CLINICAL STUDY PROTOCOL

ALN-TTRSC-004

A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN-TTRSC in Patients with Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC)

Original Protocol:	03 October 2014
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Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA
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Sponsor Signature:	[redacted] Date: 22 Feb 2016
Name (print):	[redacted]

CONFIDENTIAL

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

Authorized Signatories

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

Principal Investigator

Signature _____ Date _____

Name (print) _____

STUDY SYNOPSIS

Protocol Title	A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN-TTRSC in Patients With Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC)
Indication	Treatment of patients with TTR mediated FAC
Protocol Number	ALN-TTRSC-004
Phase of Development	3
Design	This is a multicenter, multinational, randomized, double-blind study comparing the efficacy and safety of ALN-TTRSC (International Nonproprietary Name: revusiran) to placebo in patients with TTR mediated FAC. Consented eligible patients will be randomized to receive either 500 mg ALN-TTRSC or placebo in a 2:1 ratio (ALN-TTRSC:placebo) in a blinded manner. Treatment groups will be balanced at entry for New York Heart Association (NYHA) classification (I and II vs III), TTR mutation (V122I versus other FAC mutations), and Screening/Baseline 6-minute walk distance (6-MWD [≤325 meters vs >325 meters]). Patients will receive ALN-TTRSC or placebo for 5 daily doses during the first week and then once every week for approximately 18 months. Patients will return to clinic for a follow-up visit approximately 4 weeks after their last dose of study drug. Patients will undergo efficacy and safety assessments at Screening/Baseline, each month for first 3 months and then at 3-6 month intervals. In addition, pharmacokinetics (PK) of ALN-TTRSC and its effect on quality of life and pharmacoeconomics will be characterized at selected time points. Eligible patients who complete study dosing and the 18 month efficacy assessments may be eligible to participate in a ALN-TTRSC open-label extension study. An independent Data Monitoring Committee (DMC) will be implemented for the study and will operate under a prespecified charter. An independent Clinical Adjudication Committee (CAC) will adjudicate the secondary endpoints of mortality and hospitalization.
Study Sites	This study is to be conducted at approximately 60 study sites worldwide.
Investigational Drug	ALN-TTRSC is comprised of a small interfering ribonucleic acid (siRNA) targeting mutant and wild-type (WT) TTR messenger RNA (mRNA) with a covalently attached N-acetylgalactosamine (GalNAc) ligand formulated in water for injection.
Dosage, Route of Administration and Duration of Treatment of Investigational Drug	Patients randomized to ALN-TTRSC will receive 5 daily subcutaneous (SC) injections of 500 mg of ALN-TTRSC (Day 0 through Day 4). The same dose will be administered at Day 7 and then once weekly through 18 months.
Control Drug	Placebo (normal saline 0.9% for SC administration). Placebo will be packaged and administered identically to ALN-TTRSC.
Dosage, Route of Administration and	Patients randomized to placebo will receive SC normal saline (0.9%) using the

Duration of Treatment of Control Drug	same dosing schedule as the active treatment group.
Time on Study	The duration of patient participation in this study is approximately 20 months (inclusive of up to a 45 day Screening/Baseline window and up to 35 days of follow-up after the last dose).
Primary Objective	The primary objective of the study is to determine the efficacy of ALN-TTRSC in patients with FAC. This will be assessed as the difference between treatment and placebo groups at 18 months using a co-primary endpoint of: (1) change in meters in 6-MWD compared to baseline distance; and (2) percent reduction in serum TTR levels compared to baseline levels.
Sample Size	Approximately 200 patients will be randomized in this study. For the 6-MWD primary endpoint, a sample size of 180 with a 2:1 treatment allocation (N=120 on ALN-TTRSC and N=60 on placebo) has 90% power to detect a treatment difference of 0.55 standard deviations using a Finkelstein and Schoenfeld analysis with a significance level of 0.05. This assumes 20% of placebo patients and 13% of ALN-TTRSC patients die before the 18 month assessment (ie, hazard ratio [HR] = 0.6). Assuming a standard deviation of 70 meters in change from baseline, this would correspond to 90% power to detect a treatment effect of 39 meters in the 6-MWT. Assuming a 10% patient dropout rate, approximately 200 patients will be enrolled in the study. Note that power for the comparison of percent reduction in serum TTR between treatment groups is expected to be >90% for a significance level of 0.05. For this reason, overall power to establish efficacy is expected to be approximately 90% under the assumptions described above.
Inclusion Criteria	1. Are male or female of 18 to 90 years of age (inclusive). 2. Have a documented TTR mutation. 3. Amyloid deposits in cardiac or non-cardiac tissue confirmed by Congo Red (or equivalent) staining or technetium scintigraphy (^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc] or ^{99m}Tc-pyrophosphate [PYP-Tc]) with Grade 2 or 3 cardiac uptake, centrally confirmed. 4. If patient has monoclonal gammopathy, TTR amyloidosis needs to be confirmed through TTR protein identification by immunohistochemistry or mass spectrometry. 5. Have a medical history of heart failure (HF) with at least 1 prior hospitalization for HF, which may include hospitalization for arrhythmia or pacemaker placement, OR clinical evidence of HF (as evidenced by one or more of the following: elevated jugular venous pressure, peripheral edema, shortness of breath or signs of pulmonary congestion on x-ray or auscultation) that either requires/required treatment with diuretics or is/was associated with an N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) >400 ng/L or B-type natriuretic peptide (BNP) >100 ng/L. 6. Have evidence of cardiac involvement by Screening/Baseline echocardiogram including an end-diastolic interventricular septum thickness of ≥12 mm. For patients with an end-diastolic interventricular septum thickness of <12 mm, an endomyocardial biopsy showing amyloid deposition is required.

	7. Can walk ≥150 meters on a 6-minute walk test (6-MWT). 8. Have a Karnofsky performance status of ≥50%. 9. Symptoms of HF optimally managed with no CV hospitalizations within 4 weeks prior to consent or during Screening/Baseline. 10. Have adequate liver function, demonstrated by an aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.0× upper limit of normal (ULN), albumin >3 g/dL (>4.35 µmol/L), and total bilirubin <2.0 mg/dL (34.2 µmol/L), unless elevation in total bilirubin is due to Gilbert's Syndrome. 11. No active infection with hepatitis B (HBV) or hepatitis C (HCV) by serology. 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. Must be willing and able to comply with protocol-required visit schedule and visit requirements and provide informed consent or have a legal guardian who can provide informed consent.
Exclusion Criteria	1. Has estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2 (using the Modification of Diet in Renal Disease [MDRD] formula). 2. Has known primary amyloidosis (AL), leptomeningeal amyloidosis, non-FAC hereditary cardiomyopathy, hypertensive cardiomyopathy, or cardiomyopathy due to valvular heart disease. 3. Has non-amyloid diseases affecting exercise testing (e.g., severe chronic obstructive lung disease, severe arthritis, peripheral vascular disease affecting ambulation). 4. Has uncontrolled hypertension. 5. Has uncontrolled ischemic heart disease. 6. Has uncontrolled clinically significant cardiac arrhythmia. 7. Had acute coronary syndrome within the past 3 months. 8. Has a Polyneuropathy Disability score >2. 9. Has untreated hypo- or hyperthyroidism. 10. Has a New York Heart Association (NYHA) classification of IV. 11. Has known or suspected systemic bacterial, viral, parasitic, or fungal infection. 12. Has known human immunodeficiency virus (HIV) infection. 13. 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 past 2 years. 14. Has received an investigational agent or device within 30 days of

	anticipated study drug administration or 5 half-lives of the investigational drug, whichever is longer. 15. Is currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to start of study drug administration in this study. 16. Had metastatic cancer within the past 5 years. 17. History of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc). 18. Has a history of intolerance to SC injection. 19. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation. 20. Has had a heart or liver transplant, or is being considered for a transplant during the study period. 21. Known history of clinically significant chronic liver disease in the opinion of the Investigator.

Efficacy Endpoints	**Primary endpoints:** The co-primary endpoints of the study are to evaluate the difference between the ALN-TTRSC and placebo groups for: 1. Change in 6-MWD at 18 months compared to baseline 2. Percent reduction in serum TTR burden over 18 months **Secondary endpoints:** The secondary endpoints of the study are to determine the effect of ALN-TTRSC on various clinical parameters by assessing the difference between the ALN-TTRSC and placebo groups at18 months for: • Composite CV mortality and CV hospitalization • Change in New York Heart Association (NYHA) class (Appendix 1) compared to baseline • Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) compared to baseline • Cardiovascular (CV) mortality • CV hospitalization • All-cause mortality **Exploratory endpoints:** The exploratory endpoints of the study are to determine the difference between the ALN-TTRSC and placebo groups in the change from baseline at 18 months in the following measurements: • EuroQOL (EQ-5D) questionnaire • Echocardiogram parameters • Karnofsky performance status (Appendix 2) • Troponin T and I, and N-terminal prohormone of B-type natriuretic peptide (NT proBNP) levels • Cardiac magnetic resonance imaging (CMR) parameters (only at selected sites) • ^{99m}Technetium scintigraphy parameters (only at selected sites) • Amyloid in abdominal wall fat pad aspirates • Polyneuropathy Disability (PND) Score (Appendix 3) • Modified body mass index (mBMI) • Estimated glomerular filtration rate (eGFR) • HF hospitalization
Safety Assessments	The safety of ALN-TTRSC will be evaluated by: • Assessment of adverse events (AEs), including serious adverse events (SAEs)

	• Clinical laboratory safety tests (hematology, serum chemistry including liver function tests (LFTs), thyroid function, coagulation, vitamin A and urinalysis) • Measurement of anti-drug antibodies • Vital sign measurements (blood pressure, pulse rate, oral body temperature, and respiratory rate) • 12-Lead electrocardiogram (ECG) • Physical examinations • Ophthalmology examinations
Pharmacokinetic Assessments	Samples will be taken for the assessment of plasma levels of ALN-TTRSC. Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of ALN-TTRSC.
Other Assessments	Disease burden and healthcare utilization will be assessed using a patient reported pharmacoeconomics questionnaire
Statistical Methods	The following patient populations (ie, analysis sets) will be evaluated and used for presentation of the data: • Modified intent to treat (mITT) population: all patients who were randomized and received at least 1 dose of ALN-TTRSC or placebo. • Per protocol (PP) population: all patients who did not have any major protocol violations; and completed the 18-month 6-MWD assessment or died on-study. • Safety population: All patients who received at least 1 dose of ALN-TTRSC or placebo (analyzed as treated, not as randomized). The primary population for efficacy analyses will be the mITT population; key efficacy results will also be analyzed for the PP population. For efficacy analyses, patients will be grouped according to the treatment to which they were randomized. The primary population for safety analysis will be the safety population. Patients will be grouped according to treatment received for summaries of safety. There are two co-primary endpoints. The first co-primary endpoint is change from baseline (in meters) for 6-MWD conducted 18 months after randomization. The primary efficacy analysis for the comparison of 6-MWD between treatment groups will be conducted using Wilcoxon Mann Whitney-based test statistics that will take into account informative missingness due to death and the loss of ability to perform the test (stratified Finkelstein and Schoenfeld Joint Rank Test 1999). Briefly, in this stratified non-parametric rank sum analysis, all pairs of patients within a stratum are compared. A pair of patients is compared first on time to death (if death occurs before 18 months); second on time until the inability to perform the test (if it cannot be determined as to which patient in a pair lived longer); and third on the change from baseline in 6-MWD at the time of the last assessment shared by both patients (if it cannot be determined as to which patient in a pair lived longer and which retained the ability to perform the 6-MWD longer). The analysis will be stratified based on the stratification parameters that are used for randomization.

	The second co-primary endpoint is percent reduction from baseline in serum TTR using enzyme-linked immunosorbent assay. The area under the effect curve (eAUC) for percent reduction from baseline in serum TTR over time, where the y-axis is percent reduction and the x-axis is time since randomization, will be compared across groups using Analysis of Covariance (ANCOVA), in which the stratification variables and baseline serum TTR level will be included in the model as covariates. The eAUC will be computed using the trapezoidal method, where assessments missing due to death or discontinuation will be imputed using the baseline level, i.e., the percent reduction will be assumed to be 0%. The study will have demonstrated efficacy if the p-value for each co-primary endpoints is ≤ 0.05 (2-sided). Sensitivity analyses for each of the co-primary endpoints, including different methods for handling of the missing data, will assess the robustness of the primary analysis for the mITT population. Secondary endpoints will be tested hierarchically in the order presented above in Efficacy Endpoints. The secondary composite of CV mortality and CV hospitalization, as well as change in NYHA class and change in KCCQ will all be compared across treatment groups using stratified Finkelstein and Schoenfeld Joint Rank Tests. CV mortality and all-cause mortality will be compared across treatment groups using stratified log-rank tests. CV hospitalizations will be compared using stratified Anderson-Gill model for recurrent events. Analyses will be stratified using the stratification parameters that are used for randomization. Plasma pharmacokinetics (PK) will be summarized and descriptive statistics conducted for each time point. Inferential statistics of efficacy and PK/pharmacodynamic (PD) relationships will be conducted where possible. Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment emergent AEs, treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, and discontinuations due to AEs. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment. Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Details of any abnormalities will be included in patient listings. An unblinded interim analysis for futility may be conducted once approximately half the patients have completed the study. Further details will be included in the Statistical Analysis Plan (SAP).

Table 1-1: Schedule of Assessments for Site Visits

Procedure[a]	Month	Screening[b]/ Baseline	Pre-dose	Daily Dosing					Weekly Dosing																				End of Study	Early Termination[c]
												M1		M2		M3		M6		M9		M12		M15		M18	M19[y]	
	Days/Weeks	D-45 to -1	D0	D0	D1	D2	D3	D4	D7/W1	W2	W3	W4	W5-8	W9	W10-12	W13	W14-25	W26	W27-38	W39	W40-51	W52	W53-64	W65	W66-77	W78	W82	
	Visit Window (Days)[d]								± 1D	± 2D	± 2D	± 2D	± 2D	± 2D	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 7D	
Informed Consent		X																												
Study Drug Administration[e]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Inc/Exc Criteria[f]		X	X																											
Demographics		X																												
Medical History[g]		X	X																											
Physical Examination		X	X													X		X		X		X		X		X		X	X	X
Body Weight		X	X															X				X				X		X	X	X
Height		X																												
Ophthalmology Exam[b]		X																				X				X[bb]		X	X	X
12-Lead ECG[h]		X																X				X				X			X	X
Vital Signs[i]		X	X	X	X	X	X	X				X		X		X		X		X		X		X		X		X	X	X
Serum Chemistry (including LFTs)[a]		X	X					X				X		X		X	X[z]	X		X		X		X		X		X	X	X
Hematology and Urinalysis[a]		X	X															X				X				X				X
Pregnancy Test[a, j]		X	X															X				X				X[bb]		X	X	X
Coagulation Studies[a,k]		X	X									X		X		X	X[z]	X				X				X[bb]		X	X	X
Thyroid Stimulating Hormone[a]		X																				X				X[bb]		X	X	X
Serology[l]		X																												

Procedure[a]	Month	Screening[b]/ Baseline	Pre-dose	Daily Dosing					Weekly Dosing																			End of Study	Early Termination[c]
												M1		M2		M3		M6		M9		M12		M15		M18			
	Days/Weeks	D-45 to -1	D0	D0	D1	D2	D3	D4	D7/W1	W2	W3	W4	W5-8	W9	W10-12	W13	W14-25	W26	W27-38	W39	W40-51	W52	W53-64	W65	W66-77	W78	W82	
	Visit Window (Days)[d]								± 1D	± 2D	± 2D	± 2D	± 2D	± 2D	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 7D	
eGFR[a,m]		X	X															X				X				X		X
NT-proBNP, BNP, Troponin T and I[a,n]		X	X													X		X		X		X		X		X		X
TTR Protein[a,o]			X									X		X		X		X		X		X		X		X		X
Vitamin A[a]		X																X				X				X		X
Anti-drug Antibodies[a,p]		X																X				X				X		X
Exploratory Biomarkers[a,q]		X																X				X				X		X
Serum SPEP with IFE, Urine SPEP with IFE and Serum FLC[aa]		X																										
Voluntary DNA Sample[b,r]			X																									
Plasma PK Sampling[s]			X	X														X				X						X
6-MWT[a,t]		X	X													X		X				X				X		X
NYHA Classification		X																X				X				X		X
Karnofsky Performance Status		X																X				X				X		X
KCCQ		X																X				X				X		X
PND score		X																X				X				X		X
mBMI		X																X				X				X		X
EQ-5D QoL		X																X				X				X		X
Pharmacoeconomics Questionnaire		X																X				X				X		X

Procedure[a]		Screening[b]/ Baseline	Pre-dose	Daily Dosing					Weekly Dosing																			End of Study	Early Termination[c]
	Month											M1		M2		M3		M6		M9		M12		M15		M18		M19[y]	
	Days/Weeks	D-45 to -1	D0	D0	D1	D2	D3	D4	D7/W1	W2	W3	W4	W5-8	W9	W10-12	W13	W14-25	W26	W27-38	W39	W40-51	W52	W53-64	W65	W66-77	W78		W82	
	Visit Window (Days)[d]								± 1D	± 2D	± 2D	± 2D	± 2D	± 2D	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]	± 2D	±2/ ±14D[d]		± 7D	
Echocardiography by Doppler[u]		X																X				X				X			X
CMR[b,v]		X																X				X				X			X
^{99m}Tc Scintigraphy by 3D SPECT[b,w]		X																X				X				X			X
Voluntary Fat Pad Biopsy[x]		X																				X				X			X
Review/Record Concomitant Medications and AEs		X	ONGOING THROUGHOUT THE DURATION OF THE STUDY																										

White boxes are site visits whereas the grey boxes are for dosing procedures that may be conducted at home.

Abbreviations: 6-MWT = Six-minute Walk Test, ^{99m}Tc = ^{99m}Technetium; AE = Adverse event, CMR = cardiac MRI, D = Day, ECG = Electrocardiogram, eGFR = estimated glomerular filtration rate, FLC = Free light chain, KCCQ = Kansas City Cardiomyopathy Questionnaire, LFT = Liver function test, MRI = magnetic resonance imaging, NT-proBNP = N-terminal prohormone of B-type natriuretic peptide, NYHA = New York Heart Association, PD = Pharmacodynamic, PK = Pharmacokinetic, PND Score = polyneuropathy disability score, QoL = Quality of life; SPECT = single-photon emission computed tomography, SPEP with IFE = serum protein electrophoresis with Immunofixation Electrophoresis, TSH = thyroid stimulating hormone, TTR = Transthyretin.

a On dosing days, procedure to be perform prior to dosing.

b Screening assessments are to be performed within 45 days of first dose, with the exception of LFTs and 6-MWT, which must be performed within 28 days of the first dose. Screening/Baseline assessments may be performed during several site visits. Patients are not required to repeat CMR and ^{99m}Tc scintigraphy or the ophthalmology examination if assessments were performed, respectively, within 6 months and 90 days of randomization. The voluntary DNA sample and the voluntary fat pad biopsy should only be obtained once during Screening. Screening laboratory tests can be repeated once if results are expected to be transient and reversible. Additional repeats require discussion with the Medical Monitor.

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

d Dosing on Days 1, 2, 3, and 4 must be performed approximately 24±4 hours after the preceding dose of study drug. After Day 7, doses will be administered weekly (±2 days). Doses may be administered at the clinical site or at home by a health care professional trained in the protocol. An additional window (±14 days) is only allowed for study assessments.

e SC injection of ALN-TTRSC into the abdomen on Day 0 and then on subsequent days into other quadrants of the abdomen. The upper arm or thigh may also be used.

f The results from the laboratory samples collected on Day 0 are not needed prior to dosing.

g On Day 0 pre-dose, only interval medical history will be collected. Changes in medical history during the dosing period will be captured as treatment-emergent adverse events (TEAEs) or concomitant medication(s) as appropriate.

h For the 12-lead ECG, each lead shall be recorded for at least 3 beats at a speed of 25 mm/s. Triplicate recordings will be obtained. The electrophysiological parameters assessed will be rhythm, ventricular rate, PR interval, QRS duration, QT interval, ST and T waves, Fredericia-corrected QT interval (QTcF), and Bazett-corrected QT (QTcB).

i Vital signs include blood pressure, pulse rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the patient has rested comfortably for 10 minutes. Vital signs should be collected at each site visit.

j The pregnancy test will be performed for women of child-bearing potential (WOCBP) only. A serum pregnancy test will be performed at Screening/Baseline and urine pregnancy tests at all designated visits thereafter and anytime pregnancy is suspected. Urine pregnancy test may also be performed more frequently (monthly) based on local country requirements. The results of the pregnancy test at Screening/Baseline and the Day 0 pre-dose visit must be known prior to administration of study drug.

k Coagulation studies include PT, aPTT, and INR.

l Serology tests include HBsAb, HBsAg, and anti-HCV Ab.

m eGFR will be calculated by the central lab and reported with the lab results.

n BNP is only collected during Screening/Baseline. NT-proBNP, Troponin T and I are collected at each timepoint.

o All samples should be taken within 1 hour pre-dose.

p Blood samples for anti-drug antibody testing will be collected prior to study drug dosing. A sample will be collected at the Early Termination visit, if applicable.

q Where allowed per local regulations and IRB/EC approval, serum and plasma samples for exploratory biomarker testing will be collected.

r Where allowed per local regulations, IRB/EC approval and patient consent, DNA sample will be collected.

s PK will be assessed within 1 hour predose and 2.5±1 hour postdose.

t The 6-MWT will be conducted twice during the Screening/Baseline visit (practice and actual test to be performed at least 1 hour apart) and both tests must be completed within 28 days of Day 0. The assessments will include pre- and post-walk assessment of O_2 saturation, blood pressure, heart rate, and the Borg scale ratings for fatigue and dyspnea. The higher of the 2 values at Screening/Baseline will be used for eligibility purposes. The 6-MWT will be conducted only once, prior to dosing, at all subsequent time points.

u An ECHO done at Screening/Baseline and for all subsequent time points will be evaluated by a central laboratory.

v Cardiac MRI with late gadolinium enhancement (LGE) is only to be obtained in patients without contraindications (i.e., pacemakers, defibrillators, inadequate renal function or allergy to gadolinium) at selected sites on a subset of patients (up to 60). All time points will be evaluated by a central lab.

w ^{99m}Tc scintigraphy by 3D SPECT during the study is an exploratory assessment and is not intended for diagnostic purposes or to fulfill eligibility criteria for the study. Either ^{99m}Tc pyrophosphate (^{99m}Tc-PYP) or ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) can be used as a tracer. The tracer should not be changed for the patient during the study. This assessment will only be performed at selected sites on a subset of patients (up to 60). All time points will be evaluated by a central lab.

x This assessment is voluntary and will only be performed at selected sites. Additional time points may not be collected depending on the status of the Screening/Baseline biopsy sample. Repeat Screening/Baseline biopsy samples may be collected if the initial sample is not of sufficient quality.

y Patients enrolling in the open-label extension study (ALN-TTRSC-006) will not need to complete the Month 19 visit. For these patients, Month 18 assessments will constitute the End of Study assessments.

z Serum chemistry (including LFTs) and coagulation tests are to be performed at Week 17 and Week 21.

aa Serum SPEP with IFE, urine SPEP with IFE and serum FLC is to be performed at Screening/Baseline. If available, documented local results obtained within 1 year of Screening/Baseline may be used to fulfill this requirement.

bb These assessment will only be performed for patients enrolling in the ALN-TTRSC-006 study.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
6-MWD	Six-minute walk distance
6-MWT	Six-minute Walk Test
^{99m}Tc	^{99m}Technetium
AA	Amyloid A
ADA	Anti-drug antibody
AE	Adverse event
AL	Amyloid light-chain
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
ASGPR	Asialoglycoprotein receptor
AST	Aspartate transaminase
ATTR	Transthyretin-mediated amyloidosis
BNP	B-type natriuretic peptide
bpm	Beats per minute
BUN	Blood urea nitrogen
CAC	Clinical Adjudication Committee
CFR	Code of Federal Regulations
CMR	Cardiac magnetic resonance imaging (Cardiac MRI)
CRF	Case Report Form
CRO	Clinical research organization
CV	Cardiovascular (related)
CYP	Cytochrome P450
DMC	Data monitoring committee
DPD-Tc	^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid
eAUC	Area under the effect curve
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
ET	Early termination

Abbreviation or Specialist Term	Explanation
FAC	Familial amyloidotic cardiomyopathy
FAP	Familial amyloidotic polyneuropathy
FNAFP	Fine-needle aspirate of the abdominal fat pad
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HF	Heart failure
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional review board
IRS	Interactive response system
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDH	Lactate dehydrogenase
LFT	Liver function test
MAD	Multiple ascending dose
mBMI	Modified body mass index
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
mRNA	Messenger ribonucleic acid
NHP	Non-human primate
NOAEL	No-observed-adverse-effect-level

Abbreviation or Specialist Term	Explanation
NOEL	No-observed-effect-level
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
OTC	Over-the-counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PND	Polyneuropathy Disability
PP	Per protocol
PT	Prothrombin time
PV & DSS	Pharmacovigilance and Drug Safety Services
PYP-Tc	^{99m}-Tc-Pyrophosphate
QoL	Quality of life
QTcB	Bazett-corrected QT interval
RBC	Red blood cell
RBP	Retinol binding protein
RNAi	RNA interference
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
siRNA	Small interfering ribonucleic acid
SOA	Schedule of assessments
SSA	Senile systemic amyloidosis
SUSARs	Suspected Unexpected Serious Adverse Reactions
T4	Thyroxine
T60A	Threonine to alanine substitution at position 60
TEAE	Treatment-emergent adverse events
TSH	Thyroid stimulating hormone
TTR	Transthyretin
TRACS	TTR amyloidosis cardiac study
ULN	Upper limit of normal
UK	United Kingdom
US/USA	United States
USP/EP	United States Pharmacopeia/European Pharmacopoeia
WBC	White blood cell

Abbreviation or Specialist Term	Explanation
WHO	World Health Organization
WOCBP	Women of child-bearing potential
WT	Wild-type

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. Amyloid deposits typically contain both mutant and wild-type (WT) TTR in addition to serum amyloid P protein and glycosaminoglycans, and over time these deposits lead to significant tissue injury.

1.1.2. Disease Overview

1.1.2.1. Transthyretin-mediated amyloidosis definition and familial amyloidotic cardiomyopathy

Transthyretin-mediated amyloidosis (ATTR) is caused by deposition of TTR amyloid fibrils in various tissues. The hereditary form of ATTR is caused by an autosomal dominant mutation in the TTR gene that leads to destabilization of the TTR tetramer and aggregation of misfolded monomers; this, in turn, results in cardiac and neuronal extracellular deposition of TTR amyloid fibrils culminating in life-threatening cardiomyopathy and/or debilitating neuropathy. There are over 100 reported TTR genetic mutations[2] that phenotypically result in at least 2 distinct clinical syndromes of ATTR: familial amyloidotic cardiomyopathy (FAC) and familial amyloidotic polyneuropathy (FAP), both of which are characterized by amyloid deposits of mutant and WT-type TTR.[3] Senile systemic amyloidosis (SSA) is a sporadic form of ATTR occurring in the elderly (predominantly males) and characterized by deposition of WT TTR in the heart tissue.[4]

FAC is a serious, life-threatening orphan disease. The estimated worldwide prevalence of FAC is 40,000 to 50,000. However, the number of identified FAC patients is substantially smaller due to limited disease awareness resulting in underdiagnoses or misdiagnosis. FAC is primarily identified and diagnosed at a few amyloidosis centers in the United States (US), and Europe. The TTR mutations most commonly associated with cardiac-predominant disease include valine to isoleucine substitution at position 122 (V122I; seen in the US and UK), threonine to alanine substitution at position 60 (T60A; seen in US, UK, and Northern Ireland), leucine to methionine substitution at position 111 (L111M; seen in Denmark), and isoleucine to leucine substitution at position 68 (I68L; seen in Italy).

The V122I mutation is the most common and estimated to be present in up to 4% of African Americans and in over 5% of West African populations.[5] Disease develops predominantly in males with the mean age at diagnosis of approximately 70 years, and symptom onset typically occurring after the age of 60. In the US there are estimated to be approximately 100,000-150,000 African American males over age 65 who are heterozygous carriers of the V122I allele.[6] However, the extent of disease penetrance is currently unknown.

The T60A mutation found in 1% of the population in County Donegal in North-West Ireland, is the next most common FAC mutation worldwide, and the commonest TTR variant in the British population. The median age of onset of cardiac symptoms in this population is approximately 60 years. It should be noted that while T60A is categorized as FAP rather than FAC, it is nonetheless predominantly a disease of the heart and autonomic nerves, with <25% of patients developing peripheral sensorimotor neuropathy.[7]

1.1.2.2. Pathogenesis and Outcome

Cardiomyopathy in FAC occurs when insoluble TTR amyloid fibrils deposit in cardiac tissue causing heart wall thickening with diastolic and systolic dysfunction, conduction defects, and arrhythmias, leading to congestive heart failure and death. Neuropathy is uncommon in FAC.

While there is a paucity of longitudinal clinical data on FAC, a few published reports have shown that FAC patients have a significantly worse prognosis compared to other causes of heart failure, with rapid deterioration of functional capacity, including their ability to walk as measured by the 6-MWD, and quality of life (QOL) resulting in early mortality.

The median survival of V122I patients from time of diagnosis in two retrospective studies was 27[8] to 41 months[8,9] and in the prospective Transthyretin Amyloidosis Cardiac Study (TRACS) study median survival was 26 months.[10]

1.1.2.3. Current Management and Unmet Medical Need

There are currently no approved treatment options for patients with FAC. Patients are largely managed with supportive care aimed at alleviation of heart failure symptoms, including restriction of salt intake, diuretics, pacemakers, and arrhythmia management. Heart transplantation has been used rarely, as many patients are too old to undergo the procedure. There is a high unmet need for novel therapeutics to treat FAC.

ALN-TTRSC (International Nonproprietary Name: revusiran) is currently being developed as an RNA interference (RNAi) therapeutic for patients with FAC.

1.1.3. RNA Interference

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering ribonucleic acids (siRNAs).[11] Typically, synthetic siRNAs are 19 to 23 base pair double-stranded oligonucleotides in a staggered duplex with a 2-nucleotide overhang at one or both of the 3' ends. Such siRNAs can be designed to target 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.[12] 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.[13] As a result, various formulations and/or chemical modifications of the siRNAs are 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.[13,14,15] 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 (ASGPR) 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 and non-human primates (NHPs), including TTR (see the ALN-TTRSC Investigator's Brochure [IB] for further details). Importantly, this approach for delivering siRNA to hepatocytes has also shown translation in humans with ALN-TTRSC.

1.1.4. Investigational Drug ALN-TTRSC Overview

ALN-TTRSC 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, ALN-TTRSC targets TTR mRNA for degradation, resulting in reduction of mutant and WT TTR protein via the RNAi mechanism. Since TTR is almost exclusively synthesized in the liver, ALN-TTRSC is postulated to reduce levels of mutant and WT monomers and prevent amyloid fibril deposition, resulting in clinical benefit to patients with FAC.

1.1.5. Therapeutic Hypothesis

ALN-TTRSC is a novel investigational therapeutic for the treatment of FAC, a serious life threatening orphan disease. The therapeutic hypothesis for treatment with ALN-TTRSC in patients with FAC is that potent and sustained lowering of serum TTR protein through inhibition of hepatic production will result in clinical benefit. Support for this approach comes from evidence that lowering of the amyloidogenic protein by ≥50% improves clinical outcomes in other amyloidotic disorders, including both primary amyloid light-chain (AL) amyloidosis and secondary Amyloid A (AA) amyloidosis. The AL amyloidosis example is particularly relevant, since cardiac involvement is the main cause of morbidity and mortality, and the lowering of serum free light chains through chemotherapy and stem cell transplantation has been shown to improve cardiac function and overall survival. In TTR-mediated FAP, the elimination of mutant TTR by transplantation of the liver has been shown to slow neuropathy progression and improve survival in early-stage V30M patients. Similarly, studies in FAP patients with tafamidis have shown that reducing circulating TTR monomers via stabilization of the TTR tetramer results in

improved clinical outcomes. These precedents suggest that potent lowering of circulating TTR with ALN-TTRSC could potentially confer clinical benefit in patients with FAC.

1.2. Summary of ALN-TTRSC Nonclinical Data

The safety pharmacology and toxicology of ALN-TTRSC was evaluated in a series of in vitro and in vivo nonclinical studies.

- [redacted]
- A safety pharmacology study conducted with revusrian in cynomolgus monkeys demonstrated that the no-observed-effect-level (NOEL) for the cardiovascular (electrocardiogram [ECG], QT interval changes, and hemodynamics) and respiratory systems was 100 mg/kg revusrian (the highest dose tested).
- The toxicity profile of SC administered ALN-TTRSC was initially evaluated in 6-week (10-dose) toxicology studies in rats and cynomolgus monkeys. ALN-TTRSC is pharmacologically active in monkeys but not in rats. Repeated SC administration of ALN-TTRSC was clinically well tolerated by rats and monkeys. In rats, the no observed adverse effect level (NOAEL) was 30mg/kg based on minimal to moderate hepatocellular vacuolation with correlating transient mild (<50%) changes in liver function tests noted at ≥100 mg/kg. The NOAEL in monkeys was greater than the highest dose tested (≥300 mg/kg).
- [redacted]
- [redacted]

Further nonclinical information can be found in the ALN-TTRSC IB.

1.3. Summary of Clinical Data with ALN-TTRSC

Study ALN-TTRSC-001 was a Phase 1 randomized, double -blind, placebo-controlled study of ALN-TTRSC 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 ALN-TTRSC, 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, ALN-TTRSC 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 ALN-TTRSC-treated subjects. One subject who received 600 mg ALN-TTRSC 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 ALN-TTRSC was dose-dependent and resulted in >85% reduction of TTR at ≥5 mg/kg of ALN-TTRSC and was accompanied by reduction of RBP and vitamin A. Fixed doses of 500 mg and 600 mg ALN-TTRSC 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 ALN-TTRSC administered to patients with ATTR cardiac amyloidosis. Patients received ALN-TTRSC 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 ALN-TTRSC 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 ALN-TTRSC 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 ALN-TTRSC dosing was observed.

ALN-TTRSC-003 is an ongoing, Phase 2 open-label extension study to evaluate long-term treatment with ALN-TTRSC for patients who completed the ALN-TTRSC-002 study. Patients receive ALN-TTRSC 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 ALN-TTRSC for approximately 8 months (range 1-13 months). Multiple doses of ALN-TTRSC 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 ALN-TTRSC in patients with FAC. Patients receive ALN-TTRSC 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 ALN-TTRSC IB.

1.4. Study Design Rationale

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter, multinational study to evaluate the efficacy and safety of ALN-TTRSC in FAC patients. The patients proposed for this study are reflective of the FAC population encountered by clinicians in various different countries worldwide, including patients with a range of disease severity and spectrum of TTR mutations.

The target population for this study is FAC patients with clinical evidence of mild-to-moderate heart failure. The study is being restricted to FAC in order to minimize the phenotypic heterogeneity and focus on a genetically-defined population where the disease pathogenesis is more clearly defined and where there is the greatest unmet need. Patients with FAC appear to have more rapid disease progression compared to patients with SSA, thereby providing a greater opportunity to demonstrate a disease-modifying effect with ALN-TTRSC treatment. Heart failure severity will be limited to New York Heart Association (NYHA) class I, II and III, and patients must have a Karnofsky performance status of ≥ 50%. Since a 6-minute walk distance (6-MWD) of <150 meters is associated with early poor outcomes,[16,17] and since disease in such patients may be too advanced to be impacted by ALN-TTRSC, eligible patients must minimally have a 6-MWD of ≥150 meters. Analysis of the UK natural history dataset (National Amyloidosis Center, unpublished results) that includes information on both 6-MWD and NYHA class suggests that a 6-MWD cut-off of 150 meters will enrich for NYHA class I-II and early class III patients.

The inclusion of placebo as a control allows for unbiased analysis of the treatment effect of ALN-TTRSC on TTR-mediated FAC. Saline will be used as placebo. FAC is currently managed by treatment of symptoms, mostly with the use of diuretics and antiarrhythmic drugs, which will be permitted during the study.

Given the orphan nature of the disease and the significant, progressive morbidities associated with FAC, randomization to ALN-TTRSC or placebo will be performed in a 2:1 ratio (ALN-TTRSC:placebo) to increase the probability that patients will receive active drug. Since NYHA class and 6-MWD are predictive of outcomes in heart failure,[18,19] treatment groups will be balanced at entry for NYHA classification (I and II vs III), and Screening 6-MWD (≤325 meters vs >325 meters). Patients will also be stratified for V122I versus all other mutations, in order to balance for phenotypic heterogeneity among the different FAC mutations with the prognosis being worse for V122I (the most common FAC mutation worldwide) compared to T60A,[7,9] and outcomes less well described for other FAC mutations is considered prudent.

The co-primary endpoint for this study is the change from baseline in meters walked during the 6-minute walk test (6-MWT) at 18 months and percent reduction from baseline in serum TTR levels over 18 months compared between treatment groups. Serum TTR levels are expected to reach nadir within approximately 3 weeks following the onset of dosing. The 18-month endpoint was selected based on the rapid rate of 6-MWD decline with V122I FAC patients, derived from a natural history dataset from the UK (National Amyloidosis Center, unpublished results) and the prospective TRACS study. From these data it is estimated that FAC patients decline in 6-MWD by 74 to 118 meters in 18 months, thereby providing adequate disease progression for the detection of a treatment effect in ALN-TTRSC treated patients. The clinical relevance of TTR lowering is supported by improved survival of patients with FAP after liver transplantation[20,21,22] and improved survival in AL and AA patients after treatment that effectively reduces the amount of circulating amyloidogenic protein.[23,24] It is anticipated that a marked, sustained reduction in serum TTR levels over 18 months by ALN-TTRSC will result in stabilization or improvement in cardiac amyloid deposition, with a corresponding beneficial effect on cardiac function and clinical outcomes, including the 6-MWD.

1.5. Dose Selection and Rationale

Dose selection for proposed Phase 3 trial is based on the therapeutic hypothesis that maximal TTR suppression is required to fully realize clinical benefit with ALN-TTRSC. Clinical data demonstrate that administration of multiple doses of ALN-TTRSC 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 subjects, with a TTR lowering effect that matched 5.0 and 10.0 mg/kg. In the ongoing 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 lowering 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 the Phase 3 study. The dose selection is also supported by the absence of new findings in the ongoing long term toxicology studies in rats and monkeys. ALN-TTRSC will be administered via SC injections once daily for the first 5 days, followed by dosing on Day 7, and then once weekly through 18 months.

1.6. Risk-Benefit Assessment

FAC is a rare disease, that leads to significant morbidity and mortality. There are no approved therapies and patients are currently managed with supportive care aimed at alleviation of heart failure symptoms. Clinical experience with ALN-TTRSC indicates that ALN-TTRSC is well-tolerated at fixed doses of 500 mg and results in a reduction in serum levels of TTR of >85%. The hypothesis is that a reduction of mutant and WT TTR amyloid deposition in the heart will lead to clinical benefit in these patients.

1.6.1. Injection Site Reactions

ISRs have been observed in subjects receiving ALN-TTRSC in 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 ALN-TTRSC. If such reactions occur, rotation of the injection site (e.g., 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 6.6).

1.6.2. Abnormal Liver Function Tests

Elevations of ALT and/or AST have been seen in subjects receiving ALN-TTRSC 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.

The risk of liver toxicity is lowered by requiring patients to have adequate liver function at study entry, as well as regular monitoring of LFTs during the study. 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.

Dose reduction may be considered in some cases after consultation with the Medical Monitor (see Section 6.6).

1.6.3. Vitamin A Lowering

The suppression of serum levels of TTR and RBP is expected to result in the lowering of circulating vitamin A levels. Preclinical and clinical data have shown that the lowering of circulating vitamin A associated with suppression of RBP does not result in severe vitamin A deficiency. Furthermore, there are individuals with RBP/TTR mutations who have life-long low levels of circulating vitamin A and are essentially in good health, suggesting that there are compensatory transport mechanisms for vitamin A that are yet undescribed. This has also been confirmed in TTR knockout mice, which do not exhibit any manifestations of vitamin A deficiency, with vitamin A uptake by most tissues continuing in the absence of RBP. Provided there is adequate vitamin A in the diet, tissue stores of vitamin A should not be affected by the

lowering of TTR and RBP. However, as the vitamin A content of the diet may vary between different countries and different individuals within a country, all patients on the study will be asked to take a supplement containing the recommended daily allowance of vitamin A. Furthermore, the safety of lowering vitamin A through TTR suppression has been further confirmed by the absence of any vitamin A deficiency-related AEs in NHPs, 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% lowering of both TTR and vitamin A. Periodic eye exams are planned for patients in this study to assess any potential impact of vitamin A lowering.

Please see the ALN-TTRSC IB for expanded risk/benefit assessment.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to determine the efficacy of ALN-TTRSC in patients with FAC.

This will be assessed as the difference between treatment and placebo groups at 18 months using a co-primary endpoint of: (1) change in meters in 6-MWD compared to baseline distance; and (2) percent reduction in serum TTR levels compared to baseline levels.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, multinational, randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the clinical efficacy and safety of ALN-TTRSC in patients with TTR mediated FAC.

Approximately 200 consented eligible patients will be randomized to receive either ALN-TTRSC or placebo at a 2:1 ratio (ALN-TTRSC to placebo) in a blinded manner as a subcutaneous administration. Treatment groups will be balanced at randomization for NYHA classification (I and II versus III), TTR mutation (V122I versus other FAC mutations), and 6-MWD (≤325 meters versus >325 meters). Patients will receive ALN-TTRSC or placebo daily for 5 days during the first week, a single dose on Day 7, and then once weekly for 18 months.

Patients will undergo efficacy and safety assessments at Screening/Baseline, each month for first 3 months, and then at 3-6 month intervals.

The duration of patient participation in this study is approximately 20 months (inclusive of up to a 45 day Screening/Baseline window and up to 35 days of follow-up after the last dose).

3.2. Number of Patients

Approximately 200 patients will be enrolled in this study.

3.3. Efficacy Endpoints

3.3.1. Primary endpoints:

The co-primary endpoints of the study are to evaluate the difference between the ALN-TTRSC and placebo groups for:

1. Change in 6-MWD at 18 months compared to baseline
2. Percent reduction in serum TTR burden over 18 months

3.3.2. Secondary endpoints:

The secondary endpoints of the study are to determine the effect of ALN-TTRSC on various clinical parameters by assessing the difference between the ALN-TTRSC and placebo groups at18 months for:

- Composite CV mortality and CV hospitalization
- Change in New York Heart Association (NYHA) class (Appendix 1) compared to baseline
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) compared to baseline
- Cardiovascular (CV) mortality
- CV hospitalization

- All-cause mortality

3.3.3. Exploratory endpoints:

The exploratory endpoints of the study are to determine the difference between the ALN-TTRSC and placebo groups in the change from baseline at 18 months in the following measurements:

- EuroQOL (EQ-5D) questionnaire
- Echocardiogram parameters
- Karnofsky Performance Status (Appendix 2)
- Troponin T and I, and N-terminal prohormone of B-type natriuretic peptide (NT proBNP) levels
- Cardiac magnetic resonance imaging (CMR) parameters (only at selected sites)
- ^{99m}Technetium scintigraphy parameters (only at selected sites)
- Amyloid in abdominal wall fat pad aspirates
- Polyneuropathy Disability (PND) Score (Appendix 3)
- Modified body mass index (mBMI)
- Estimated glomerular filtration rate (eGFR)
- HF hospitalization

3.4. Safety Assessments

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

3.5. Pharmacokinetic Assessments

Pharmacokinetics will be assessed by collecting periodic plasma samples for measure of ALN-TTRSC as well as metabolite concentrations.

3.6. Other Assessments

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

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

To be enrolled in the study, each patient must meet all of the following criteria during the Screening/Baseline visit(s):

1. Are male or female of 18 to 90 years of age (inclusive).
2. Have a documented TTR mutation.
3. Amyloid deposits in cardiac or non-cardiac tissue confirmed by Congo Red (or equivalent) staining or technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc] or ^{99m}Tc-pyrophosphate [PYP-Tc]) with Grade 2 or 3 cardiac uptake, centrally confirmed.
4. If patient has monoclonal gammopathy, TTR amyloidosis needs to be confirmed through TTR protein identification by immunohistochemistry or mass spectrometry.
5. Have a medical history of heart failure (HF) with at least 1 prior hospitalization for HF, which may include hospitalization for arrhythmia or pacemaker placement, OR clinical evidence of HF (as evidenced by one or more of the following: elevated jugular venous pressure, peripheral edema, shortness of breath or signs of pulmonary congestion on x-ray or auscultation) that either requires/required treatment with diuretics or is/was associated with an NT-proBNP > 400 ng/L or B-type natriuretic peptide (BNP) >100 ng/L.
6. Have evidence of cardiac involvement by Screening/Baseline echocardiogram including an end-diastolic interventricular septum thickness of ≥12 mm. For patients with an end-diastolic interventricular septum thickness of <12mm, an endomyocardial biopsy showing amyloid deposition is required.
7. Can walk ≥150 meters on a 6-minute walk test (6-MWT).
8. Have a Karnofsky performance status of ≥50%.
9. Symptoms of HF optimally managed with no CV hospitalizations within 4 weeks prior to consent or during Screening/Baseline.
10. Have adequate liver function, demonstrated by an AST and ALT ≤2.0×ULN, albumin >3 g/dL (>4.35 µmol/L), and total bilirubin <2.0 mg/dL (34.2 µmol/L), unless elevation in total bilirubin is due to Gilbert's Syndrome.
11. No active infection with hepatitis B (HBV) or hepatitis C (HCV) by serology
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 (see Section 5.2.1)
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. Must be willing and able to comply with protocol-required visit schedule and visit requirements and provide informed consent or have a legal guardian who can provide informed consent.

4.2. Patient Exclusion Criteria

Patients will be excluded from enrollment in the study if they meet any of the following criteria during the Screening/Baseline visit(s):

1. Has estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2 (using the Modification of Diet in Renal Disease [MDRD] formula).
2. Has known primary amyloidosis (AL), leptomeningeal amyloidosis, non-FAC hereditary cardiomyopathy, hypertensive cardiomyopathy, or cardiomyopathy due to valvular heart disease.
3. Has non-amyloid diseases affecting exercise testing (e.g., severe chronic obstructive lung disease, severe arthritis, peripheral vascular disease affecting ambulation).
4. Has uncontrolled hypertension.
5. Has uncontrolled ischemic heart disease.
6. Has uncontrolled clinically significant cardiac arrhythmia.
7. Had acute coronary syndrome within the past 3 months.
8. Has a Polyneuropathy Disability score >2.
9. Has untreated hypo- or hyperthyroidism.
10. Has a New York Heart Association (NYHA) classification of IV.
11. Has known or suspected systemic bacterial, viral, parasitic, or fungal infection.
12. Has known human immunodeficiency virus (HIV) infection.
13. 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 past 2 years.
14. Has received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever is longer.
15. Is currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to start of study drug administration in this study.
16. Had metastatic cancer within the past 5 years.

17. History of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc).
18. Has a history of intolerance to SC injection.
19. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
20. Has had a heart or liver transplant, or is being considered for a transplant during the study period.
21. Known history of clinically significant chronic liver disease in the opinion of the Investigator.

4.3. Study Drug Discontinuation

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
- Is found to be considerably non-compliant 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.

Patients who discontinue study drug for any reason will be encouraged to remain on the study and complete their remaining clinic visits through the 18-month visit. Patients who discontinue study drug may receive local standard of care treatment for their disease.

4.4. Patient Withdrawal

Patients are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. There will be no replacements of patients who withdraw from this study. Patients may 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 if they are willing to consent to either be contacted by telephone or to allow non-patient contact follow-up (eg, medical record check) 18 months after enrolling onto the study to document their overall health status.

5. TREATMENT OF PATIENTS

5.1. Concomitant Medications

Use of tafamidis, diflunisal, doxycycline, or tauroursodeoxycholic acid within 14 days prior to the first dose of study medication in this protocol or use of any other investigational agent or device within 30 days prior to the first dose of study medication is prohibited (see exclusion criteria, Section 4.2). Similarly, these agents or investigational devices are prohibited during the study.

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

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

Use of all concomitant medications from Screening/Baseline 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 given by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. For coding of concomitant medication, an internationally recognized and accepted coding dictionary will be used.

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

5.2. Contraceptive Requirements

5.2.1. Requirements for Women of Child-bearing Potential

Women of child-bearing potential 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).

Women of child-bearing potential 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 and should be used per availability in each country and local requirements:

- Hormonal: established use of oral (except low-dose gestagens [eg, lynestrenol and norethisterone]), implantable, injectable, or transdermal 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Interaction between ALN-TTRSC and hormonal contraceptives is not anticipated; there were no effects of ALN-TTRSC on the reproductive organs (including histopathology) in any of the animal (rat and NHP) studies conducted to date. Moreover, ALN-TTRSC showed no inhibition *in vitro* of cytochrome P_{450} (CYP)1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (both testosterone and midazolam were used as substrates in human liver microsomes).

5.2.2. 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 ALN-TTRSC may be included in this study.

It is unknown if ALN-TTRSC 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 it is not available, 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 ALN-TTRSC.

5.3. 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 multiple consecutive doses, 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 prior to their next dose, they should receive the missed dose as soon as possible, otherwise the missed dose will not be made up. Patients should never receive more than one dose of study drug a day.

5.4. Randomization and Blinding

This is a randomized double blind study, and patients will be randomized via an interactive response system (IRS).

5.5. Patient Numbering

Each patient will be uniquely identified in the study by a combination of the site number and screening number. The site number will be assigned by the Sponsor. Upon signing the ICF, the patient will be assigned a screening number by the IRS. The Investigator or his/her delegate will contact the IRS (via phone or web) after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. The patient will be randomized via the IRS, assigned a randomization number in the IRS and a study treatment. A combination of the site number, screening number, randomization number, and patient initials will create the unique patient identifier. In countries with regulations prohibiting the use of patient initials, a strategy consistent with local regulations will be used to generate replacement values for the patient initials.

5.6. Blinding

All site personnel and patients will be blinded to study drug treatment. ALN-TTRSC and placebo will be packaged identically and all vial contents will be masked. The study drug will be administered by a healthcare professional (see Section 6.5); prior to withdrawing the study drug from the vial, the syringe will be masked. See the Pharmacy Manual for additional details.

Injection site reactions have been known to occur in patients receiving both ALN-TTRSC and placebo; the consent form will inform patients about the potential for injection site reactions regardless of treatment assignment.

5.7. Breaking the Blind

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

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

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Presentation of Study Drug

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

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

ALN-TTRSC will be supplied as a sterile 200 mg/mL solution. The ALN-TTRSC drug product will be packaged in a glass vial. The container closure system consists of a United States Pharmacopeia/European Pharmacopoeia (USP/EP) Type I borosilicate glass vial, a Teflon-faced butyl rubber stopper and an aluminum flip-off cap.

The control drug for this study will be a placebo (normal saline 0.9% for SC administration). Placebo will be packaged identically to ALN-TTRSC.

6.2. Study Drug Packaging and Labeling

All packaging and labeling as well as the preparation of ALN-TTRSC and placebo will be in compliance with Good Manufacturing Practice (GMP) specifications, and any other or local applicable regulations.

6.3. Study Drug Storage

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

No special procedures for the safe handling of ALN-TTRSC or placebo 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

Patients will be randomized using an IRS system to receive either 500mg of ALN-TTRSC or the equivalent volume (2.5 mL) of placebo for five daily doses for the first week and then weekly for approximately 18 months.

Study drug supplies will be blinded, and the pharmacist or qualified designee will use the pre-labeled study drug vials assigned by the IRS system. The pharmacist or qualified designee managing the study drug will prepare the study drug using aseptic techniques. The procedure for preparing study drug is provided in the Pharmacy Manual.

6.5. Administration

Patients who have met the eligibility criteria will be assigned to either the placebo or ALN-TTRSC treatment group based on the randomization code. As this is a double blinded study, neither the Investigator nor the patient will know their group assignment. Doses will be administered as per the dosing scheme (see Table 1-1).

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. At home dosing may be administered by a healthcare professional. To maintain the blind, the syringes are to be masked prior to study drug withdrawal. A full description of the blinding procedure is included in the Pharmacy Manual.

The preferred site of SC injection is the abdomen. Optional additional sites are the upper arms and thighs. The site of injection will be rotated and recorded.

Detailed instructions can be found in the Pharmacy Manual.

6.6. Dosing Modification Criteria

During the study, if a patient has an elevation of AST, ALT, or total bilirubin (unless due to Gilbert's Syndrome) >3×ULN, repeat assessments of AST, ALT, and total bilirubin should be performed within 72 hours. The patient should be followed closely, with LFT assessments performed weekly, and as medically indicated to guide patient management. Close monitoring may be discontinued when ALT, AST, and total bilirubin return to ≤3×ULN. Additional, and repeat assessments, 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 a hepatologist as deemed necessary, will decide on appropriate action regarding frequency of repeat LFTs and resumption of dosing.

If a patient experiences an AE considered to be related to study drug, and the Investigator has any potential concerns with regard to further dosing, the Medical Monitor and Investigator will review all available safety data for the patient. Based on this review, it may be determined that further administration of study drug will be discontinued or study drug administration at the same dose may resume.

If a patient has recurrent or severe ISRs, or clinically significant LFT abnormalities, the Investigator and the Medical Monitor should determine whether the patient is a candidate for a dose reduction of study drug. In suitable candidates, dose reduction to 250 mg ALN-TTRSC (or placebo equivalent) is allowed. In patients who have been dose reduced, subsequent re-challenge at the full dose may be considered based on the judgment of the Investigator and Medical Monitor.

6.7. Study Drug Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of all study drugs including dates of receipt. In addition, accurate records will be kept by the pharmacist or designee of 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. At the completion of the study, there will be a final reconciliation of all study drugs.

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.

6.8. 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 site according to applicable regulations.

7. STUDY ASSESSMENTS

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

7.1. Informed Consent

The patient (or the patient's legal guardian) will be given a verbal explanation of the study, including information about the study drug and the study procedures, and will have all questions adequately addressed. The patient (or the patient's legal guardian) must sign and date a consent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the Screening/Baseline procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated informed consent form.

If a patient withdraws from the study, in an attempt to minimize the extent of missing data, they will be asked if they would be willing to consent to either be contacted by telephone or to allow non-patient contact follow-up (eg, medical record check) 18 months after enrolling onto the study to document their overall health status.

7.2. Demographics and Medical History

Patient demographic data will be obtained at Screening/Baseline. A complete medical history will be obtained at Screening/Baseline.

7.3. Efficacy Assessments

7.3.1. Six-Minute Walk Test

The 6-MWT will be administered by staff trained in the procedure included in the Site Operation Manual. The staff administering the 6-MWT will be different from the Investigator or designee managing the care of the patient.

The 6-MWT will be performed to assess functional exercise capacity and will include pre- and post-walk assessment of O_2 saturation, blood pressure, heart rate, and the Borg scale rating for dyspnea and fatigue.[25] The Screening/Baseline visit assessment will include a practice and an actual 6-MWT at least 1 hour apart and must be done within 28 days prior to randomization. The higher of the two values at Screening/Baseline visit will be used for eligibility purposes. At all other visits, the test should be performed only once at approximately the same time of the day. On dosing days, including Day 0, the 6-MWT should be performed prior to study drug administration. Patients who are hospitalized during the course of the study should wait at least two weeks after hospitalization before completing a 6-MWT assessment.

7.3.2. Transthyretin

On scheduled visits, serum samples will be collected within one hour prior to dosing and analyzed for total TTR levels using an enzyme linked immunosorbent assay (ELISA) method at a central laboratory.

7.3.3. Modified Body Mass Index

Assessment of nutritional status, which has been linked to autonomic dysfunction will be measured by the mBMI. Since the mBMI takes into account the serum albumin values along with BMI (function of height and weight), it corrects for hypoalbuminemia and is considered more reflective of nutritional status than BMI alone. This calculation will be performed by the Sponsor on the reported data (ie, whenever body weight is recorded, except end of study) and not performed at the site.

7.3.4. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate will be calculated using the MDRD formula by the central laboratory. If this parameter met eligibility criteria at Screening/Baseline, then dosing can proceed prior to receiving pre-dose Day 0 results.

7.3.5. Fat Pad Biopsy

Fine-needle aspirates of the abdominal fat pad (FNAFP) for amyloid quantification will be collected only at certain sites and in only patients who have provided additional voluntary consent. Subsequent scheduled biopsies may not be collected depending on the status of the Screening/Baseline biopsy sample. Repeat Screening/Biopsy samples may be collected if the initial sample is not of sufficient quality. The voluntary fat pad biopsy should only be obtained once during Screening.

Details on FNAFP collection, processing, and shipment will be in the Site Operations Manual.

7.3.6. Karnofsky Performance Status

Each patient's Karnofsky Performance Status (Appendix 2) will be assessed.

7.3.7. Polyneuropathy Disability Score

Ambulation will be evaluated through the PND score (Appendix 3).

7.3.8. NYHA Classification

New York Heart Association classification will be recorded. The NYHA classification scale is provided in Appendix 1.

7.3.9. Imaging

7.3.9.1. Echocardiography

An echocardiogram with Doppler will be used for assessment of cardiac structure and function. Echoes obtained at the Screening/Baseline visit will be used to assess eligibility criteria.

Details for image acquisition and upload for central review can be found in the ALN-TTRSC Site Operations Manual.

7.3.9.2. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging with late gadolinium enhancement will only be performed on patients without contraindications (ie, pacemakers, severe renal failure with eGFR <30 mL/min/1.73 m^2, defibrillators, or allergy to gadolinium). This test will be performed only at select sites and in a subset of patients (up to 60). Patients are not required to repeat CMR if the assessment is performed within 6 months of randomization.

Details for image acquisition and upload for central review can be found in the ALN-TTRSC Site Operations Manual.

7.3.9.3. Technetium Imaging

Technetium imaging assessments performed as part of the study are for research and are not intended to be used for diagnostic purposes.

^{99m}Tc imaging by 3D SPECT during the study will be performed only at selected sites and in a subset of patients (up to 60). Either PYP-Tc or DPD-Tc can be used as the tracer. The tracer used for a patient should not be changed during the study. This test will be performed only at select sites. All time points will be evaluated by a central lab. Patients are not required to repeat ^{99m}Tc scintigraphy if assessment was performed within 6 months of randomization.

Technetium scintigraphy used to fulfill the inclusion criterion for evidence of cardiac amyloid deposition are not performed as part of the study assessments, but will be evaluated by a central reader for confirmation of the required cardiac uptake.[26, 27, 28]

Details for the image acquisition and upload for central review can be found in the ALN-TTRSC Site Operations Manual.

7.3.10. Questionnaires

7.3.10.1. Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-administered, 23-item questionnaire that assesses physical function, symptoms, social function, self-efficacy and knowledge, and QoL. Each patient is to complete this questionnaire.

7.3.10.2. EQ-5D Quality of Life

Quality of life will be assessed through the use of the EQ-5D, a standardized 5 question instrument for use as a measure of health outcomes. Each patient is to complete this questionnaire.

7.3.11. NT-proBNP, BNP, Troponin T, and Troponin I

Blood samples will be collected and analyzed for the quantification of troponin T, troponin I, and NT-proBNP (biomarkers of cardiac status). BNP will only be collected at Screening/Baseline. Quantification of these biomarkers will be performed at a central laboratory.

7.3.12. Mortality and Hospitalization

All events will be recorded from Day 0 and beyond; reasons for mortality and hospitalization will be adjudicated by an independent Clinical Adjudication Committee.

7.4. Pharmacokinetic Assessment

Blood samples will be taken for the assessment of plasma levels of ALN-TTRSC at the following time points during the study:

- Days 0, Month 6 and Month 12: within 1 hour predose and 2.5±1 hour postdose
- A sample will be collected at the Early Termination visit, if applicable.

Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of ALN-TTRSC.

7.5. Safety Assessments

7.5.1. Physical Examination

Routine physical examinations will be performed. 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.

7.5.2. Vital Signs

Vital sign measurements include blood pressure, pulse rate, oral body temperature, and respiratory rate. Vital signs will be measured manually in the supine position after the patient has rested comfortably for 10 minutes. Each patient's blood pressure should be taken using the same arm. Oral temperature will be obtained in degrees Celsius, heart rate will be counted for a full minute and recorded in beats per minute (bpm), and respirations will be counted for a full minute and recorded in breaths per minute.

When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled time point, and the vitals will be obtained prior to the blood draw. On dosing days, vital signs should be obtained prior to dosing.

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

7.5.3. Weight and Height

Height will be measured only at Screening/Baseline Visit.

Body weight will be measured in kilograms (kg) at the time points specified in the schedule of assessments (SOA).

7.5.4. Electrocardiogram (ECG)

Standard computerized 12-lead ECG recordings will be obtained. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/sec. Triplicate recordings will be obtained prior to

dosing. 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 blood draws, the blood draws will be obtained at the scheduled time points and the ECG will be obtained prior to the scheduled blood draw.

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 CRF. For any clinically significant changes from Screening/Baseline (e.g., 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.

7.5.5. Laboratory Assessments

The following clinical laboratory tests will be performed by a central laboratory, unless indicated otherwise:

Hematology

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

Serum Chemistry

- Sodium
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Lactate dehydrogenase (LDH)
- Glucose
- Potassium
- Phosphate
- Albumin
- Calcium
- Carbon dioxide
- Chloride

Liver Function Tests

- AST
- ALT
- Alkaline phosphatase (ALP)
- Bilirubin (total and direct)

Coagulation Studies

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR)

Thyroid Function Test

- Thyroid stimulating hormone (TSH)

Serology Parameters

- Hepatitis B surface antigens (HBsAg)
- Anti-hepatitis C virus antibodies (HCV Ab)
- Hepatitis B surface antibodies (HBsAb)

Urinalysis

- Visual inspection for appearance and color
- pH (dipstick)
- Specific gravity
- Ketones
- Protein
- Glucose
- Bilirubin
- Nitrite
- RBCs
- Urobilinogen
- Leukocytes
- Microscopy (if clinically indicated)

Pregnancy Testing (WOCBP only)

- β-human chorionic gonadotropin

Other

- Vitamin A
- Serum SPEP with IFE (or documented local results within last year)
- Urine SPEP with IFE (or documented local results within last year)
- Serum FLC (or documented local results within last year)

WOCBP = women of child bearing potential

Additional and repeat testing may be performed at the discretion of the Investigator.

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.

7.5.5.1. Anti-drug Antibodies

Serum samples will also be collected at scheduled time points prior to dosing to evaluate ADAs.

7.5.5.2. Pregnancy Screen

A serum pregnancy test will be performed for women of child bearing potential (WOCBP) at Screening/Baseline. A urinary pregnancy test will be performed any time pregnancy is suspected, and in accordance with the SOA. Urine pregnancy test may also be performed more frequently (monthly) based on local country requirements. The results of the pregnancy test must be known prior to 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 (see Section 8.10).

7.5.6. Ophthalmologic Examination

An ophthalmologic examination will be performed at Screening/Baseline and in accordance with the Table 1-1. Patients are not required to repeat the ophthalmologic examination if the assessment was performed within 90 days of randomization. Visual acuity should be evaluated at the beginning of each specified visit (ie, prior to slit-lamp examination). Manifest refraction will be performed at each specified visit, where possible, prior to visual acuity testing and will be used to obtain a correction for visual acuity evaluations. Visual acuity testing should be done with best (most recent) correction and be tested in bright and dim light conditions.

Further details regarding the ophthalmologic examinations will be provided in the Site Operations Manual.

7.5.7. Concomitant Medications

All medications the patient receives during the Screening/Baseline period through the Follow-up Visit will be recorded. The indication for the medication must be assessed to determine if a new AE is present. See Section 5.1 for more details on prohibited and acceptable concomitant medications.

7.5.8. Adverse Events

Starting on Day 0, adverse events will be assessed and recorded. The reporting guidelines are provided in Section 8.

7.6. Other Assessments

7.6.1. Exploratory Biomarkers

Where local regulations permit, blood samples will also be collected at scheduled time points prior to dosing to evaluate exploratory biomarkers (mutant: WT TTR levels and additional cardiac and hepatic-derived proteins that may include galectin 3 and ST2). Aliquots of plasma and serum samples will be taken and frozen, to permit testing of the effect of ALN-TTRSC on the expression of these exploratory biomarkers.

Collection of samples for exploratory biomarker analysis will be subject to discretionary approval from each site's IRB/IEC. 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.

7.6.2. DNA Sample

Where local regulations permit and subject to discretionary approval from each center's IRB/IEC, a voluntary blood sample for DNA extraction will be collected from each patient at Screening/Baseline. The voluntary DNA sample should only be obtained once during Screening. The results may be used as part of a later analysis, which could include a determination of the spectrum of TTR mutations in patients with ATTR and the relationship between TTR gene mutation and the safety and efficacy of ALN-TTRSC. The Sponsor will only analyze DNA sequences within genes relevant to the mode of action and response to ALN-TTRSC. No additional testing will be performed on the samples collected in the study.

DNA samples will be stored by the Sponsor, or designee, in a secure, monitored, and controlled environment until analysis, and will be destroyed by the Sponsor after all worldwide obligations have been met, or sooner if required by local regulations.

7.6.3. Pharmacoeconomics Questionnaire

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

8. ADVERSE AND SERIOUS ADVERSE EVENTS

8.1. Adverse Events Definition

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

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

All injection site reactions will be recorded as AEs.

8.1.1. 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

8.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires 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 (e.g. 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).

8.3. Eliciting Adverse Event Information

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

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

8.4. Adverse Event Reporting

The Investigator is responsible for reporting all AEs that are observed or reported after the first dose of study drug regardless of their relationship to study drug through the end of the reporting periods defined in Section 8.5.

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

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

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.

For patients with hepatic AEs, local laboratory results may be collected to monitor LFT levels or other laboratory parameters.

Refer to the CRF completion guidelines for details on reporting events in the supplemental AE of clinical interest eCRF form(s). When the form(s) is/are completed, [redacted] personnel will be notified electronically and may follow-up with queries.

8.5. Adverse Event Reporting Period

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

- For patients who complete the study, AEs will be assessed through the End of Study Visit, Week 82. All AEs that occur after the start of study drug administration on Day 0 must be reported in detail on the appropriate eCRF page and followed to satisfactory resolution, or through the End of Study Visit after the last dose of study drug administration. Serious AEs will be followed through the End of Study Visit, or

until satisfactory resolution, or until the SAE is considered by the Investigator to be chronic or the patient is stable.

- For patients who withdraw from the study early, ongoing AEs will be followed until resolution or 28 days from last dose, whichever occurs first. Serious AEs will be followed through 28 days from the last dose of study drug, or until satisfactory resolution, or until the SAE is considered by the Investigator to be chronic or the patient is stable.

8.6. Assessment of Causality

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

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

8.7. Assessment of Severity

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

Mild:	Mild events are those which are easily tolerated with no disruption of normal daily activity.
Moderate:	Moderate events are those which cause sufficient discomfort to interfere with 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).

8.8. Coding of Adverse Events

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

8.9. 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 seriousness criteria above (Section 8.2) must be reported to the CRO within 24 hours from the time that site personnel first learn of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

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

To report the SAE, complete the paper SAE form and fax it to [redacted] (fax number is provided in the Site Operations Manual) within 24 hours of awareness. SAE information must also be entered into the EDC system on the Adverse Events page within 5 calendar days of awareness.

Follow-up information must be provided to [redacted] using the paper SAE report (fax number is provided in the Site Operations Manual) within 24 hours of the information becoming available. The Investigator should also submit any supporting documentation such as a patient discharge summary or autopsy reports. Updated/follow-up SAE information must also be entered into the EDC system on the Adverse Events page within 5 calendar days of receiving the information.

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.

8.9.1. Notifying the IRB/IEC

SAEs 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.

8.9.2. Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the FDA, 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 (SUSARs) 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 subjects 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 subjects.

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

8.9.3. Sponsor Reporting: Notifying 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.

8.10. Pregnancy Reporting

A female patient with a positive pregnancy test at Screening/Baseline 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 (i.e., 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 8.9.

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

9. STATISTICS

9.1. Sample Size

For the 6-MWT primary endpoint, a sample size of 180 with a 2:1 treatment allocation (N=120 on ALN-TTRSC and N=60 on placebo) has 90% power to detect a treatment difference of 0.55 standard deviations using a Finkelstein and Schoenfeld analysis with a significance level of 0.05.[29] This assumes 20% of placebo patients and 13% of ALN-TTRSC patients die before the 18 month assessment (ie, Hazard Ratio [HR]=0.6). Assuming a standard deviation of 70 meters in change from baseline, this would correspond to 90% power to detect a treatment effect of 39 meters in the 6-MWT. Assuming a 10% patient dropout rate, approximately 200 patients will be enrolled in the study. Note that power for the comparison of percent reduction in serum TTR between treatment groups is expected to be >90% for a significance level of 0.05; sustained knockdown of serum TTR levels >85% has been observed in healthy volunteers and patients receiving ALN-TTRSC (Section 1.3). For this reason, overall power to establish efficacy is expected to be approximately 90% under the assumptions described above.

9.2. Statistical Methodology

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

9.2.1. Populations to be Analyzed

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

- Modified intent to treat (mITT) population: all patients who were randomized and received at least 1 dose of ALN-TTRSC or placebo.
- Per protocol (PP) population: all patients who did not have any major protocol violations; and completed the 18-month 6-MWD assessment or died on-study.
- Safety population: All patients who received at least 1 dose of ALN-TTRSC or placebo (analyzed as treated, not as randomized).

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

9.2.2. Baseline Evaluations

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

9.2.3. Efficacy Analyses

9.2.3.1. Primary Efficacy Endpoint

There are two co-primary endpoints. The first co-primary endpoint is change from baseline (in meters) for a 6-MWD conducted 18 months after randomization. The primary efficacy analysis for the comparison of 6-MWD between treatment groups will be conducted using Wilcoxon Mann Whitney-based test statistics that will take into account informative missingness due to death and the loss of the ability to perform the test.[29] Briefly, in this stratified non-parametric rank sum analysis, all pairs of patients within a stratum are compared. A pair of patients is compared first on time to death (if death occurs before 18 months); second on time until the inability to perform the test (if it cannot be determined as to which patient in a pair lived longer); and third on the change from baseline in 6-MWD at the time of the last assessment shared by both patients (if it cannot be determined as to which patient in a pair lived longer and which retained the ability to perform the 6-MWD longer). The analysis will be stratified based on the stratification parameters that are used for randomization.

The second co-primary endpoint is percent reduction from baseline in serum TTR using enzyme-linked immunosorbent assay. The area under the effect curve (eAUC) for percent reduction from baseline in serum TTR over time, where the y-axis is percent reduction and the x-axis is time since randomization, will be compared across groups using Analysis of Covariance (ANCOVA), in which the stratification variables and baseline serum TTR level will be included in the model as covariates. The eAUC will be computed using the trapezoidal method, where assessments missing due to death or discontinuation will be imputed using the baseline level, i.e., the percent reduction will be assumed to be 0%.

The study will have demonstrated efficacy if the p-value for each of the co-primary endpoints is ≤ 0.05 (2-sided).

Sensitivity analyses for each co-primary endpoints, including different methods for handling of the missing data, will assess the robustness of the primary analysis for the mITT population.

9.2.3.2. Secondary Efficacy Endpoints

The secondary composite of CV mortality and CV hospitalization, as well as change in NYHA class and change in KCCQ, will also be compared across treatment groups using stratified Finkelstein and Schoenfeld Joint Rank Tests. CV mortality and all-cause mortality will be compared across treatment groups using stratified log-rank tests. CV hospitalizations will be compared using the stratified Anderson-Gill model for recurrent events. Analyses will be stratified using the stratification parameters that are used for randomization.

Type I error control for secondary endpoints will be achieved by a hierarchical ordering procedure. Endpoints will be compared across treatment groups in the following pre-specified order:

- Composite CV mortality and CV hospitalization
- New York Heart Association (NYHA) class (Appendix 1)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

- Cardiovascular (CV) mortality
- CV hospitalization
- All-cause mortality

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

9.2.4. Safety Analyses

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

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

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

9.2.5. Pharmacokinetic Analyses

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

Plasma PK will be summarized and descriptive statistics conducted for each time point.

Inferential statistics of efficacy and PK/PD relationships will be conducted where possible.

PK-PD data will be analyzed via a population PK-PD model in order to leverage the sparse nature of the dataset. Details regarding the PKPD methods will be provided in a Pharmacokinetic Analysis Plan (PAP).

9.2.6. Interim Analysis

An unblinded interim analysis for futility may be conducted once approximately half the patients have completed the study. Further details will be included in the Statistical Analysis Plan (SAP).

10. STUDY MANAGEMENT

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

10.1. Data Handling and Quality Assurance

10.1.1. Electronic Case Report Forms

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

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

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

10.1.2. 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 site 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.

10.1.3. Inspections

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

10.2. Regulatory Guidelines

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

10.2.1. Institutional Review Board/Independent Ethics Committee

National regulations and ICH require that approval be obtained from an IRB or an IEC prior to participation of patients in research studies. Prior to the study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB or IEC.

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

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

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

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

10.2.2. Regulatory Authorities

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

10.2.3. Modification of the Protocol

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

10.2.4. Informed Consent Form

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

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

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

10.2.5. Study Reporting Requirements

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

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

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

10.2.6. Financial Disclosure Reporting Obligations

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

10.3. Study Committees

10.3.1. Data Monitoring Committee

A 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 DMC will not stop the trial for efficacy. The membership of the DMC and reporting structure are defined in the DMC Charter.

10.3.2. Independent Clinical Adjudication Committee

An independent clinical adjudication committee will perform a blinded adjudication of the causes of hospitalization and death, with the goal to identify cause of mortality (CV and

all-cause) and hospitalization (CV and HF). Each review will follow procedures detailed in the committee's charter.

10.4. Ancillary Research

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

10.5. Study Record Retention

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

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

10.6. Discontinuation of the Study by the Sponsor

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

10.7. Confidentiality

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

Following the principles of the Good Clinical Practice, if local regulations specify a patient's number and initials will be used to identify the patient on their study records. Laboratory samples may be labeled with an independent numbering code, and the label will not contain any other personal identification information. The numbering code associated with these labels will be held by the study CRO and the Sponsor, thereby allowing no unwarranted access to the information. When reporting results for interim safety assessment and at the end of the study, the code will be shared per standard operating procedures with the responsible member of the

Biostatistical and Data Management Departments of the CRO. The numbering code will also be held for samples in storage until marketing approval of ALN-TTRSC in the countries where this study was conducted, or until clinical development of ALN-TTRSC is halted.

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

10.8. Publications/Reports

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 prior to its submission, and according to any additional publication details in the Investigator Agreement.

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12. APPENDICES

APPENDIX 1. NEW YORK HEART ASSOCIATION CLASSIFICATION OF HEART FAILURE

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

APPENDIX 2. KARNOFSKY SCALE

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

APPENDIX 3. POLYNEUROPATHY DISABILITY SCORE

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