window (Days)[c]					NA					±1D	±2D	±7D	±2D	±7D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D	±2D	±14D		±7D

HBsAb=hepatitis B virus antibodies; HCVAb=hepatitis C virus antibodies; HIV=human immunodeficiency virus; HP=heat pain; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; LFT=liver function test; mBMI=modified body mass index; mNIS=Modified Neurological Impairment Score; M=month; NA=not applicable; NIS=Neurological Impairment Score; NT-proBNP=N-terminal prohormone of B-type natriuretic peptide; OLT=orthotopic liver transplant; PK=pharmacokinetic; PND=polyneuropathy disability; NYHA=New York Heart Association; PT=prothrombin time; QOL-DN=Quality of Life-Diabetic Neuropathy; QTcB=Bazett corrected QT; QTcF=Fredericia-corrected QT interval; TP=touch pressure; TSH=thyroid stimulating hormone; TTR=transthyretin; W=week; WOCBP=women of child-bearing potential.

Note: White boxes are visits to the clinical study centers; whereas, grey boxes are for dosing procedures that may be conducted at home. If, at any time during the study, a liver biopsy is performed per standard of care procedures, an optional evaluation of residual liver tissue may also be performed. Additionally, patients will be monitored for possible liver allograft rejection; any biopsies performed to rule out allograft rejection will be evaluated according to the Banff Working Group on Liver Allograft Pathology criteria, a set of consensus criteria for the causes of liver allograft dysfunction.

[a] The Screening/Baseline visit must be performed within 21 days before the first dose of study drug (Day 0). The Baseline visit must be conducted at least 24 hours, but not more than 7 days, after the Screening/Baseline visit. In consultation with the Medical Monitor(s), the Investigator may re-screen a patient after a minimum of 5 days have elapsed from the last screening assessment.

[b] The withdrawn patient will be asked to consent to either be contacted by telephone or to allow non-patient contact follow-up (eg, medical record check) for up to 18 months after enrolling in the study to document overall health status.

[c] Dosing on Days 1, 2, 3, and 4 must be performed 24±4 hours after the preceding dose of study drug. After Day 7±1, study drug will be administered weekly (±2 days). A 14-day window is permitted for study visits after Month 2 (excluding study drug administration).

[d] LFTs must be assessed within 14 days of Day 0 (Predose) and results must be known before the first dose of study drug. Other results from the clinical laboratory samples collected on Day 0 are not needed before dosing.

[e] A complete medical history of FAP and OLT will be collected. An interval medical history will be collected during the Screening/Baseline and Baseline visits and only changes in medical history will be recorded. As part of the complete medical history, if available, the prior 6 months of LFTs will also be collected.

[f] Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position (should be consistent for each patient), after the patient has rested comfortably for 10 minutes. Vital signs should be collected at each clinical study center visit.

[g] The preferred region of SC injection is the abdomen; optional additional regions include the upper arm or thigh. The site of injection within a given region will be rotated and recorded. Refer to Section 6.5 for details on study drug administration, including administration at home by a healthcare professional or self or caregiver administration. Patients (or caregivers) administering study drug will be contacted at least once per month by the clinical study center staff to assess AEs, concomitant medications, and to confirm pregnancy testing is being performed.

[h] Prior immunosuppressive agent administration and blood levels from the 6 months before signing of the ICF will be collected, if available.

[i] A pregnancy test will be performed for WOCBP only. A serum pregnancy test will be performed at Screening and urine pregnancy tests at all study visits thereafter (W4, W8, W12, W16, W20, W24, W28, W32, W36, W40, W44, W48, W52, W56, W60, W64, W68, W72, and W76) and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration.

[j] Coagulation assessments include PT, aPTT, and INR.

[k] Blood samples for antidrug antibody testing must be collected before study drug administration. A sample will be collected at the Early Termination visit, if applicable.

[l] Blood samples for TTR analysis should be obtained within 1 hour predose.

[m] Blood sample for TTR analysis should be collected at Week 18 and Week 24 only.

[n] Blood sample for TTR analysis should be collected at Week 57 only.

[o] Where permitted per local regulations and IRB/IEC approval, blood samples for long-term storage to permit testing of additional proteins related to FAP will be collected.

[p] Blood samples for plasma PK analysis will be collected predose and 2.5±1 hours postdose.

[q] Immunosuppressive agent monitoring will be analyzed locally. Unscheduled assessments may be performed if clinically indicated per local standard of care.

[r] The NIS (weakness, reflexes, and sensation) will be assessed at Screening to determine the likelihood that a patient will meet NIS eligibility criteria at the Screening/Baseline visit; a NIS of 5-130 [inclusive] must be met at the Screening/Baseline visit. The documented results of previously performed NIS assessments may be used at Screening if these tests were performed within 60 days before the date of informed consent.

[s] The mNIS+7 consists of the modified NIS tool (weakness and reflexes), NCS 5 attributes ($\sum$5), quantitative sensory testing by body surface area including TP and HP, and postural blood pressure. At each time point, 2 independent assessments will be performed for the mNIS+7 and the Grip Strength Test. The clinical study center will make every effort to have these assessments performed by the same study staff. Assessments are to be performed ≥24 hours, but ≤7 days apart.

[t] ECHO assessments will be evaluated by a central laboratory.

[u] A triplicate 12-lead ECG will be recorded at baseline; thereafter, single 12-lead ECGs will be recorded. Additional ECGs may be collected at the discretion of the Investigator. When an ECG is scheduled at the same time as a blood sample collection, the ECG will be obtained before the scheduled blood sample.

[v] Assessment must be completed at a single time point during 1 of the specified visits, at the discretion of the Investigator.

[w] Serum chemistry, including LFTs, and coagulation assessments must be collected at Week 15, Week 18, and Week 22.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATTR	Transthyretin-mediated amyloidosis
BNP	B-type natriuretic peptide
COMPASS	Composite Autonomic Symptom Score
CI	Confidence interval
CRO	Contract research organization
CYP	Cytochrome P_{450}
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated glomerular filtration rate
EQ-5D	European quality of life questionnaire – 5 dimensions
EU	European Union
FAC	Familial amyloidotic cardiomyopathy
FAP	Familial amyloidotic polyneuropathy
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous (ly)
LFT	Liver function test
mBMI	Modified body mass index
MedDRA®	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mNIS	Modified neurological impairment score
mRNA	Messenger ribonucleic acid
NCS	Nerve conduction studies
NHP	Non-human primate
NIS	Neurological impairment score
NOAEL	No-observed-adverse-effect-level
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
OLT	Orthotopic liver transplant
OTC	Over-the-counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PND	Polyneuropathy disability
QOL-DN	(Norfolk) Quality of Life Diabetic Neuropathy
QST	Quantitative sensory testing
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
RBP	Retinol binding protein
RNAi	RNA interference
SAE	Serious adverse event
SC	Subcutaneous(ly)
siRNA	Small interfering ribonucleic acid
SSA	Senile systemic amyloidosis
T4	Thyroxine
TEAE	treatment-emergent adverse event
TTR	Transthyretin
ULN	Upper limit of normal
WOCBP	Women of child-bearing potential
WT	Wild-type
US	United States

1. INTRODUCTION

1.1. Background and Rationale

1.1.1. Transthyretin Biology

Transthyretin (TTR), also known as prealbumin, is a tetrameric protein produced predominantly by hepatocytes (>95% of TTR is liver-derived), with small fractions produced in the choroid plexus and retina.[1] The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A) through its interaction with retinol binding protein (RBP); it also plays a minor role as a carrier for thyroxine (T4). In humans, approximately 15% of T4 circulating in the plasma is bound to TTR; the remainder is predominantly bound to thyroxine-binding globulin.

Mutations in the TTR protein lead to destabilization of the tetrameric form and dissociation into dimers and monomers. The misfolding of mutated monomers results in tissue deposition of oligomers and amyloid fibrils, which lead to significant tissue injury.

1.1.2. Disease Overview

1.1.2.1. Transthyretin-mediated Amyloidosis and Familial Amyloidotic Polyneuropathy

Transthyretin-mediated amyloidosis (ATTR) is caused by deposition of TTR amyloid fibrils in various tissues. The hereditary form of ATTR amyloidosis is caused by an autosomal dominant mutation in the TTR gene. There are over 100 reported TTR genetic mutations[2,3] that phenotypically result in at least 2 clinical syndromes: familial amyloidotic cardiomyopathy (FAC) and familial amyloidotic polyneuropathy (FAP), both of which are characterized by amyloid deposits of mutant and wild-type (WT) TTR.[4]

The estimated worldwide prevalence of FAP is 5,000 to 10,000, with the majority of cases in Portugal, Sweden, France, Mallorca, Japan, Brazil, and the United States (US).[5,6,17] The most common causative mutation of FAP is TTR valine substitution for methionine at position 30, with the onset of symptoms typically occurring between 30 and 55 years of age.[7] 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.[8,9,10,11] Several mutations, also manifest with cardiac pathology during later stages of disease due to amyloid infiltration of the sinus node, the atrioventricular conduction system, and infiltration of the myocardium.[12,13] Involvement of the conduction system can lead to sudden death due to dysrhythmias, and myocardial infiltration can lead to diastolic dysfunction and biventricular heart failure.[14] Death typically occurs within 10 years of diagnosis of FAP.[15] A TTR tetramer stabilizer, tafamidis, was approved in the European Union (EU) in 2011 for use in the treatment of symptomatic FAP patients with Stage 1 disease. Diflunisal is a generic, nonsteroidal anti-inflammatory agent that has been demonstrated in in

vitro assays to bind to and stabilize the TTR tetramer in a manner similar to tafamidis. A recently published National Institutes of Health-sponsored study showed that diflunisal slowed neuropathy progression in FAP,[16] and its use is contraindicated in patients with severe congestive heart failure (New York Heart Association [NYHA] class IV), renal insufficiency (estimated creatinine clearance <30 mL/min), or those undergoing anticoagulation therapy. Diflunisal is not currently licensed for use in the treatment of FAP in the US or EU, and there is limited evidence for its effectiveness in the treatment of patients with FAP. However, there are no approved treatments for patients with later stages of FAP or for patients with disease progression post-orthotopic liver transplant (OLT).

1.1.2.2. Familial Amyloidotic Polyneuropathy After Orthotopic Liver Transplant

Since the liver is the primary source of WT and mutant TTR, OLT has been used since 1990 as a potential approach for the treatment of FAP [1] and is the current standard of care in select patients who are eligible for transplant. More than 2000 patients have been transplanted in the world since 1990. However, OLT carries significant risks: life-threatening complications due to allograft rejection, hepatic artery thrombosis, or infections. The 1-year mortality rate post-OLT in FAP patients is approximately 10%.[23] Additionally, disease progression occurs in at least one third of patients post-OLT, presumably due to continued deposition of WT TTR protein from the transplanted liver.[17,18] Amyloid deposits before liver transplant consist of both mutant and WT TTR.[19,20] However, postliver transplant nerve and cardiac tissue contains increased amounts of WT TTR in patients with disease progression despite removal of mutant TTR with liver transplant.[21,36,22] Disease progression may occur as early as 1 year post-transplant leading to loss of ambulation in 20% of patients.[18] Additionally, as with disease progression in FAP patients who have not undergone liver transplant, progression post-OLT most commonly manifests as worsening of polyneuropathy and/or cardiac disease. Neurological progression is marked by an increase in Neurological Impairment Score (NIS) of 8.84 per year and reduction in strength by 22% per year as assessed by the handgrip test. Thirty percent of patients with clear progression of neuropathy died in follow-up. Even in FAP patients where both the liver and heart have been transplanted, neuropathy progression continues, leaving the patient with marked disability.[36] Causes of death after liver transplant include cardiac impairment (22%), liver-related complications (14%), and septicemia (22%).[18]

None of the available therapeutic agents are considered truly disease modifying, nor has any treatment demonstrated the ability to halt disease progression in a majority of patients, which is particularly important in a setting where continued disease progression ultimately leads to marked disability and death. Importantly, there are no approved treatment options for FAP patients whose disease continues to progress post-OLT, and this subset of patients is not eligible for ongoing clinical trials in FAP.

1.1.3. 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).[24] Typically, synthetic siRNAs are 19 to 23 base pair double-stranded oligonucleotides in a staggered duplex with a 2-nucleotide overhang at 1 or both of the 3' ends. Such siRNAs can be designed to target endogenous or exogenous (infectious organisms) disease causing genes. 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.[25] The ability to selectively and potently degrade the mRNA encoding the TTR protein using a 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.[26] As a result, various formulations and/or chemical modifications of the siRNAs have been used to increase distribution to tissues, and to facilitate their uptake into the relevant cell type.

One approach that has been used successfully in humans for delivery of siRNAs to the liver employs intravenous (IV) administration of siRNAs formulated in lipid nanoparticles.[26,27,28] Another approach for liver-specific gene silencing has been to use subcutaneously (SC) administered siRNA conjugated to an N-acetylgalactosamine (GalNAc) ligand. It has been shown that conjugation of a triantennary GalNAc ligand to the 3' end of the sense strand of siRNA results in high affinity (ie, nM) binding to the hepatic expressed asialoglycoprotein receptor and subsequent receptor-mediated uptake into hepatocytes. Single and multiple doses of SC administered siRNA-GalNAc conjugates have achieved sustained suppression of multiple different hepatocyte-expressed targets in rodents, nonhuman primates (NHPs), and humans, including TTR (see the revusiran Investigator's Brochure [IB] for further details).

1.2. Overview of Revusiran

Alnylam Pharmaceuticals, Inc. (the Sponsor), in collaboration with Genzyme Corporation, has a synthetic RNAi therapeutic targeting liver TTR mRNA in clinical development for the treatment of ATTR amyloidosis (revusiran), which has received orphan drug designation in the EU. Revusiran is comprised of a siRNA targeting mutant and WT TTR mRNA with a covalently-attached triantennary GalNAc ligand formulated in water for injection. The siRNA consists of a 21-mer duplex oligonucleotide targeting the 3'UTR of the TTR mRNA, thereby conferring homology to WT TTR and all reported TTR mutations. Once delivered to hepatocytes, revusiran targets TTR mRNA for degradation, resulting in reduction of mutant and WT TTR protein via the RNAi mechanism. Therefore, revusiran is expected to directly address the etiology of ATTR amyloidosis and improve the disease course of patients. This is consistent with results in other systemic amyloidoses (eg, amyloid light chain and secondary amyloidosis) where reduction in circulating pathogenic protein levels is associated with attenuation in end-organ damage.[29,30,31,32]

1.2.1. Summary of Revusiran Nonclinical Data

A series of nonclinical studies were conducted to elucidate the pharmacology, pharmacokinetics (PK), and toxicology of revusiran.

A cardiovascular/respiratory safety pharmacology study conducted in NHPs demonstrated no functional cardiovascular or respiratory effects, with a no-observed-effect-level of ≥100 mg/kg. In addition, genetic toxicity studies were negative.

The toxicity of revusiran was evaluated in 6-month chronic toxicity studies in rats and NHPs (the pharmacologically relevant species). In the 6-month rat study the

no-observed-adverse-event-level (NOAEL) was 30 mg/kg based on histopathological findings in the liver in conjunction with transient mild liver function test (LFT) changes. In the 9-month NHP study, there were no dose-limiting findings and the NOAEL was greater than the highest dose tested (>200 mg/kg).

Further nonclinical information can be found in the revusiran IB.

1.2.2. Summary of Revusiran Clinical Data

Study ALN-TTRSC-001 was a Phase 1 randomized, double -blind, placebo-controlled study of revusiran administration in healthy subjects. Subjects received single ascending doses or multiple ascending doses of up to 10 mg/kg or fixed doses of up to 600 mg of revusiran, or placebo. In the multiple dose cohorts, subjects received a total of 10 doses over a 35 day period administered as 5 daily SC doses followed by 5 weekly doses.

In this study, revusiran was generally well-tolerated. The majority of treatment-emergent adverse events (AEs) were mild or moderate in severity and considered unrelated to study treatment. There were no serious adverse events (SAEs). Injection site reactions (ISRs) were the most common AEs related to study treatment. All ISRs were mild or moderate in severity and resolved without sequelae. Overall, the incidence of alanine transaminase (ALT) and aspartate transaminase (AST) elevation >1× upper limit of normal (ULN) was similar in placebo and revusiran-treated subjects. One subject who received 600 mg revusiran developed an asymptomatic elevation of ALT (4.3×ULN) and AST (1.9×ULN), which was defined in the protocol as a dose limiting toxicity and resulted in study discontinuation. There were no other AEs leading to dose interruption or dose reduction. No elevations in cytokines, C-reactive protein, or other abnormal clinical findings were noted. The pharmacodynamic (PD) effect of revusiran was dose-dependent and resulted in >85% reduction of TTR at ≥5 mg/kg of revusiran and was accompanied by reduction of RBP and vitamin A. Fixed doses of 500 mg and 600 mg revusiran also demonstrated similar safety and PD effect over a wide range of body weights compared to that observed in cohorts with weight based dosing.

ALN-TTRSC-002 was an open-label, multiple-dose Phase 2 study of revusiran administered to patients with ATTR cardiac amyloidosis. Patients received revusiran 5 mg/kg or 7.5 mg/kg for 10 doses over a 35 day period administered as 5 daily SC doses followed by 5 weekly doses. Multiple doses of revusiran were generally well-tolerated. The majority of AEs were mild or moderate in severity, not related to study drug and expected for the population under study. Three patients experienced 1 SAE each, 2 of which were unrelated to study drug (non-cardiac chest pain and implantable defibrillator insertion). The third SAE was asymptomatic elevation of ALT (4.2×ULN) and AST (3.2×ULN) after administration of 6 doses of 5 mg/kg revusiran and was considered mild in severity and possibly related to study drug. Study drug was interrupted for 1 dose and then resumed with subsequent normalization of ALT and AST during the remaining period of dosing. The most common AEs related to study treatment were ISRs which were localized, mild in severity, self-limiting and did not result in interruption or discontinuation of treatment. There were no other AEs leading to dose interruption or dose reduction. A PD effect of >85% TTR reduction with 5 mg/kg or 7.5 mg/kg revusiran dosing was observed.

ALN-TTRSC-003 is an ongoing, Phase 2 open-label extension study to evaluate long-term treatment with revusiran for patients who completed the ALN-TTRSC-002 study. Patients

receive revusiran 500 mg administered as 5 daily SC doses, followed by weekly SC doses for approximately 2 years. As of 05 January 2016, 25 patients have been treated with revusiran for approximately 8 months (range 1-13 months). Multiple doses of revusiran have been generally well-tolerated. The majority of AEs were mild or moderate in severity. The most common AEs related to study drug have been ISRs, usually characterized by transient erythema, pruritus, pain, or swelling at or around the injection site. Occasionally, these reactions have been recurrent, of longer duration and increased intensity. In some cases, ISRs have led to interruption or discontinuation of study drug. Elevations of ALT and AST have been observed, the majority of which have been mild, transient, <3×ULN and not associated with any changes in total bilirubin or clinical symptoms. In several subjects, the elevations may have led to interruption and/or dose reduction of study treatment. There were no serious hepatic AEs.

ALN-TTRSC-004 is an ongoing, Phase 3 randomized, double-blind, placebo-controlled study of revusiran in patients with FAC. Patients receive revusiran 500 mg or placebo administered as 5 daily SC doses, followed by weekly SC doses for 18 months. As of 14 January 2016, 83 patients have been treated with blinded study drug for approximately 3 months (range 0-13 months). The majority of AEs were mild or moderate in severity. The most common AEs considered related to blinded study treatment have been ISRs. One patient developed symptoms of anorexia, weight loss, and a cholestatic liver enzyme profile. The patient was hospitalized and an evaluation was consistent with drug-induced acute hepatitis and cholestasis. The event was considered possibly related to study treatment and a contributory role could not be excluded. The subject also had a number of other potential contributory factors.

Further details on these clinical studies can be found in the revusiran IB.

1.3. Study Design Rationale

There is a high unmet medical need for treatment alternatives in FAP. Very few treatment options exist once a patient has progressed after receiving an OLT. Post-OLT patients no longer have mutant TTR circulating or depositing into tissues; however, those with disease progression after transplant suffer from continued WT TTR amyloid deposition in a variety of tissues including the peripheral nervous system.[33,36]

Preliminary Phase 2 open-label extension study data with patisiran, a liquid nanoparticle-formulated siRNA targeting hepatic TTR production, has shown stabilization of neuropathy after 1 year in FAP patients associated with >80% TTR reduction. Given the IV route, shared mechanism of action, and similar magnitude of TTR reduction (both WT and mutant) with both revusiran and patisiran to date, it is anticipated that revusiran will lead to a similar degree of TTR reduction in FAP patients, and thus have the potential to affect neuropathy in FAP patients who are progressing post-OLT.

In this study, patients will receive 5 daily SC injections of 500 mg revusiran during the first week (Day 0 to Day 4) and then SC injections of 500 mg revusiran once every week for approximately 18 months. This dose and schedule maximizes TTR reduction (>85%) in healthy volunteers and FAC patients at the lowest revusiran exposure with a favorable safety profile, and is being used in the ongoing revusiran Phase 2 open-label extension study and Phase 3 study in FAC patients. Furthermore, the level of TTR reduction obtained with this regimen of revusiran is comparable to the TTR reduction observed with patisiran in the Phase 2 open-label extension study where TTR reduction was associated with clinical stabilization of neuropathy in patients with FAP.

The primary endpoint is the percent reduction from baseline in serum TTR level at 6 months. In healthy volunteers, mean reduction of 88% in serum TTR has been observed from baseline to Day 35 with a standard deviation of 6%. If this study yields a mean reduction of 80% at 6-months with a standard deviation of 6%, 12 patients would yield a 95% confidence interval (CI) of approximately 77% to 83%.

The primary endpoint of the percent reduction from baseline in serum TTR level at 6 months is an objective measurement and not susceptible to bias of clinical study center staff or study patients and therefore does not require a blinded placebo group for accurate interpretation. Secondary endpoints include TTR reduction over 18 months compared to baseline, modified Neurological Impairment Score (mNIS+7), NIS, Norfolk Quality of Life Diabetic Neuropathy (QOL-DN) questionnaire, and polyneuropathy disability (PND) score.

1.4. Dose Selection Rationale

Dose selection for this trial is based on the fundamental role of TTR in the pathogenesis of the disease, data from liver transplantation in FAP, and the therapeutic hypothesis that maximal TTR reduction is required to fully realize clinical benefit with revusiran. Clinical data demonstrate that administration of multiple doses of revusiran in healthy volunteers resulted in >85% mean TTR reduction at nadir with doses of 5.0 to 10.0 mg/kg or with fixed doses of 500 and 600 mg; these doses were well tolerated. The fixed dose of 500 mg had a wide PD and safety window across both heavy and light patients, with a TTR reduction effect that matched 5.0 and 10.0 mg/kg (ALN-TTRSC-001). In the Phase 2 study in patients with FAC and SSA, doses of 5.0 and 7.5 mg/kg have resulted in similar degrees of TTR reduction as were seen in healthy volunteers. Based on these consistent PD data in both healthy volunteers and FAC/SSA patients showing maximization of TTR reduction with either fixed or mg/kg dosing at a total dose of ≥500 mg, along with the favorable safety profile observed with the 500 mg fixed dose, 500 mg is the planned dose for this study. The dose selection is also supported by the absence of findings in the long-term toxicology studies in rats and monkeys.

1.5. Risk-Benefit Assessment

Familial amyloidotic polyneuropathy and FAC are diseases with significant morbidity and mortality and limited treatment options. Orthotopic liver transplantation has been considered the standard treatment for early stage FAP patients; however, approximately one-third of patients demonstrate neuropathy progression post-transplant, with progression marked by a reduction of ambulation in which 20% of patients become bedridden.[18] Once a patient continues to progress post-OLT overall outcome is very poor and treatment options are limited. The potential benefit of treatment with revusiran is that reduction of wild-type and mutant TTR deposition may result in clinical benefit in these patients. Based on the mechanism of action of siRNAs and the lack of effect of revusiran in nonclinical *in vitro* cytochrome P_{450} (CYP) inhibition, induction, and phenotyping studies, as well as transporter studies, an interaction between revusiran and concomitantly administered immunosuppressive agents is not expected. The main risks associated with revusiran treatment and TTR reduction are summarized below and support a favorable risk/benefit assessment.

Refer to the IB for additional information.

1.5.1. Injection Site Reactions

ISRs have been observed in subjects receiving revusiran in completed and ongoing clinical studies. The majority have been mild or moderate in severity. Typically, the reactions consist of localized erythema, pain, swelling, pruritus, or rash at or around the injection site, and are transient in nature. Occasionally, these reactions have been of longer duration, more severe in nature and/or recurrent. In some subjects, this resulted in discontinuation of revusiran. If such reactions occur, rotation of the injection site (eg, to the extremities) is recommended as a potential mitigation strategy (see Section 6.5). Dose reduction may be considered in some cases after consultation with the Medical Monitor (see Section 3.5).

1.5.2. Abnormal Liver Function Tests

Elevations of ALT and/or AST have been seen in subjects receiving revusiran in completed and ongoing clinical studies. The majority of abnormalities have been mild and transient elevations of ALT and/or AST <3×ULN, and are not associated with changes in total bilirubin or clinical symptoms. In some subjects, higher ALT and/or AST elevations have been observed and led to interruption or discontinuation of study treatment. Serious hepatic adverse events have also been reported, including a case of possible drug-induced hepatitis and cholestasis; in this case a contributory role of study drug could not be excluded.

In this study, patients will be required to have normal liver function at study entry, and regular monitoring of LFTs will be performed throughout study participation. If a patient develops clinical signs or symptoms such as unexplained anorexia, fatigue, jaundice, or dark urine, the Investigator should consider liver injury as a potential etiology. Patients receiving revusiran after OLT will be a minimum of 12 months from transplant with no recent rejection episodes and on stable immunosuppressive medication to ensure that complications secondary to liver transplant are minimized. Dose reduction may be considered in some cases after consultation with the Medical Monitor (see Section 3.5).

1.5.3. Vitamin A Reduction

The reduction of serum levels of TTR and RBP is expected to result in reduced circulating vitamin A levels. Preclinical and clinical data have shown that reducing circulating vitamin A associated with reduction of RBP does not result in severe vitamin A deficiency. Individuals with RBP/TTR mutations have life-long reduced levels of circulating vitamin A with good health, suggesting that compensatory transport mechanisms for vitamin A exist. Furthermore, reducing vitamin A has not been associated with any vitamin A deficiency-related AEs in healthy volunteers, and patients with FAP, treated with patisiran (another RNAi therapeutic with an siRNA targeting TTR formulated in a lipid nanoparticle) who experienced >80% reduction of both TTR and vitamin A. Periodic eye exams are planned for patients in this study to assess any potential impact of vitamin A reduction on visual function. Additionally, all patients on the study will be asked to take a daily supplement containing the recommended daily allowance of vitamin A.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

- Assess the efficacy of revusiran in patients with TTR-mediated FAP with disease progression post-OLT by evaluating the reduction in serum TTR level compared to baseline

2.2. Secondary Objectives

- Evaluate the safety and tolerability of revusiran when administered to TTR-mediated FAP patients with disease progression post-OLT
- Characterize PK of revusiran
- Describe the effect of revusiran on neurologic impairment

2.3. Exploratory Objective

- Evaluate the effect of revusiran on various clinical activity parameters including quality of life, disease stage, modified body mass index (mBMI), and cardiac function

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, and PK of SC administered revusiran in patients with TTR-mediated FAP with disease progression post-OLT. It is anticipated that patients from approximately 5 clinical study centers will participate in this study.

Eligible, consenting patients will receive 5 daily doses of revusiran (Days 0 through 4) and a dose at Day 7, followed by once weekly doses for the duration of the study.

Visits will be held at the clinical study center for Screening, Screening/Baseline, and Baseline, and Daily Dosing (Days 0 through 4) as well as each month for the first 3 months, and approximately every 3 months through Month 18 (or Early Termination), and at the End of Study (approximately 28 days after last dose). The remaining study visits may be conducted at the clinical study center or in the patient's home.

The primary objective of the study will be evaluated by the collection of serum samples for the measurement of total TTR levels. After screening and baseline measurements, TTR will be assessed on a monthly basis for 3 months, approximately every 3 months, thereafter, and at ET.

Adverse events will be collected throughout the treatment period and at the End of Study visit.

Patients will participate in the study for approximately 21 months (inclusive of a 42-day screening period and a follow-up visit 28 days after the last dose of study drug) and will be treated with study drug for 18 months.

An independent Data Monitoring Committee will be implemented for the study and will operate under a prespecified charter.

3.2. Number of Patients

Approximately 12 patients are planned for enrollment in this study.

3.3. Treatment Assignment

This is an open-label study.

3.4. Efficacy and Clinical Activity Endpoints:

3.4.1. Primary Endpoint

The primary endpoint is the percent reduction from baseline in serum TTR level at 6 months.

3.4.2. Secondary Endpoints

The secondary endpoints of the study are the change from baseline over 18 months for the following:

- Serum TTR

- mNIS+7
- Norfolk Quality of Life-Diabetic Neuropathy questionnaire
- PND Score

3.4.3. Pharmacokinetic Assessments:

Blood samples will be obtained for the assessment of plasma levels of revusiran. Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of revusiran.

3.4.4. Safety Assessments

The safety of revusiran will be evaluated by:

- Adverse events (AEs), including liver allograft rejection
- Vital sign measurements
- Clinical laboratory evaluations
- 12-lead ECG
- Physical examinations
- Ophthalmology examinations
- Concomitant medications, including immunosuppressive agent monitoring

3.4.5. Exploratory Endpoints

The exploratory endpoints of the study are to assess the change from baseline over 18 months for the following:

- mBMI
- FAP Stage
- NIS
- Grip Strength Test
- NYHA classification
- Karnofsky Performance Status
- Echocardiogram (ECHO) parameters
- Cardiac biomarkers
- EuroQoL questionnaire in 5-dimensions (EQ-5D)
- Composite Autonomic Symptom Score (COMPASS) 31 questionnaire
- Columbia Suicide Severity Rating Scale Questionnaire
- Pharmacoeconomics questionnaire
- Optional exploratory residual liver tissue evaluation

3.5. Dose Adjustment Criteria

3.5.1. Safety Criteria for Adjustment or Stopping Doses

If, after study drug administration, AST, ALT, or total bilirubin (unless due to Gilbert's Syndrome) >2×ULN, repeat AST, ALT, and total bilirubin within 72 hours and implement close monitoring with continued study drug dosing. Close monitoring consists of AST, ALT, and total bilirubin measurement twice weekly. Close monitoring can be stopped when ALT, AST, and total bilirubin return to ≤2×ULN. Additional and repeat testing may be performed at the discretion of the Investigator.

Dosing will be held for the following LFT abnormalities:

- AST or ALT elevation of ≥3×ULN in association with either total bilirubin elevation of ≥1.5×ULN or gastrointestinal symptoms including nausea, vomiting, and/or abdominal pain
- AST or ALT elevation of ≥5×ULN

Under these circumstances, the contract research organization (CRO) Medical Monitor and Investigator, in consultation with the Alnylam Medical Monitor and/or a hepatologist, as deemed necessary, will decide on appropriate action regarding frequency of repeat LFTs and resumption of dosing.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the Medical Monitor and Investigator will review all available safety data for that patient and for all other patients enrolled in the study. Based on the judgment of the Investigator and the Medical Monitor, it may be decided that further revusiran administration be discontinued, or that the patient may continue or resume revusiran dosing at the same dose or at a lower dose of 250 mg weekly.

3.5.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

No formal PK criteria have been established for adjusting or stopping dosing of revusiran for this study.

3.6. Criteria for Study Termination

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the clinical study center does not recruit at a reasonable rate, the study may be closed for recruitment and/or terminated at that center. Should the study be terminated and/or the clinical study center closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

3.6.1. 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.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Male or female ≥18 years of age
2. Diagnosis of FAP with documented TTR mutation
3. Received an OLT ≥12 months before the date of informed consent
4. An increase in polyneuropathy disability (PND) score (eg, a PND change from 1 to 2 or 3a to 3b) compared to a preliver transplant assessment OR increase in PND score between any 2 assessments postliver transplant, which in the opinion of the Investigator is due to underlying FAP progression
5. On stable immunosuppressive regimen with ≤10 mg/day of prednisone for at least 3 months before the date of informed consent
6. Neurological impairment score of 5 to 130 (inclusive)
7. Polyneuropathy Disability score of ≤3b
8. Karnofsky Performance Status ≥60%
9. No liver allograft rejection episodes (chronic, acute, or subacute) in the past 6 months before the date of informed consent
10. Normal liver function, including AST, ALT, and total bilirubin (≤ULN), unless elevation in total bilirubin is due to Gilbert's Syndrome, based on central laboratory evaluation
11. Adequate renal function demonstrated by estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 (calculated by a central laboratory using the Modification of Diet in Renal Disease formula, where eGFR in mL/min/1.73m^2 = 175 × [serum creatinine in mg/$dL^{-1.154}$] × [$Age^{-0.203}$] × [1.212 if Black] × [0.742 if female]).
12. Women of child-bearing potential (WOCBP) must have a negative pregnancy test, cannot be breastfeeding, and use 1 highly effective method of contraception in combination with a barrier method throughout study participation, and for 28 days after last dose of study drug
13. Males with partners of child-bearing potential, must agree to use a condom, accompanied with spermicidal foam, gel, film, cream, or suppository, except in countries where spermicide is not available for use in combination with condom, throughout study participation and for 28 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 28 days after the last dose of study drug
14. Patient, or patient's legal representative, is able and willing to provide written informed consent and the patient is willing to comply with the study requirements

4.2. Exclusion Criteria

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Untreated hypo- or hyperthyroidism
2. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed before the first dose of study drug administration
3. Active infection with hepatitis B or hepatitis C (based on serology)
4. Known human immunodeficiency virus infection
5. NYHA classification of >2
6. Known leptomeningeal amyloidosis
7. Other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease)
8. Known type I diabetes
9. Type II diabetes mellitus for ≥5 years from the time of informed consent
10. Vitamin B12 levels below the lower limit of normal
11. Current, heavy alcohol use, defined as regular consumption of greater than 2 to 3 units/day for women and 3 to 4 units/day for men (a unit of alcohol equals 1 glass of wine [125 mL], 1 measure of spirits, or ½ pint of beer), or a known history of alcohol abuse within the last 2 years from the time of informed consent
12. Received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the study drug, whichever is longer
13. Currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day washout before start of study drug administration in this study
14. Malignancy within the last 2 years from the time of informed consent, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
15. History of allergic reaction to an oligonucleotide or GalNAc
16. History of intolerance to SC injection
17. Other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation

4.3. Study Drug Discontinuation

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

The Investigator or designee may discontinue dosing in a patient if the patient:

- Is in violation of the protocol

- Experiences a serious or intolerable AE
- Requires a prohibited medication
- Is found to be considerably noncompliant with the protocol-required visits

The Investigator will confer with the Sponsor or CRO Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from dosing immediately. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the 18-month visit so that their experience is captured in the final analyses; however, a patient may withdraw consent to participate in the study at any time. Patients who discontinue study drug may receive local standard of care treatment for their disease.

4.4. Withdrawal Criteria

While patients who discontinue drug are encouraged to remain in the study to complete study assessments (Section 4.3), they are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Patients who withdraw or have a dose reduction before 6 months of study participation may be replaced. Patients will also be withdrawn if the study is terminated.

If a patient chooses to withdraw from the study, every effort should be made to conduct the Early Termination visit. When a patient withdraws from the study, the primary reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible.

The withdrawn patient will be asked to consent to either be contacted by telephone or to allow nonpatient contact follow-up (eg, medical record check) for up to 18 months after enrolling onto the study to document their overall health status.

5. TREATMENT OF PATIENTS

5.1. Description of Study Drug

As this is an open-label study, all patients will receive the same study treatments. Beginning on Day 0, all patients will receive 5 daily SC doses of 500 mg of revusiran administered as 2 injections. The same dose will be administered at Day 7 and then weekly from Week 2 through 18 months. Dose reductions will be allowed during the study, see Section 3.5 for details.

5.2. Concomitant Medications

Use of tafamidis, diflunisal, doxycycline, or tauroursodeoxycholic acid within 14 days before the first dose of study medication in this protocol or use of any other investigational agent or device within 30 days (or 5 half-lives of the study drug, whichever is longer) before the first dose of study medication is prohibited for study entry and during study participation.

Medications and treatments other than those specified previously, including palliative and supportive care approved by the Investigator for disease-related symptoms (eg, immunosuppressive agents) are permitted during the study and will be recorded. Previous immunosuppressive agent administration and blood levels from the 6 months before signing of the ICF will be collected, if available, as part of prior concomitant medications.

All patients on the study will be asked to take a daily supplement containing the recommended daily allowance of vitamin A.

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

During the study, patients are also advised not to consume alcohol over the levels stated in the eligibility criterion.

Use of all concomitant medications from the Screening visit through the Follow-up visit will be recorded on the patient's eCRF. This will include all prescription drugs, herbal preparations, OTC medications, vitamins (including the supplemental vitamin A), and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator; however, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF.

5.3. Contraceptive Requirements

5.3.1. Contraceptive Requirements for Female Patients

Women of child-bearing potential (WOCBP) may be included in this study and include any female who has experienced menarche and who is not postmenopausal or permanently sterilized (eg, tubal occlusion, hysterectomy, or bilateral salpingectomy).

WOCBP must have a negative pregnancy test and must be using 1 highly effective method of contraception in combination with a barrier method from the signing of the informed consent

form (ICF), throughout study participation, and for 28 days after the last dose of the study drug. Highly effective methods of birth control result in a low failure rate (ie, less than 1% per year). Acceptable forms of effective contraception are defined as follows:

- Hormonal: established use of oral (except low-dose gestagens [eg, lynestrenol and norethisterone]), implantable or injectable methods of contraception in conjunction with spermicide, condom, or diaphragm
- Placement of an intrauterine device (IUD) in conjunction with spermicide or condom
- Placement of an intrauterine system (IUS) (for example, progestin-releasing coil) in conjunction with spermicide or condom
- Bilateral tubal occlusion in conjunction with spermicide, condom, or diaphragm
- 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) in conjunction with spermicide, condom, or diaphragm
- Sexual true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

Interaction between revusiran and hormonal contraceptives is not anticipated; there were no effects of study drug on the reproductive organs (including histopathology) in any of the animal (rat and NHP) studies conducted to date. Moreover, revusiran showed no inhibition in vitro of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (both testosterone and midazolam were used as substrates in human liver microsomes).

5.3.2. Contraceptive Requirements for Male Patients

Males with partners of child-bearing potential who agree to use appropriate means of contraception throughout study participation until 28 days after the last dose of study drug may be included in this study.

It is unknown if revusiran poses any potential risk of drug exposure through the ejaculate. Male patients (including men who have had vasectomies), particularly those with partners who are pregnant, must use a condom, accompanied with spermicidal foam, gel, film, cream, or suppository, except in countries where spermicide is not available for use in combination with condom, as the appropriate means of contraception for the duration of the study and until 28 days after the last administration of study drug.

Males should also abstain from sperm donation after the first dose of study drug through study participation and for 28 days after the last dose of study drug.

5.4. Treatment Compliance

Treatment compliance with study drug administration is dependent on the proper preparation and administration of SC injections. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 3 consecutive doses at any time during the study, the Investigator, in consultation with the CRO Medical Monitor, will discuss whether the patient will

be able to continue on the study. If a patient misses a dose of study drug, and remembers before their next dose, they should receive the missed dose as soon as possible within the visit window, otherwise the missed dose will not be made up. Patients should never receive more than 1 dose of study drug a day.

5.5. Randomization and Blinding

This is an open-label, single-arm study, therefore no randomization or blinding will be needed in this study.

5.6. Patient Numbering

Each patient will be uniquely identified in the study by a combination of the clinical study center number and screening number. The clinical study center number will be assigned by the Sponsor. A combination of the center number and screening number will create the unique patient identifier.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

All study drugs may be dispensed only by the Investigator or trained individual as defined in the Pharmacy Manual and Homecare Nursing Manual.

Revusiran Solution for Injection (SC use) is comprised of an siRNA targeting mutant and WT TTR mRNA with a covalently attached triantennary GalNAc ligand formulated in water for injection.

Revusiran will be supplied as a sterile 200 mg/mL solution.

6.2. Study Drug Packaging and Labeling

All packaging and labeling as well as the preparation of revusiran will be in compliance with Good Manufacturing Practice specifications, and any other or local applicable regulations.

6.3. Study Drug Storage

All study drugs will be stored refrigerated at approximately 5°C±3°C, protected from light. Any deviation from the recommended storage conditions should be reported to the Sponsor and/or the CRO.

No special procedures for the safe handling of revusiran are required.

The Sponsor will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

No study drug may be administered to any person not enrolled in the study.

Additional storage details are provided in the Pharmacy Manual.

6.4. Study Drug Preparation

The study drug will be prepared by clinical study center staff, a healthcare professional, the patient, or caregiver according to the procedures detailed in the Pharmacy Manual.

6.5. Administration

Beginning on Day 0, patients will receive 5 daily SC doses of 500 mg of revusiran administered as 2 injections. The same dose will be administered at Day 7 and then weekly from Week 2 through 18 months. Study drug will be administered at the clinical study center on Days 0 through 4 by qualified clinical study center staff under the supervision of the Investigator, or designee.

After Day 4 study drug may be administered at home by a healthcare professional trained in the administration of study drug or at the clinic. At the discretion of the Investigator, after the Month 6 dosing visit, and if the patient has not previously experienced any severe AE or SAEs considered related to the study drug within the previous 12 weeks, that the Investigator and Medical Monitor believe should preclude the patient from self-administration, patients/caregivers

may be trained by the Investigator or qualified clinical study center staff in the administration of the study drug, according to the protocol dosing requirements. If a severe AE or related SAE occurs, patients should not self-administer study drug for a 12-week period, unless prior approval is obtained from the Medical Monitor. The preferred region of SC injection is the abdomen. Optional additional regions include the upper arms and thighs. The site of injection within a given region will be rotated and recorded.

Detailed instructions can be found in the Pharmacy Manual.

6.6. Study Drug Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of all study drugs including dates of receipt. Accurate records will be kept detailing when and how much study drug is dispensed and used by each patient in the study. Any reason for departure from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available for verification by the Sponsor Monitor or designee. Periodically throughout the study, there will be a reconciliation of all study drug.

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

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

6.7. Study Drug Handling and Disposal

Remaining study drug (all used, partially used, and unused vials) will be returned to the Sponsor or its agent or destroyed at the clinical study center according to applicable regulations.

7. PHARMACOKINETIC ASSESSMENTS

7.1. Blood Sample Collection

Blood samples will be collected for the assessment of plasma levels of revusiran at the time points in the Schedule of Assessments (Table 1).

Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of revusiran.

7.2. Sample Analysis

Pharmacokinetic samples will be analyzed by a central laboratory. Instructions for storage and handling of PK samples can be found in the Study Reference Manual.

8. ASSESSMENT OF EFFICACY

The timing of assessments is in the Schedule of Assessments (Table 1).

8.1. Primary Efficacy Assessment

Serum samples will be collected within 1 hour predose for the measurement of total TTR levels. Samples will be analysed using an enzyme-linked immunosorbent assay method at a central laboratory.

8.2. Secondary Efficacy Assessments

8.2.1. 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 (including NIS weakness, reflexes, and sensation. Note: sensation is not included in the mNIS+7 score)
- Electrophysiologic measures of small and large nerve fiber function (+7) including:
  - Nerve conduction studies (NCS) 5 attributes (Σ5)
  - Quantitative sensory testing (QST) by body surface area including touch pressure and heat pain
- Autonomic function (postural blood pressure)

A summary of the scoring of the components of the mNIS+7 is in Appendix 16.1.

At each time point, 2 independent assessments will be performed. Each clinical study center will make every effort to have these assessments performed by the same study staff. 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, the source documents and results from 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.

8.2.2. 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-small fiber, large fiber, and autonomic nerve function.[37]

8.2.3. Polyneuropathy Disability Score

Changes in ambulation will be evaluated through the PND score; the PND scale is in Appendix 16.2.[38,39]

8.3. Exploratory Assessments

Additional details can be found in the revusiran Study Reference Manual.

8.3.1. Modified Body Mass Index

Using Body weight data, the mBMI will be calculated (body mass index × albumin). This calculation will take place programmatically; the calculation will not be performed by the clinical study center staff.

8.3.2. Familial Amyloidotic Polyneuropathy Stage

Changes in ambulation will be evaluated through the FAP stage; the FAP stage scale is in Appendix 16.3.[38,39]

8.3.3. Neurological Impairment Score

The NIS includes measurements of weakness, sensation, and reflexes. The NIS weakness and reflex sub-components are the same as the mNIS+7. The sensory component in mNIS+7 uses QST a more quantitative approach to assessing a broader range of somatic sensory function than the sensory sub-score within the NIS. At each time point, 2 independent assessments will be performed in the same manner as described for mNIS+7.

8.3.4. Grip Strength Test

Hand grip strength will be measured by dynamometer. Clinical study center staff will be trained on the use of a 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 study visit day and 2 independent assessments will be performed ≥24 hours, but ≤7 days apart. Every effort will be made to use the same dynamometer for a patient throughout the duration of the study.

8.3.5. New York Heart Association Classification

New York Heart Association classification will be recorded. The NYHA classification scale is provided in Appendix 16.4.

8.3.6. Karnofsky Performance Status

Performance status will be assessed according to the Karnofsky Performance Status scale; the scale is in Appendix 16.5.

8.3.7. Echocardiogram

An echocardiogram (ECHO) with Doppler will be used for assessment of cardiac structure and function and will be assessed by a central laboratory.

Details for image acquisition and upload for central review can be found in the revusiran Study Reference Manual.

8.3.8. Cardiac Biomarkers

Blood samples will be collected and analyzed for the quantification of troponin T, troponin I, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP; biomarkers of cardiac status), and B-type natriuretic peptide (BNP). Quantification of these biomarkers will be performed at a central laboratory.

8.3.9. EuroQOL Questionnaire in 5 Dimensions

Quality of life will be assessed through the use of the EuroQOL questionnaire in 5 dimensions (EQ-5D), a standardized 5-question instrument for use as a measure of health outcomes.[34]

8.3.10. Composite Autonomic Symptom Score

To evaluate changes in autonomic symptoms, patients will complete the Composite Autonomic Symptom Score (COMPASS 31) questionnaire. The questionnaire consists of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, secretomotor, gastrointestinal, bladder, and pupillomotor).[35]

8.3.11. Columbia Suicide Severity Rating Scale Questionnaire

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to assess the mental status of the patient as it relates to suicidal ideation and behavior. This questionnaire will be administered to the patient by trained study personnel.[41]

8.3.12. Pharmacoeconomics Questionnaire

Disease level and healthcare utilization will be assessed using a patient reported pharmacoeconomics questionnaire.

8.3.13. Optional Exploratory Assessment

8.3.13.1. Optional Residual Liver Tissue Evaluation

If, at any time during the study, a liver biopsy is performed per standard of care procedures, an optional evaluation of residual liver tissue may also be performed; and, if allowed by local regulations, this evaluation will include measurement of the concentration of revusiran in residual tissue and a possible evaluation of the mechanism of action for revusiran.

Details can be found in the revusiran Study Reference Manual.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

9.1.1. Demographic and Medical History

Patient demographic data will be obtained at the Screening visit. A complete medical history will be obtained at Screening. As part of the complete medical history, if available, the prior 6 months of LFTs will also be collected. An interval medical history will be collected during the Screening/Baseline and Baseline visits and only changes in medical history will be recorded.

9.1.2. Vital Signs

Vital sign measurements include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position (should be consistent for each patient), after the patient has rested comfortably for 10 minutes. Blood pressure should be taken using the same arm. Oral body temperature will be obtained in degrees Celsius, heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

When vital signs are scheduled at the same time as blood samples, vital signs should be obtained before the blood sample. On dosing days, vital signs should be obtained before dosing.

For the safety of the patient, additional vital sign assessments may be added at the discretion of the Investigator.

9.1.3. Weight and Height

Height will be measured only at the Screening visit. Body weight will be measured in kilograms.

9.1.4. Physical Examination

Routine physical examinations will include the examination of the following: general appearance, head, eyes, ears, nose and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric.

9.1.5. Ophthalmologic examination

Visual acuity should be evaluated at the beginning of each specified visit (eg, before slit-lamp examination). Manifest refraction will be performed at each specified visit, where possible, before visual acuity testing and will be used to obtain a correction for visual acuity evaluations. Visual acuity testing should be done with best (most recent) correction and be tested in bright and dim light conditions.

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

9.1.6. Immunosuppressive Agent Monitoring

Blood samples for immunosuppressant monitoring will be collected at the time points in the Schedule of Assessments and for any suspected episodes of allograft rejection. Samples may also be collected at unscheduled time points when clinically indicated per local standard of care procedures. Sample analysis will take place at a local laboratory.

9.1.7. Liver Allograft Status

Patients will be monitored for possible liver allograft rejection; any biopsies performed to rule out allograft rejection will be evaluated according to the Banff Working Group on Liver Allograft Pathology criteria, a set of consensus criteria for the causes of liver allograft dysfunction.[40]

9.1.8. Electrocardiogram

A triplicate 12-lead ECG will be recorded at baseline; thereafter, single 12-lead ECGs will be recorded. Additional ECGs may be collected at the discretion of the Investigator. Standard computerized 12-lead electrocardiogram (ECG) recordings will be obtained. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/s. Recordings will be obtained before dosing, after the patient has rested comfortably for approximately 10 minutes. The electrophysiological parameters assessed will be rhythm, ventricular rate, PR interval, QRS duration, QT interval, ST and T-waves, Bazett-corrected QT interval (QTcB) and Fredericia-corrected QT interval (QTcF).

When an ECG is scheduled at the same time as a blood sample collection, the ECG will be obtained before the scheduled blood sample.

The Investigator or designee is responsible for reviewing the ECGs to assess whether the results have changed since the Screening/Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. For any clinically significant changes from the Screening/Baseline visit (eg, ischemic ECG changes, wave/interval changes, or arrhythmia), the Investigator must contact the CRO Medical Monitor to discuss continued participation of the patient in the study.

9.1.9. Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. 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.

Hematology	
Hematocrit	Neutrophils, absolute and %
Hemoglobin	Lymphocytes, absolute and %
RBC count	Monocytes, absolute and %
WBC count	Eosinophils, absolute and %
Mean corpuscular volume	Basophils, absolute and %

Mean corpuscular hemoglobin	Platelet count
Mean corpuscular hemoglobin concentration	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine[a]	Albumin
Uric acid	Calcium
LDH	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation Assessments	
PT	INR
aPTT	
Thyroid Function Test	
TSH	
Serology Parameters	
HBsAg	HBsAb
HCV Ab	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Pregnancy Testing (WOCBP only)	
β-human chorionic gonadotropin	
Other	
Vitamin A	Vitamin B12

Abbreviations: AST=aspartate transaminase; ALP=alkaline phosphatase; ALT=alanine transaminase; BUN=blood urea nitrogen; HBsAg=hepatitis B surface antigen; HBsAb=hepatitis B surface antibodies; HCVAb=antihepatitis C virus antibodies; INR=international normalized ratio; LDH=lactate dehydrogenase; PT=prothrombin time; aPTT=activated partial prothrombin time; RBC=red blood cells; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=women of child bearing potential.

[a] eGFR will be calculated by a central laboratory using the Modification of Diet in Renal Disease formula, where eGFR in mL/min/1.73m^2 = 175 × [serum creatinine in mg/dL$^{-1.154}$] × [Age$^{-0.203}$] × [1.212 if Black] × [0.742 if female].

9.1.9.1. Pregnancy Screening

A serum pregnancy test will be performed for WOCBP at screening. A urinary pregnancy test will be performed monthly and at any time pregnancy is suspected. The results of the pregnancy test must be known before administration of study drug. Patients who are pregnant are not eligible for study participation. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (Section 9.8).

9.1.9.2. Exploratory Biomarkers

Where local regulations permit, predose blood samples will be collected. Collection of blood samples for long-term storage to permit testing of additional proteins related to FAP and exploratory biomarker analysis will be subject to discretionary approval from the IRB/IEC at the clinical study centers. Samples will be stored by the Sponsor or designee in a secure and controlled environment until analysis, and will be destroyed by the Sponsor or designee after all worldwide obligations have been met, or sooner if required by local regulations.

9.1.9.3. Antidrug Antibodies

Blood samples will be collected to evaluate antidrug antibodies. Blood samples for antidrug antibody testing must be collected before study drug administration.

9.2. Adverse and Serious Adverse Events

9.2.1. Definition of Adverse Events

9.2.1.1. Adverse Event

An AE is defined as any unfavorable and unintended change in structure, function, or chemistry of the body temporally associated with the use of the investigational product, whether or not it is considered related to the use of the product.

Any medical condition that is present when a patient is screened and does not deteriorate should not be reported as an AE; however, if the medical condition does deteriorate at any time after administration of the first dose of study drug, it should be reported as an AE.

9.2.1.2. Serious Adverse Event

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 in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality 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 and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse)

9.2.1.3. Adverse Events of Clinical Interest

The following events are considered to be AEs of clinical interest:

- ISRs
- Hepatic AEs, including LFT abnormalities considered clinically significant by the Investigator

9.2.2. 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 that are relevant to patient safety.

9.3. Adverse Event Reporting

The Investigator is responsible for reporting all AEs that are observed or reported after administration of the first dose of study drug regardless of their relationship to study drug through the end of study (28 days after administration of the last dose of study drug).

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must 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).

For AEs that are considered AEs of clinical interest, additional clinical information may be collected based upon the severity or nature of the event.

If a patient has ISRs meeting any of the following criteria, the Investigator or delegate should contact the Medical Monitor and submit a supplemental ISR eCRF:

- ISRs that are recurrent and/or demonstrate a pattern of increasing severity
- Any ISR that is determined to be severe and/or a cause for study drug discontinuation
- Any ISR which, in the opinion of the Investigator, requires further medical evaluation or treatment

In some cases, where it is medically appropriate, further evaluation may include photographs, referral to a dermatologist, skin biopsy, or other laboratory testing. If a biopsy was obtained, the

Sponsor may request that the biopsy also be reviewed by a central dermatopathologist. To better understand the safety profile of the study drug, additional analysis of biopsy tissue may be performed according to local regulations.

For patients with hepatic AEs, additional information, including, clinical history, course of event, and local laboratory results to monitor LFT levels or other laboratory parameters, may be collected.

9.4. 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.

9.5. 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 normal daily activities.
Severe	Severe events are those which incapacitate and prevent usual activity.

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

9.6. Coding of Adverse Events

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

9.7. 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 SAE criteria in Section 9.2.1.2 must be reported to the CRO within 24 hours from the time that clinical study center staff first learns 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, and
- Preliminary assignment of causality to study drug

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided below.

SAE Reporting Contact Information

Medpace, Inc.

medpace-safetynotification@medpace.com

Country-specific fax numbers will be included in the Study Reference Manual

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.

9.7.1. Notifying the Institutional Review Board/Independent Ethics Committee

Serious adverse events will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

9.7.2. Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for suspected unexpected serious adverse reactions and other reportable events:

Immediately and within 7 calendar days

- Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and fatal or life threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days

- Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and serious, but not fatal or life threatening, and there is evidence to suggest a causal relationship between the study drug and the reaction.
- Any finding from tests in laboratory animals that: suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the trial patients.

In addition, periodic safety reporting to regulatory authorities will be done by the Sponsor or its representative according to national and local regulations.

9.7.3. Sponsor Notification of Participating Investigators

All Investigators will be informed by the Sponsor or its representative of relevant clinical safety findings from this or other clinical studies, as well as any new findings from tests in laboratory animals that significantly impact the benefit/risk to patients in this study. All reports should be transmitted to the IEC/IRB that approved the study.

9.8. Pregnancy Reporting

A female patient with a positive pregnancy test at screening is ineligible for this study. If a female patient becomes pregnant during the course of this study (or during the first month following the last dose of study drug), the patient must be instructed to stop all study drug administration, and the Investigator must 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 (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), then the Investigator should follow the procedures for reporting an SAE as outlined in Section 9.7.

If the female partner of a patient becomes pregnant during the course of this study, the Investigator must report the pregnancy to the CRO within 24 hours of being notified of the pregnancy. The pregnancy should be followed by the Investigator until its conclusion.

10. STATISTICS

10.1. Sample Size

This is an open-label study to evaluate efficacy, safety, and PK of revusiran in patients with TTR-mediated FAP with disease progression post-OLT. In healthy volunteers, mean reduction of 88% in serum TTR has been observed from baseline to Day 35 with a standard deviation of 6%. If this study yields a mean reduction of 80% at 6 months with a standard deviation of 6%, 12 patients would yield a 95% confidence interval (CI) of approximately 77% to 83%.

10.2. Statistical Methodology

A full statistical plan will be finalized before database lock.

The primary efficacy analysis will be performed after all patients have finished 6 months of treatment with study drug.

Analyses will be performed using SAS® for Windows (version 9.2 or higher). Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of nonmissing values in the dose group. All study data will be presented in by-patient/patient data listings.

10.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

Evaluable Analysis Set: All patients who have received at least one dose of study drug and have a non-missing serum TTR result at the Month 6 (Week 26) visit.

Safety Analysis Set: All patients who received at least a single dose of study drug.

PK Analysis Set: All patients who received at least a single dose of study drug and have at least 1 postdose blood sample for PK parameters and who have evaluable PK data.

The primary population used to evaluate efficacy will be the Evaluable Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses.

10.2.2. Baseline Evaluations

Demographic and key disease characteristics data will be summarized. Data to be tabulated consist of gender, age, ethnicity, and race, as well as other key disease characteristics.

10.2.3. Efficacy Analyses

10.2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percent reduction from baseline in serum TTR level at 6 months. This analysis will be a 2-sided 95% CI for the mean of the primary endpoint. A t-test,

in which the null hypothesis of no reduction is compared against the alternative hypothesis of a change, will also be performed.

Sensitivity analyses, including different methods for handling the missing data, will assess the robustness of the primary endpoint for the Evaluable Analysis Set.

10.2.3.2. Secondary Efficacy Endpoints

The secondary endpoints of the study are the change from baseline over 18 months for the following: serum TTR, mNIS+7, Norfolk QOL-DN, and PND score.

For continuous parameters, measurements will be summarized using descriptive statistics. Actual measurement, change, and percentage change from baseline to each scheduled visit will be summarized. To understand the effect of revusiran, the mean change from baseline at 18 months with the associated 80% and 95% CIs will also be summarized.

For categorical parameters, frequencies and percentages will be presented. To understand the effect of revusiran from baseline, the frequency and percentage of patients at each of the category shifts from baseline at 18 months will be summarized.

10.2.3.3. Exploratory Endpoints

The exploratory endpoints of the study are to assess the change from baseline over 18 months for the following: mBMI, FAP stage, NIS, a grip strength test, NYHA classification, Karnofsky Performance Status, ECHO parameters, cardiac biomarkers, EQ-5D and COMPASS 31 questionnaires, and an optional exploratory residual liver tissue evaluation, if available. Analyses for these endpoints will be conducted in a similar fashion as specified for secondary efficacy endpoints.

10.2.4. Safety Analyses

Safety assessments include AEs (including liver allograft rejection), clinical laboratory parameters (hematology and serum chemistry, including liver function tests, renal function, thyroid function, coagulation, and urinalysis), vital signs (oral body temperature, blood pressure, heart rate, and respiration rate), 12-lead ECGs, physical and ophthalmologic examinations, and concomitant medications (including immunosuppressive agent monitoring).

10.2.4.1. Adverse Events

Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. Separate tabulations will be generated for treatment-emergent AEs (TEAEs), TEAEs by maximum severity, treatment-related AEs, SAEs, and discontinuation of study drug due to AEs. A patient listing will be produced for all AEs, deaths, SAEs, and AES leading to discontinuation of study drug.

10.2.4.2. Vital Signs, Clinical Laboratory Safety Tests, 12-lead Electrocardiograms, Physical and Ophthalmologic Examinations

For each continuous laboratory safety parameter (including, but not limited to, hematology, serum chemistry, coagulation, and urinalysis) results will be categorized as low, normal, or high based on the laboratory normal ranges. Shifts from baseline laboratory grade to the maximum

laboratory grades will be examined for key safety parameters. All out-of-range and clinically significant laboratory results will be identified in data listings. Descriptive statistics will also be provided as actual value and change from baseline over time.

Descriptive statistics for vital signs and ECG interval data will be presented by actual values and changes over time from baseline. Details of any abnormalities will be included in the data listings.

For ophthalmologic examinations, descriptive statistics of changes in eye examinations from baseline over time will be presented. Separate listings will be generated for any abnormalities noted during the eye examination.

10.2.4.3. Concomitant Medications

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary. Additional safety analyses will focus on therapy, frequency, and dose of immunosuppressive agents.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

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

11.2. Audits and Inspections

Authorized representatives of Alnylam Pharmaceuticals, Inc., a regulatory authority, an IEC, or an IRB may visit the clinical study center to perform audits or inspections, including source data verification. The purpose of an Alnylam Pharmaceuticals, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Alnylam Pharmaceuticals, Inc. immediately if contacted by a regulatory agency about an inspection.

11.3. Institutional Review Board

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study including the patient ICF and recruitment materials must be maintained by the Investigator and made available for inspection.

11.4. Quality Control and Quality Assurance

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

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

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

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

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

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

12. ETHICS

12.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to Alnylam Pharmaceuticals, Inc. before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Alnylam Pharmaceuticals, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and Alnylam Pharmaceuticals, Inc.'s policy.

12.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to withdraw from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

13. DATA HANDLING AND RECORD KEEPING

13.1. Inspection of Records

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

13.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Alnylam Pharmaceuticals, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

14. PUBLICATION POLICY

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed manuscript must be provided and confirmed received at Alnylam at least 30 days before submission, and according to any additional publication details in the Investigator Agreement.

15. LIST OF REFERENCES

1. Stangou, A.J., Hawkins, P.N. Liver transplantation in transthyretin-related familial amyloid polyneuropathy. Curr Opin Neurol. 2004;17(5):615-620.
2. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants. Amyloid. 2003;10:160-184.
3. Tsuchiya A, Yazaki M, Kametani F, Takei Y-i, Ikeda S-i. Marked regression of abdominal fat amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. Liver Transplantation. 2008;14:702-706.
4. Yazaki M., Tokuda T, Nakamura A, et al. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. Biochem Biophys Res Commun. 2000;274(3):702-706.
5. Suhr OB. Impact of liver transplantation on familial amyloidotic polyneuropathy (FAP) patients' symptoms and complications. Amyloid. 2003;10(Suppl 1):77-83.
6. Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. Arch Neurol. 2005;62(7):1057-1062.
7. Coelho T, Adams D, Silva A, et al. Safety and Efficacy of an RNAi Therapeutic Targeting Transthyretin (TTR) for TTR Amyloidosis. NEJM. 2013, accepted for publication.
8. Carvalho M, Alves M, Luis M. Octreotide--a new treatment for diarrhoea in familial amyloidotic polyneuropathy. J Neurol Neurosurg Psychiatry. 1992;55(9):860-861.
9. Connors LH, Yamashita T, Yazaki M, Skinner M, Benson MD. A rare transthyretin mutation (Asp18Glu) associated with cardiomyopathy. Amyloid. 2004;11(1):61-66.
10. Soares ML, Coelho T, Sousa A, et al. Susceptibility and modifier genes in Portuguese transthyretin V30M amyloid polyneuropathy: complexity in a single-gene disease. Hum Mol Genet. 2005;14(4):543-553.
11. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007;36(4):411-423.
12. Eriksson P, Olofsson BO. Pacemaker treatment in familial amyloidosis with polyneuropathy. Pacing Clin Electrophysiol. 1984;7(4):702-706.
13. Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necropsy patients. Am J Cardiol. 1983;52(1):137-146.
14. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. Arch Intern Med. 2006;166(17):1805-1813.
15. Plante-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol. 2011;10(12):1086-1097.
16. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013;310(24):2658-2667.

17. Reines JB, Vera TR, Martín MU, et al. Epidemiology of transthyretin-associated familial amyloid polyneuropathy in the Majorcan area: Son Llatzer Hospital descriptive study. Orphanet J Rare Dis. 2014;9:29.

18. Adams D, Mincheva Z, Antonini T, et al. Worsening of familial amyloid polyneuropathy after liver transplant. J Peripheral Nervous System. 2013;18(Supplement): S2.

19. Benson MD. Liver transplantation and transthyretin amyloidosis. Muscle Nerve. 2013;47(2):157-162.

20. Tsuchiya-Suzuki A, Yazaki M, Kametani F, Sekijima Y, Ikeda S. Wild-type transthyretin significantly contributes to the formation of amyloid fibrils in familial amyloid polyneuropathy patients with amyloidogenic transthyretin Val30Met. Hum Pathol. 2011;42:236–43.

21. Yazaki M, Mitsuhashi S, Tokuda T, et al. Progressive wild-type transthyretin deposition after liver transplantation preferentially occurs onto myocardium in FAP patients. Am J Transplantation. 2007;7(1):235-242.

22. Ihse E, Suhr OB, Hellman U, Westermark P. Variation in amount of wild-type transthyretin in different fibril and tissue types in ATTR amyloidosis. J Mol Med (Berl). 2011;89(2):171-180.

23. Ericzon BG,Wilczek HE. Liver transplantation for hereditary transthyretin amyloidosis: After 20 years still the best therapeutic alternative? Transplantation. 2015.

24. Vaishnaw AK, Gollob J, Gamba-Vitalo C, et al. A status report on RNAi therapeutics. Silence. 2010 Jul 8;1(1):14.

25. Elbashir SM, Lendeckel W, Tuschi T. RNA interference is mediated by 21- and 22-nucleotide RNAs. Genes Dev. 2001 Jan 15;15(2):188-200.

26. Soutschek J, Akinc A, Bramlage B, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004 Nov 11;432:173-178.

27. Coelho T, Silva A, Suhr OB, et al. Final Phase 1 safety, pharmacokinetic and pharmacodynamics results for ALN-TTR01, a novel RNAi therapeutic for the treatment of transthyretin amyloidosis. 13th International Symposium of Amyloidosis, 2012 Oral Presentation.

28. Fitzgerald K, Frank-Kamenetsky M, Mant T, et al. Phase I safety, pharmacokinetic and pharmacodynamics results for ALN PCS02, a novel RNAi therapeutic for the treatment of hypercholesterolemia. Arteriosclerosis, Thrombosis, and Vascular Biology 2012 Scientific Sessions. Oral Presentation.

29. Lachmann HJ, Gallimore R, Gillmore JD, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Br J Haematol. 2003;122(1):78-84.

30. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356(23):2361-2371.

31. Gillmore JD, Hawkins PN. Drug Insight: emerging therapies for amyloidosis. Nat Clin Pract Nephrol. 2006;2(5):263-270.

32. Stangou AJ, Banner NR, Hendry BM, et al. Hereditary fibrinogen A alpha-chain amyloidosis: phenotypic characterization of a systemic disease and the role of liver transplantation. Blood. 2010;115(15):2998-3007.

33. Oshima T, Kawahara S, Ueda M, et al. Changes in pathological and biochemical findings of systemic tissue sites in familial amyloid polyneuropathy more than 10 years after liver transplantation. J Neurol Neurosurg Psychiatry. 2014;85(7):740-6.

34. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy.1990;16(3):199-208.

35. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS-31: a refined and abbreviated composite autonomic symptom score. Mayo Clin Proc. 2012;87:1196-1201.

36. Liepnieks JJ, Zhang LQ, Benson MD. Progression of transthyretin amyloid neuropathy after liver transplantation. Neurology. 2010;75:324–327.

37. Vinik EJ, Vinik AI, Paulson JF, Merkies ISJ, Packman J, Grogan DR, and CoelhoT. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. Journal of the Peripheral Nervous System. 2014;19:104–114.

38. Yamamoto S, Wilczek HE, Nowak G, et al. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. Am J Transplant. 2007;7:2597-604.

39. Coutinho P, DeSilva AM, Lima JL, Barbosa AR. Forty years of experience with type I amyloid neuropathy: review of 483 cases. In: Glenner GG, Pinho P, Costa E, Falcao de Freitas A, Eds. Amyloid and Amyloidosis. Amsterdam: Excerpta Medica;1980:88-98.

40. Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, et al. Banff Working Group. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 2006;44:489-501.

41. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168:1266-77.

16. APPENDICES

16.1. Modified Neurological Impairment Score +7 Components

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

Abbreviations: ∑5=5 attributes; CMAP=compound muscle action potential; QST-BSATP+HP=quantitative sensory testing, body surface area, touch pressure plus heat pain; SNAP=sensory nerve action potential.

16.2. 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 1 stick or crutch Walking with the help of 2 sticks or crutches
IV	Confined to a wheelchair or bedridden

16.3. 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

16.4. New York Heart Association Classification of Heart Failure

Class	Symptomology
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 1 to 2 blocks on the level and climbing more than 1 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.

16.5. Karnofsky Performance Status

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 is not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead