Official Title:	**HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)**
NCT Number:	**NCT03759379**
Document Date:	**Clinical Study Protocol, 19 February 2021**

CLINICAL STUDY PROTOCOL

ALN-TTRSC02-002

Protocol Title:	HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)
Short Title:	HELIOS-A: A Phase 3 Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with hATTR Amyloidosis
Study Drug:	ALN-TTRSC02
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Date:	Original protocol: 11 October 2018
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

12 Oct. 2018

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTRSC02-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

Short Title

HELIOS-A: A Phase 3 Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with hATTR Amyloidosis

Study Drug

ALN-TTRSC02

Phase

3

Study Centers

The study will be conducted at up to 80 clinical study centers worldwide.

Objectives and Endpoints

The co-primary, and most secondary and exploratory efficacy endpoints are in comparison to the placebo arm of the Phase 3 pivotal patisiran-LNP study (ALN-TTR02-004, also referred to as the APOLLO study) as specified in the statistical analysis section of the HELIOS-A protocol. The primary analysis will be conducted at Month 9. An additional analysis of all efficacy endpoints will be conducted at Month 18.

Objectives	Endpoints
Primary	
• To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment and on quality of life	Co-Primary: • Change from baseline in the Modified Neurologic Impairment Score +7 (mNIS+7) compared to the placebo arm of the APOLLO study • Change from baseline in Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) total score compared to the placebo arm of the APOLLO study
Secondary	
• To determine the efficacy of ALN-TTRSC02 on gait speed, nutritional status, and disability • To characterize the effect of ALN-TTRSC02 on serum TTR levels • To evaluate patient mortality and hospitalization	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Timed 10-meter walk test (10-MWT) – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R-ODS) • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran-LNP arm

Objectives	Endpoints
	• Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study • Composite events of all-cause deaths and/or all-cause hospitalizations in patients with cardiac involvement (over 18 months) compared to patients with cardiac involvement in the placebo arm of the APOLLO study
Exploratory	
• To determine the effect of ALN-TTRSC02 on: – Manifestations of cardiac amyloid involvement – Other assessment of neurologic impairment – Other assessments of quality of life – Disease stage – Performance of daily activities • To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and patisiran-LNP on vitamin A levels • To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran-LNP • To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran-LNP	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters, Troponin I and T levels, New York Heart Association (NYHA) class – Neurologic Impairment Score (NIS) – EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQoL-Visual Analog Scale (EQ-VAS) – Familial Amyloidotic Polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score – Karnofsky Performance Status (KPS) • Change from baseline in technetium scintigraphy cardiac parameters • Percent reduction in serum vitamin A levels • PK profile of ALN-TTRSC02 and patisiran-LNP • Incidence and titers of ADA to ALN-TTRSC02 and patisiran-LNP
Safety	
• To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

Study Design

This is a global, Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran-LNP, a reference comparator. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, an 18-month Treatment Extension Period which will include collection of safety and efficacy in patients who switch from patisiran-LNP to ALN-TTRSC02 treatment, and up to a 1-year Follow-up Period after the last dose of study drug as shown in Figure 1.

After the Screening period, and at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as a subcutaneous (SC) injection once every 3 months (q3M) or patisiran-LNP administered as an intravenous (IV) infusion once every 3 weeks (q3w). During the 18-month Treatment Period, patients will undergo assessments for efficacy and/or safety (as outlined in the Schedule of Assessments), with key efficacy assessments being performed prior to first dose, at Month 9 (primary efficacy analysis time-point) and at Month 18; samples for TTR assessment will be collected more frequently throughout the 18-month Treatment Period.

During the Treatment Extension Period, starting at Week 84/Month 19, all patients on the patisiran-LNP arm will switch to treatment with ALN-TTRSC02 (first dose) and remain on ALN-TTRSC02 q3M treatment for the remainder of the study. During the Treatment Extension Period, patients will undergo safety assessments quarterly and efficacy assessments every 9 months at Month 27 and at Month 36.

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential will be followed until serum TTR levels return to ≥80% of baseline. Patients who discontinue treatment early while on patisiran-LNP will undergo a follow-up visit 30 days after the last dose of study drug.

The placebo arm of the APOLLO study will be used as an external control for the primary, most secondary, and most exploratory efficacy analyses. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, percent TTR reduction, and the composite of all cause deaths and/or all cause hospitalizations. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

Number of Planned Patients

Approximately 160 patients are planned for enrollment in this study.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L at baseline.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, with a documented TTR mutation, and a confirmed diagnosis of symptomatic hATTR amyloidosis with an NIS of 5 to 130 (inclusive), a PND score of ≤3b, and KPS ≥60%.

Study Drug, Dose, and Mode of Administration

ALN-TTRSC02 drug product is a subcutaneously (SC) administered N-acetyl galactosamine ligand (GalNAc)-conjugated small interfering RNA (siRNA) targeting liver-expressed transthyretin (TTR) messenger RNA (mRNA).

ALN-TTRSC02 will be administered as a 25 mg SC injection q3M (12 weeks).

Reference Treatment, Dose, and Mode of Administration

Patisiran-LNP drug product is an intravenously (IV) administered siRNA targeting liver-expressed TTR mRNA formulated with lipid excipients (DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline.

Patisiran-LNP will be administered as a 0.3 mg/kg IV infusion once every 3 weeks (q3w) ± 3 days. All patients will receive premedication prior to patisiran-LNP infusions as described further in the protocol.

Duration of Treatment and Study

The estimated time on study for each patient is approximately 3 years, inclusive of 42 days of Screening, and up to 36 months of open-label treatment (including the 18-month Treatment Period plus an 18-month Treatment Extension Period).

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

Statistical Methods

A full statistical analysis plan (SAP) will be finalized prior to first patient dosed.

The co-primary endpoints are changes from baseline at Month 9 for mNIS+7 and Norfolk QoL-DN total scores. The co-primary endpoints will each be tested at a significance level of 0.05 and both must be significant to declare a positive trial. The primary comparison will be conducted at Month 9 and additional analyses will be performed at Month 18.

For the co-primary endpoint mNIS+7, change in mNIS+7 from baseline at Month 9 will be compared between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least-square (LS) means using an analysis of covariance (ANCOVA) model with baseline mNIS+7 score as a covariate and factors including treatment group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M), and age of disease onset (<50 vs ≥50 years old).

The other co-primary endpoint Norfolk QoL-DN, change in Norfolk QoL-DN total score from baseline at Month 9 will be compared between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least-square (LS) means using an

analysis of covariance (ANCOVA) model with baseline score as a covariate and factors including treatment group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M), age of disease onset (<50 vs ≥50 years old), and baseline NIS score (<50 vs ≥50).

The co-primary endpoints for the patisiran-LNP group in this study will be summarized descriptively.

Secondary clinical efficacy endpoints will be analyzed similarly. Overall type I error control for secondary endpoints will be achieved by a hierarchical testing procedure.

The TTR percent reduction through Month 9 will be derived as the average trough TTR percent reduction from Month 6 to 9 which is the steady state period for both ALN-TTRSC02 and patisiran-LNP. A Hodges-Lehmann method stratified by previous TTR stabilizer use (yes vs no) will be used to estimate the 95% confidence interval (CI) for the median difference between the ALN-TTRSC02 and patisiran-LNP groups in this study. Non-inferiority will be declared if the lower limit of the 95% CI for the treatment difference is greater than –10%. A sensitivity analysis will be conducted to compare the TTR percent reduction between the ALN-TTRSC02 group from this study and the pooled patisiran-LNP groups from this Phase 3 study and the APOLLO study.

The composite endpoint of all-cause hospitalization and death events over 18 months will be analyzed using recurrent event method Andersen-Gill model with treatment group (ALN-TTRSC02 vs placebo) as an independent variable. The endpoint will be analyzed for both the overall population and in patients with cardiac involvement.

The analysis of exploratory efficacy endpoint will be described in the SAP.

Safety data will be summarized descriptively.

Figure 1: Study Design

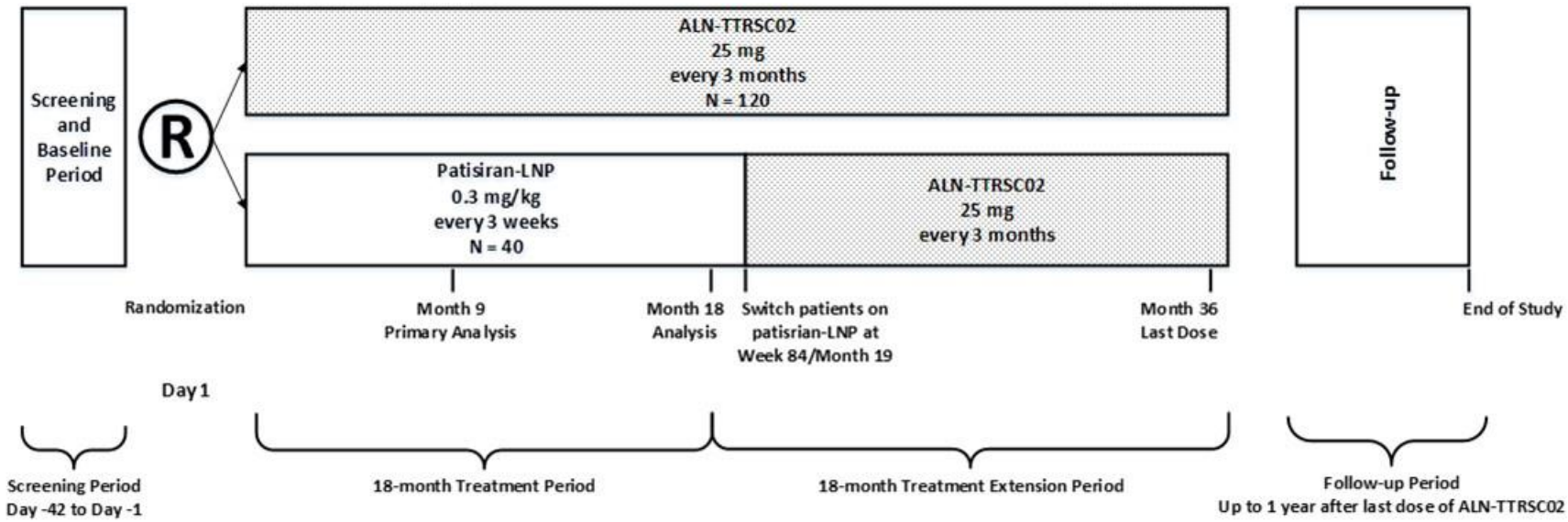


Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window						0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Informed Consent	Section 6.1	X																	
Inclusion/Exclusion	Section 4.1; Section 4.2	X	X																
Demographics and Medical/Disease History	Section 6.1.3	X	X	X															
Vital signs; Physical Exam (PE); Weight	Section 6.5.1; Symptom-directed PE unless specified as Full see Section 6.5.3 Section 6.5.2	X PE Full	Vital signs only	X	X - No PE	Vital signs only	X	X	X	X	X	X	X	X	X	X	X	X - PE Full	X- No PE
Height	Section 6.5.2.	X																	
mBMI, NYHA Class, KPS	Section 6.2.5 Section 6.2.10.4 Section 6.2.11	X								mBMI only				mBMI only					X
PND Score	Section 6.2.9		X	X															
FAP Stage	Section 6.2.9		X – Single assessment at any of these visits																
Serum Chemistry, Hematology, Urinalysis, Coagulation	Section 6.5.6	X			X					X				X					X
LFT	See below Table 1 notes. Results from both V1 and V2 must meet eligibility criteria. Section 6.5.6; Section 6.5.6.3	X	X		X		X		X		X		X		X		X		

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window						0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
FSH (only to confirm postmenopausal status if applicable)	Section 6.5.6	X																	
Pregnancy Test	At V1 serum pregnancy test; after V1, either urine or serum pregnancy test. Section 6.5.6.2	X			X					X				X				X	
Cardiac Biomarker Samples	Section 6.2.10.2	NT-proBNP only		X						X				X					X
TTR Protein; Vitamin A	Section 6.3			X	X		X	X		X		X		X		X		X	X
ADA	On dosing days, collect ADA within 1 hour before dosing, Section 6.5.6.1				X		X			X				X				X	
ALN-TTRSC02 Arm PK Sampling	See Table 4 for detail timepoints				X	X				X				X				X	
Patisiran-LNP Arm PK Sampling	See Table 5 for detail timepoints				X	X	X					X						X	
Sample for Exploratory Analysis	Section 6.6			X				X				X						X	X
Norfolk QoL-DN, R-ODS	Section 6.2.3; Section 6.2.6;		X– single at any of these visits																X

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Screening	Baseline				Treatment Period												Month 9 Efficacy	
		V1	V2	V3	Pre-dose	Post-dose														
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273	
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39	
±Visit Window						0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA	
EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact and Patient Experience Surveys	Section 6.2.8; Section 6.5.5; Section 6.7.1 Section 6.7.3			X– single at any of these visits															X	
NIS, mNIS+7, HRdb,	See below Table 1 Notes; and Section 6.2.1, Section 6.2.2		X	X															X	X
10-MWT	See below Table 1 Notes; and Section 6.2.4		X – Two assessments performed at any of these visits																X	X
Single (unless indicated) 12-Lead ECG	Section 6.5.4		X-Triplicate performed at any of these visits							X									X	
Echocardiogram	Section 6.2.10.1		X - Single performed at any of these visits																X	
Technetium scintigraphy imaging (select sites only)	Section 6.2.10.3		X - Single performed at any of these visits																	
Randomization	Window: -5D prior to Day 1				X															
ALN-TTRSC02 Study Drug Admin.	Section 5.2.2.1				X					X				X				X		

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window						0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Patisiran-LNP Arm: Premedication Admin.	Section 5.2.2.2				X		X	X	X	X	X	X	X	X	X	X	X	X	
Patisiran-LNP Study Drug Admin.	Section 5.2.2.2				X		X	X	X	X	X	X	X	X	X	X	X	X	
Review/Record Hospitalization, Urgent care visits; Procedures	Section 6.7.2		X - Collected through Day 1 predose			Continuous Monitoring													
Review/Record AEs, Con. Med,	Section 6.5.7; Section 5.3;					Continuous Monitoring													

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Admin.=administration; Con. Med.=concomitant medications; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EQ-5D-5L= EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS=EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; FSH=follicle-stimulating hormone; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NT-proBNP= B-type natriuretic peptide; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN= Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin; V=visits

Table 1 Notes:

- The Screening and Baseline visits (V1, V2 and V3) will be performed on separate days and can each occur over multiple days. V2 (first Baseline NIS, mNIS+7, HRdb assessment) must be performed within 21 days prior to the first dose of study drug (Day 1). V3 (second Baseline NIS, mNIS+7, HRdb assessment) must be conducted within approximately 24 hours after Visit 2 but not more than 7 days after. See Section 6.1 for retesting and re-screening instructions.
- Pre-randomization 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart.
- LFT for screening: Day 1 predose LFT does not need to be performed if there are available LFT results within 28 days of first dose.
- LFT for after randomization: For the ALN-TTRSC02 cohort, LFTs must be obtained with results available within 28 days before the clinic visit on which ALN-TTRSC02 dosing is scheduled. LFTs can be analyzed locally, but if a local assessment is drawn, a sample must also be drawn for analysis at the central laboratory. For the patisiran-LNP cohort, LFTs should be performed according to patisiran-LNP visit windows and do not need to be available prior to dosing.
- Unless otherwise specified, assessments on dosing days are predose.
- For the Month 9, NIS, mNIS+7, HRdb and 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Components that are shared between the mNIS+7 and NIS will be performed once at each assessment (eg, the weakness component should not be performed more than once on any given day).

Table 2: Schedule of Assessments – Treatment Period from Month 9 through Month 18

	Note	Treatment Period														Month 18 Efficacy
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**
±Visit Window		**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	
Vital signs; Physical Exam (PE);	Section 6.5.1; Symptom-directed PE Section 6.5.3;	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X - weight and vitals only
ALN-TTRSC02 Arm: Weight	Section 6.5.2				X				X				X			X
Patisiran-LNP Arm: Weight	Section 6.5.2.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class; KPS; PND and FAP; mBMI	Section 6.2.10.4; Section 6.2.11; Section 6.2.9; Section 6.2.5				mBMI only				mBMI only				mBMI only			X
Serum Chemistry, Hematology, Urinalysis, Coagulation	Section 6.5.6				X				X				X			X-Serum chemistry only
LFT	Section 6.5.6 Section 6.5.6.3				X				X				X			
Pregnancy Test	Section 6.5.6.2				X				X				X			X
Cardiac Biomarker Samples	Section 6.2.10.2				X				X				X			X
TTR Protein Vitamin A	Section 6.3				X		X		X		X		X		X	X
ADA	On dosing days, collect ADA within 1 hour before dosing, Section 6.5.6.1				X								X			X

Table 2: Schedule of Assessments – Treatment Period from Month 9 through Month 18

	Note	Treatment Period														Month 18 Efficacy	
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**	
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**	
±Visit Window		**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**		
ALN-TTRSC02 Arm PK	See Table 4 for detail timepoints				X				X				X				
Patisiran-LNP Arm PK	See Table 4 for detail timepoints	X					X								X		
Samples for Exploratory Analysis	Plasma, serum, urine; Section 6.6				X			X								X	
Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact and Patient Experience Surveys	Section 6.2.3; Section 6.2.6; Section 6.2.8; Section 6.5.5; Section 6.7.1 Section 6.7.3															X	
NIS; mNIS+7; HRdb; 10-MWT	See below Table 2 Notes; Section 6.2.1; Section 6.2.2; Section 6.2.4															X	X
Single 12-Lead ECG	Section 6.5.4				X											X	
Echocardiogram	Section 6.2.10.1															X	
Technetium scintigraphy imaging (select sites only)	Section 6.2.10.3															X	

Table 2: Schedule of Assessments – Treatment Period from Month 9 through Month 18

	Note	Treatment Period														Month 18 Efficacy
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**
±Visit Window		**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	
ALN-TTRSC02 Study Drug Administration	Section 5.2.2.1				X				X				X			
Patisiran-LNP: Premedication Administration	Section 5.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patisiran-LNP Study Drug Administration	Section 5.2.2.2	X – Dose after Month 9 efficacy assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status check																X
AEs, Con. Med, Hospitalization, Urgent care visits; Procedures	Section 6.5.7; Section 5.3; Section 6.7.2	Continuous Monitoring														

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con. Med.=concomitant medications; C-SSRS= Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EQ-5D-5L=EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS=EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin

Table 2 Notes:

- Unless otherwise specified, assessments on dosing days are predose.
- For the Month 18 NIS; mNIS+7; HRdb and 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Components that are shared between the mNIS+7 and NIS will be performed once at each assessment (eg, the weakness component should not be performed more than once on any given day).

Table 3: Schedule of Assessments: Treatment Extension Period, Other Visits, and Follow-up Period

	Note	Treatment Extension Period				Early Drug Discontinuation Visit		Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18				FU Period
		Last Patisiran-LNP Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	Month 27 Efficacy and Dosing Visit		Month 36 Efficacy Visit		4 (+1) Weeks from Last Dose		Month 9		Month 18		See Notes below Table 3
Study Week		**81**	**84, 96, 108, 120, 132, 144, and 156**	**120**		**160**		**-**		**36-39**		**79-80**		**-**
±Visit Window		**±3D**	**±7D**	**±2 weeks**		**±2 weeks**		**-**		**-**		**-**		**-**
NYHA class; KPS; PND and FAP; mBMI	Section 6.2.10.4; Section 6.2.11; Section 6.2.9; Section 6.2.5			X		X		X		X		X		
Vital Signs	Section 6.5.1	X	X	X		X								
Full Physical Examination (PE); Weight,	Section 6.5.3; Section 6.5.2			X		X		X		X		X		X
NIS; mNIS+7; HRdb	See below Table 3 Notes; Section 6.2.1; Section 6.2.2;			X	X	X	X	X	X	X	X	X	X	
10-MWT	Section 6.2.4			X	X	X	X	X	X					
Questionnaires: Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; all Pharmacoeconomic assessments	Section 6.2.3; Section 6.2.6;; Section 6.2.8; Section 6.5.5 Section 6.7			X		X		X - No Patient Preference Survey		X – No C-SSRS		X – No C-SSRS		
Single 12-Lead ECG	Section 6.5.4;							X						

Table 3: Schedule of Assessments: Treatment Extension Period, Other Visits, and Follow-up Period

	Note	Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran-LNP Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	Month 27 Efficacy and Dosing Visit	Month 36 Efficacy Visit	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		**81**	**84, 96, 108, 120, 132, 144, and 156**	**120**	**160**	**-**	**36-39**	**79-80**	**-**
±Visit Window		**±3D**	**±7D**	**±2 weeks**	**±2 weeks**	**-**	**-**	**-**	**-**
Echocardiogram	Section 6.2.10.1			X	X	X			
Technetium scintigraphy imaging (select sites only)	Section 6.2.10.3			X	X	X			
Serum Chemistry, Hematology, Urinalysis, Coagulation and Liver Function Tests	Section 6.5.6; Section 6.5.6.3.	LFT only; applies to both arms	X	X	X	X	Serum Chemistry and LFTs only	Serum Chemistry and LFTs only	X
Pregnancy Test	Section 6.5.6.2.		X	X	X	X	X	X	X
Cardiac Biomarker Samples	Section 6.2.10.2		X - Every 24 weeks starting at Week 96			X	X	X	
TTR Protein; Vitamin A	Prior to each dose on dosing days Section 6.3		X	X	X	X	X	X	X
ADA	On dosing days, collect within 1 hour before dosing, Section 6.5.6.1;		X -Every 24 weeks starting at Week 96			X			
ALN-TTRSC02 PK	See Table 4 for PK collection timepoints					X	X	X	

Table 3: Schedule of Assessments: Treatment Extension Period, Other Visits, and Follow-up Period

	Note	Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran-LNP Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	Month 27 Efficacy and Dosing Visit	Month 36 Efficacy Visit	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		**81**	**84, 96, 108, 120, 132, 144, and 156**	**120**	**160**	**-**	**36-39**	**79-80**	**-**
±Visit Window		**±3D**	**±7D**	**±2 weeks**	**±2 weeks**	**-**	**-**	**-**	**-**
Samples for Exploratory Analysis	Section 6.6			X	X	X			
AEs; Con. Meds; Hospitalizations, Urgent care visits and Procedures	Section 6.5.7; Section 5.3; Section 6.7.2		X	X	X	X	X	X	X - Through week 12 after last dose
ALN-TTRSC02 Study Drug Administration	Section 5.2.2.1		X - Every 12 weeks starting at Week 84 to EOT Week 156						
Patisiran-LNP: Premedication Administration	Section 5.2.2.2	X							
Patisiran-LNP Study Drug Administration	Section 5.2.2.2	X							
Vital status check	See note below Table 3							X	

Abbreviations: ADA=antidrug antibodies; AE=adverse event; Con. Med.=concomitant medications; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=End of Treatment; EQ-5D-5L=EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS= EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; FU=Follow-up; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin

Table 3 Notes:

- For the NIS; mNIS+7; HRdb;10-MWT performed as part of the Early Drug Discontinuation Visit and the Modified Month 9 and 18 Efficacy Visit(s): Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart.
- See Section 4.3 for instructions on early discontinuation of study drug procedures.
- Follow-up for patients who discontinued ALN-TTRSC02: All patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential will be followed until serum TTR levels return to ≥80% of baseline. The frequency of follow-up visits will be as follows:
  - Patients who discontinue study treatment early will be requested to follow the planned visit schedule and will be asked to complete the Month 9 and Month 18 efficacy assessment visits as described in Section 4.3.1 as per the Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18 column, and also completing the assessments in the Follow-Up column.
  - Patients who complete the study will be followed every 12 weeks, completing the assessments in the Follow-Up column.
- Follow-up for patients who discontinue patisiran-LNP: Patients will undergo a follow-up visit 30 days after the last dose of study drug (completing the assessments in the Follow-Up column).
- Vital status: All patients who discontinue study drug will have a vital status check approximately 18 months after the first dose of study drug either in person during the modified Month 18 visit or , as appropriate, by utilizing different follow options including by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians, or from review of medical records.
- SAE, AECI will be collected throughout the Follow-up Period; AEs will be collected until 3 months after the last dose of study drug.

Table 4: Pharmacokinetic Time Points: ALN-TTRSC02

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr)	X
	06:00 (±1 hr)	X
	24:00 (±2 hr)	X
Day 85 and Day 169 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr)	X
Day 337, Day 421, and Day 505 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr)	X
Early Drug Discontinuation Visit	Collect any time within the visit window	X
Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18	Collect any time within the visit window	X

Table 5: Pharmacokinetic Time Points: Patisiran-LNP

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before dosing)	X
	00:30 (±5 min)	X
	06:00 (±1 hr)	X
	24:00 (±2 hr)	X
Day 22, Day 127, Day 274, Day 379, and Day 547 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr)	X

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
AE	Adverse event
ALN-TTRSC02	Name of study drug product
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
APOLLO	Name of patisiran-LNP pivotal Phase 3 clinical study ALN-TTR02-004
ASGPR	Asialoglycoprotein receptor
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CAS	Central Assessment Sites
CASE	Computer Aided Sensory Evaluator
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
Con. Med	Concomitant medication
CRF	Case Report Form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency

Abbreviation	Definition
EOT	End of Treatment
EQ-5D-5L	EuroQoL 5-Dimensions 5-Levels
EQ-VAS	EuroQoL visual analogue scale
EU	European Union
FAC	Familial amyloidotic cardiomyopathy, also known as hATTR amyloidosis with cardiomyopathy
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
GalNAc	N-acetyl galactosamine ligand
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HRdb	Heart rate variability with deep breathing
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio
IRB	Institutional review board
IRR	Infusion related reaction
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
KPS	Karnofsky Performance Status
LFT	Liver function test
LLN	Lower limit of normal
LS	Least-square

Abbreviation	Definition
LV	Left ventricle
mBMI	Modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease Study
mITT	Modified Intent-to-Treat
10-MWT	10-meter walk test
mNIS+7	Modified Neurologic Impairment Score +7
mRNA	Messenger RNA
NCS	Nerve conduction studies
NCS Σ5	NCS sum of 5 attributes
NIS	Neurologic Impairment Score
NIS-R	NIS reflexes
NIS-S	NIS sensation
NIS-W	NIS weakness
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	B-type natriuretic peptide
NYHA	New York Heart Association
OLT	Orthotopic Liver Transplantation
Patisiran-LNP	Name of patisiran drug product; patisiran-lipid nanoparticles
PCS	Patient Care Sites
PD	Pharmacodynamics
PK	Pharmacokinetics
PND	Polyneuropathy Disability
PT	Prothrombin time
q3M	Once every 3 months
q3w	Once every 3 weeks
QoL or QOL	Quality of life
QST	Quantitative sensory testing
QST-BSA_{HP}	QST heat pain by body surface area
QST-BSA_{TP}	QST touch pressure by body surface area

Abbreviation	Definition
QTc	Corrected QT interval
QTcF	QT obtained using Fridericia's formula
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
siRNA	Small interfering ribonucleic acid
SNAP	Sensory nerve action potential
SOC	System organ class
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
T3	Triiodothyronine
T4	Thyroxine
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
TUDCA	Tauroursodeoxycholic acid
ULN	Upper limit of normal
US	United States
USA	United States of America
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
WHO	World Health Organization
wt	Wild type

1. INTRODUCTION

1.1. Disease Overview

Hereditary ATTR amyloidosis (hATTR amyloidosis) is a rare, life-threatening, autosomal dominant, multi-systemic disease caused by mutations in the transthyretin (TTR) gene that results in rapidly progressive, debilitating morbidity and high mortality. The cardinal manifestations of hATTR amyloidosis are polyneuropathy and cardiomyopathy.

TTR, also known as prealbumin, is a tetrameric protein predominantly produced by hepatocytes (>95% of circulating TTR is liver-derived), with a smaller fraction produced by the choroid plexus and retina (Liz, Mar et al. 2010). The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A), which involves TTR binding to the retinol binding protein (RBP): vitamin A complex. TTR also serves as a minor carrier for thyroxine (T4).

In hATTR amyloidosis, inherited mutations in the TTR gene lead to destabilization of the tetrameric protein and disassociation of the TTR subunits into dimers and individual mutant and wild-type (wt) monomers, which subsequently misfold. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues (Hou, Aguilar et al. 2007), including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wt TTR. There are over 120 reported TTR genetic mutations associated with hATTR (Connors, Lim et al. 2003; Ando, Coelho et al. 2013). The disease is most often caused by the valine to methionine mutation at position 30 in the human TTR gene (V30M)primarily in families with heritage from Portugal, Sweden, Japan, and Brazil (Parman, Adams et al. 2016). Another common genotype is the isoleucine substitution for valine at position 122 (V122I). This mutation occurs in up to 4% of African Americans and in over 5% of West African populations (Jacobson, Pastore et al. 1997).

Historically, due to incomplete understanding of etiology and pathogenesis, 2 clinical syndromes of hATTR amyloidosis have been described in the medical literature: hATTR amyloidosis with polyneuropathy (previously known as familial amyloidotic polyneuropathy, or FAP) and hATTR amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy, or FAC), both of which are characterized by amyloid deposits comprised of both mutant and wt TTR (Yazaki, Tokuda et al. 2000). However, while patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease. Therefore, hATTR amyloidosis is increasingly viewed as a single hereditary disease with a spectrum of clinical manifestations rather than 2 distinct syndromes (Swiecicki, Zhen et al. 2015).

The clinical manifestations of the length-dependent, symmetrical polyneuropathy are the result of amyloid-mediated injury to large and small peripheral nerve fibers (Benson and Kincaid 2007; Plante-Bordeneuve and Said 2011; Ando, Coelho et al. 2013). Sensory abnormalities include painful dysesthesias in the feet and hands, as well as loss of sensation leading to thermal burns in these areas and to joint injury in the lower limbs. Progressive muscle atrophy and motor

weakness in both lower and upper limbs leads to impaired ambulation (progressing from the use of one stick to two for ambulation, followed by needing to use a wheel chair and then becoming bed-ridden over just a few years), and inability to perform other activities of daily living. Autonomic dysfunction results in debilitating orthostatic hypotension, severe gastrointestinal symptoms, and bladder dysfunction with recurrent urinary tract infections.

Polyneuropathy stage or severity is classified by FAP stage or Polyneuropathy Disability (PND) score, both of which are based on ambulatory ability. The degree of neurologic impairment has historically been measured using the Neurologic Impairment Score (NIS), which has been shown to be correlated with FAP stage and PND score; an increase from baseline in NIS score signifies worsening in neurologic impairment, which in turn correlates with a higher FAP stage designation and PND score (Adams, Coelho et al. 2015). The maximum impairment score for the NIS is 244 points, and a change from baseline of 10 to 14 points per year has been observed in untreated patients based on data from an hATTR amyloidosis clinical study and an observational natural history study (Berk, Suhr et al. 2013; Adams, Coelho et al. 2015). This is in contrast to patients with diabetic polyneuropathy where NIS progression is <1 point/year (Ziegler, Low et al. 2011). For clinical studies, the modified NIS+7 (mNIS+7) score, a more sensitive measure with a scale from 0 to 304 points, has been developed to provide a more comprehensive measure of polyneuropathy in patients with hATTR amyloidosis (Suanprasert, Berk et al. 2014).

Cardiac infiltration with amyloid leads to heart wall thickening and cardiomyopathy characterized by clinical heart failure due to both diastolic and systolic dysfunction, as well as cardiac conduction disturbances and arrhythmias (Carvalho, Alves et al. 1992; Connors, Yamashita et al. 2004; Soares, Coelho et al. 2005; Benson and Kincaid 2007; Ando, Coelho et al. 2013). Patients with symptomatic heart failure experience rapid progression of their amyloid cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less (Ruberg and Berk 2012).

1.2. Current Treatments

The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, gastroenterology, and cardiology specialties. Palliative/symptomatic therapies directed at specific symptoms such as pain, nausea/vomiting and diarrhea have been the mainstay of treatment.

Two treatment approaches that have historically been used for the treatment of hATTR amyloidosis are orthotopic liver transplantation (OLT), which serves to eliminate mutant TTR from the circulation, but does not affect the hepatic production of wt TTR (Okamoto, Wixner et al. 2009; Carvalho, Rocha et al. 2015; Ericzon, Wilczek et al. 2015), and TTR tetramer stabilizers (including tafamidis and diflunisal), which have been shown in clinical studies to reduce neuropathy in patients with early stage polyneuropathy (Coelho, Maia et al. 2012; Berk, Suhr et al. 2013). However, these therapies are restricted to a small subset of patients with hATTR amyloidosis with early stage neuropathy. Furthermore, the majority of patients receiving tafamidis continue to experience neuropathy progression with a steady decline in quality of life, ability to walk, and to perform activities of daily living (Barroso, Judge et al. 2017).

Recently, the antisense oligonucleotide inotersen and the short interfering ribonucleic acid (siRNA) patisiran-LNP were shown in randomized controlled studies to significantly reduce neurologic impairment and improve quality of life compared with placebo in patients with hATTR amyloidosis (Adams, Suhr et al. 2017; Dyck PJ 2017; Wang et al. 2017). Both novel therapies, albeit through different mechanisms, aim at reducing the expression of TTR messenger RNA (mRNA), and the amount of circulating amyloidogenic protein in patients with hATTR amyloidosis.

1.3. RNAi Therapeutics to Reduce TTR Levels

Patisiran-LNP (ONPATTRO™) developed by Alnylam, which targets the production of hepatic TTR, is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. The recommended dose of patisiran-LNP is 0.3 mg/kg administered via intravenous (IV) infusion once every 3 weeks (q3w). To minimize the risk of infusion related reactions (IRRs), all patients must receive pre-medication including corticosteroids (10 mg dexamethasone IV), histamine 1 (H1) and histamine 2 (H2) blockers, and paracetamol or equivalents 60 minutes prior to the infusion.

Patisiran-LNP utilizes the mechanism of RNA interference to selectively degrade TTR mRNA and thereby reduce the expression of its corresponding protein (Bumcrot, Manoharan et al. 2006). Patisiran-LNP is an siRNA that is formulated as lipid nanoparticles (LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam had also developed another siRNA-conjugate therapeutic, revusiran, primarily for the treatment of patients with hATTR amyloidosis with cardiomyopathy; however, this program was discontinued as described further in the ALN-TTRSC02 Investigator's Brochure (IB).

ALN-TTRSC02 is in clinical development for the treatment of ATTR amyloidosis. This molecule is designed to have greater potency and prolonged duration of action compared to current and previous siRNAs evaluated in the clinic for treatment of this disease. ALN-TTRSC02 has the same nucleotide sequence as revusiran but employs a different ratio of chemical modifications to confer increased stability of the siRNA.

ALN-TTRSC02 drug product comprises the drug substance ALN-65492, an siRNA targeting TTR mRNA that is conjugated to an N-acetyl galactosamine ligand (GalNAc) to facilitate delivery to the liver, formulated in 10 mM sodium phosphate, 110 mM sodium chloride at pH 7 for subcutaneous (SC) injection. Uptake of ALN-TTRSC02 occurs via the asialoglycoprotein receptor (ASGPR), a member of the C-type lectin family of receptors that recognizes and binds

glycoproteins with terminal galactose (Gal) or GalNAc residues (Ashwell and Morell 1974; Nair, Willoughby et al. 2014). It is expressed on the cell surface of hepatocytes at a high copy number (0.5-1 million per cell) (Baenziger and Fiete 1980; Schwartz, Rup et al. 1980), and facilitates clearance of desialylated glycoproteins from the blood (Geffen and Spiess 1992). Binding of the carbohydrate ligand to the ASGPR leads to receptor-mediated endocytosis of the ligand-receptor complex followed by release of its cargo in the endocytic pathway, and subsequent recycling of the receptor to the cell surface for successive rounds of uptake.

ALN-TTRSC02 has been shown to have increased potency and duration of TTR reduction in nonclinical species and in a clinical study in healthy volunteers described in Section 1.4.2, enabling a much lower dose, lower injection volume, and significantly less frequent dosing for patients compared to other TTR-lowering drugs.

1.4. Clinical Experience with Patisiran-LNP and ALN-TTRSC02

1.4.1. The APOLLO Study

The safety and efficacy of patisiran-LNP was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints (Adams, Gonzalez-Duarte et al. 2018). This study demonstrated that in patients with hATTR amyloidosis, who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran-LNP leads to a significant improvement in neuropathy (mNIS+7) relative to placebo at 18 months (primary analysis), as well as significant improvement in quality of life (Norfolk QoL-DN, key secondary analysis) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran-LNP is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9. Patisiran-LNP treatment was also associated with improvement compared to placebo in exploratory cardiac endpoints including key echocardiographic parameters and the biomarker NT-proBNP (Solomon 2018). In post-hoc analyses, patisiran-LNP demonstrated a reduction in the composite event rate of hospitalization and mortality.

In the patisiran-LNP group, the mean TTR percent reduction from baseline was 82.6% and 84.3% at Month 9 and Month 18, respectively. TTR percent reduction was maintained over the duration of the study. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran-LNP showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran-LNP compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.4.2. ALN-TTRSC02-001 Phase 1 Clinical Study

ALN-TTRSC02 has been evaluated in a recently completed Phase 1 study (study ALN-TTRSC02-001). ALN-TTRSC02-001 was a randomized, single-blind, placebo controlled single-ascending dose study to evaluate the safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ALN-TTRSC02 in healthy subjects and in healthy subjects of

Japanese descent. Single doses of 5, 25, 50, 100, 200 or 300 mg ALN-TTRSC02 were administered by SC injection to cohorts of 8 subjects (6:2 ratio ALN-TTRSC02 to placebo). Subjects remained blinded to treatment assignment through Day 90. Eighty healthy volunteers were randomized in 10 cohorts and followed for up to 314 days.

ALN-TTRSC02 reduced serum TTR in a dose dependent fashion with higher doses of ALN-TTRSC02 achieving deeper and longer duration of serum TTR reduction. At the proposed dose of 25 mg ALN-TTRSC02, a single dose resulted in maximum TTR reduction of 94% and mean maximum TTR reduction of 83% that was maintained for 90 days (n=12). Consistent with the expected PD effect, vitamin A levels were also reduced following a single dose of ALN-TTRSC02. Similar PD effects were observed in the subjects of Japanese descent, as compared to the subjects in the non-Japanese cohorts.

AEs were reported in 77% and 50% of ALN-TTRSC02 and placebo treated subjects, respectively. Among ALN-TTRSC02 treated patients, the majority of AEs were mild. ALN-TTRSC02 drug-related AEs included injection site reactions in 4 subjects that were mild and transient including bruising (50 mg), erythema (200 mg) and pain (200 mg and 300 mg); there were no drug-related AEs in patients receiving ALN-TTRSC02 doses ≤25 mg. There were no severe or serious AEs; no subject discontinued from the study due to an AE. A dose-dependent pattern in transaminase elevations was observed across the ALN-TTRSC02 doses tested, in particular at doses ≥100 mg; the majority were mild, transient, and none were reported as AEs. Most alanine transaminase (ALT) and aspartate transaminase (AST) elevations were ≤3 x upper limit of normal (ULN); 1 subject receiving ALN-TTRSC02 50 mg had AST >3 x ULN and 1 subject receiving ALN-TTRSC02 200 mg had ALT and AST >3 x ULN, which were asymptomatic and resolved to <ULN without intervention. There were no concurrent elevations in bilirubin or alkaline phosphatase. There were no clinically significant changes in renal function or hematologic parameters, including platelets and no clinically significant changes in electrocardiogram (ECG), vital signs or physical exam.

Further information on the chemistry, pharmacology, efficacy, and safety of ALN-TTRSC02 is provided in the current edition of the Investigator's Brochure.

1.5. Study Design Rationale

This is a global Phase 3 open-label study designed to evaluate the efficacy, safety, and PK/PD profile of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran-LNP. Patisiran-LNP is the reference comparator arm. All patients randomized to patisiran-LNP will be transitioned to ALN-TTRSC02 after completion of the 18-month Treatment Period.

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, an 18-month Treatment Extension Period, and up to a 1-year Follow-up Period after the last dose of study.

The proposed development plan for ALN-TTRSC02 builds upon learnings from the previous development of another siRNA that targets TTR, patisiran-LNP (described in Section 1.4). The completed patisiran-LNP Phase 3 APOLLO study, which enrolled a similar patient population to the current study and incorporated similar endpoints to the current study, will be used as an external control for efficacy analysis. The co-primary endpoints in this study, change from

baseline in mNIS+7 score and Norfolk QoL-DN total score at Month 9, will be compared with the placebo group from the APOLLO study at Month 9 as the primary analysis. An additional analysis of efficacy is planned at Month 18.

The use of an external control for comparison is supported by the principles outlined in the EMA guideline on clinical trials in small populations (CHMP/EWP/83561/2005), ICH E10 guidance on control groups in clinical trials, as well as the USA's 21st Century Cures Act (Section 3012 Targeted Drugs for Rare Diseases). Based on these guidelines, an external comparison is an appropriate clinical study design for diseases occurring in small populations, with well understood natural history of disease course. The natural history of hATTR amyloidosis has been well-characterized in several, large, randomized clinical trials, including the APOLLO study, as well as natural history studies. Importantly, these studies all demonstrate similar rates of disease progression despite having been conducted at substantially different points in time and in patients with different disease characteristics across different geographies (Berk, Suhr et al. 2013; Adams, Coelho et al. 2015; Maurer, Elliott et al. 2017; Adams, Gonzalez-Duarte et al. 2018). The patisiran-LNP reference comparator arm will help to validate the use of the external control for the primary and secondary efficacy analyses both by allowing descriptive comparison of the clinical efficacy endpoints between treatment arms within this study and by establishing similar (non-inferior) level of TTR reduction is achieved for ALN-TTRSC02 and patisiran-LNP.

Secondary and exploratory endpoints in this study assessing the clinical manifestations of hATTR amyloidosis are similar to those in the APOLLO study. A composite of all-cause death and/or all-cause hospitalizations has also been included to assess the impact of ALN-TTRSC02 on patient outcomes in the overall study population and in patients with cardiac involvement. Additional cardiac assessments are included in this study as exploratory endpoints. These endpoints will all be assessed in comparison to the placebo group in the APOLLO study.

Safety will be assessed by monitoring of AEs, laboratory data including liver function tests, changes in physical exam, vital signs, and ECG. Safety data will not be compared to the APOLLO study.

1.6. Dose Rationale

The proposed dose of ALN-TTRSC02 for this study is 25 mg SC given q3M. This dose was well-tolerated in the Phase 1 study (see Section 1.4.2) and is expected to provide efficacy similar to patisiran-LNP based on the anticipated magnitude of TTR lowering.

Modeling and simulation predict that the proposed 25 mg dose of ALN-TTRSC02 administered SC q3M will lead to substantial and persistent serum TTR reduction, comparable to TTR lowering observed with patisiran-LNP in the Phase 3 APOLLO study. At steady state, which is achieved by approximately 6 months, 25 mg SC q3M regimen of ALN-TTRSC02 is predicted to achieve median trough TTR reductions of 86%, which is similar to patisiran-LNP. This magnitude of TTR lowering is expected to lead to durable clinical benefit as evidenced by the statistically significant difference in mNIS+7 and all the secondary endpoints, including Norfolk QoL-DN, in the patisiran-LNP arm compared to placebo in the pivotal Phase 3 APOLLO study. Furthermore, on the Phase 3 APOLLO study, this magnitude of TTR lowering was associated with an acceptable safety profile.

Overall, available nonclinical and clinical data suggest the selected dose will appropriately balance safety and efficacy in the broad hATTR patient population.

1.7. Benefit-Risk Assessment

Based on available nonclinical and clinical data, with evidence of TTR reduction in the healthy subject study, TTR reduction by ALN-TTRSC02 is anticipated to beneficially impact disease progression in patients with hATTR amyloidosis, as has been shown with other available TTR lowering agents including patisiran-LNP and inotersen. The q3M SC regimen is infrequent, easy to administer, and does not require premedication, and thus may maximize convenience and minimize overall burden of care. In the Phase 1 clinical study in healthy subjects, single SC doses up to the highest tested dose (300 mg) of ALN-TTRSC02 were well tolerated.

Given the biological target of ALN-TTRSC02, the available nonclinical and clinical data, and the mode of administration, important potential risks for ALN-TTRSC02 are injection site reactions (ISRs), liver function test (LFT) abnormalities, and consequences of vitamin A deficiency. During the study, patients will be closely monitored, including evaluation of injections sites. As ALN-TTRSC02 is targeted for delivery to the liver, there is a potential for development of LFT abnormalities. Patients presenting with any laboratory result considered unacceptable as per exclusion criteria (see Section 4) at time of enrollment will be excluded from participation in this study, and LFTs will be routinely monitored throughout the study per the Schedule of Assessments. Criteria for dose withholding, modification and stopping ALN-TTRSC02 dosing due to LFT abnormalities are provided in Section 5.2.3. Detailed information about the known and expected benefits and risks of ALN-TTRSC02 and additional safety information may be found in the current edition of the ALN-TTRSC02 Investigator's Brochure.

For patisiran-LNP, important identified risks include infusion related reactions (IRRs). All patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran-LNP administration to reduce the risk of IRRs (see Section 5.2.2.2). Potential risks include consequences of vitamin A deficiency and severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Detailed information about the known and expected benefits and risks of patisiran-LNP and additional safety information may be found in the current edition of the patisiran-LNP Investigator's Brochure or, where approved, in the ONPATTRO prescribing/product information.

Nonclinical and clinical data with ALN-TTRSC02 and patisiran-LNP have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in severe vitamin A deficiency; transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. However, as the vitamin A content of the diet may vary between different individuals, all patients will be instructed to take the recommended daily allowance of vitamin A while on the study (see Section 5.2). Laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation beyond the recommended daily dose during treatment with ALN-TTRSC02 and patisiran-LNP.

2. OBJECTIVES AND ENDPOINTS

The co-primary, and most secondary and exploratory efficacy endpoints are in comparison to the placebo arm of the Phase 3 pivotal patisiran-LNP study (ALN-TTR02-004, also referred to as the APOLLO study) as specified in the statistical analysis section of the HELIOS-A protocol. The primary analysis will be conducted at Month 9. An additional analysis of all efficacy endpoints will be conducted at Month 18.

Objectives	Endpoints
Primary	
• To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment and on quality of life	Co-Primary: • Change from baseline in the Modified Neurologic Impairment Score +7 (mNIS+7) compared to the placebo arm of the APOLLO study • Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score compared to the placebo arm of the APOLLO study
Secondary	
• To determine the efficacy of ALN-TTRSC02 on gait speed, nutritional status, and disability • To characterize the effect of ALN-TTRSC02 on serum TTR levels • To evaluate patient mortality and hospitalization	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Timed 10-meter walk test (10-MWT); – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R-ODS) • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran-LNP arm • Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study • Composite events of all-cause deaths and/or all-cause hospitalizations in patients with cardiac involvement (over 18 months) compared to patients with cardiac involvement in the placebo arm of the APOLLO study

Objectives	Endpoints
Exploratory	
• To determine the effect of ALN-TTRSC02 on: – Manifestations of cardiac amyloid involvement – Other assessment of neurologic impairment – Other assessments of quality of life – Disease stage – Performance of daily activities • To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and patisiran-LNP on vitamin A levels • To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran-LNP • To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran-LNP	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters, Troponin I and T levels, New York Heart Association (NYHA) class – Neurologic Impairment Score (NIS) – EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQoL-Visual Analog Scale (EQ-VAS) – Familial Amyloidotic Polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score – Karnofsky Performance Status (KPS) • Change from baseline in technetium scintigraphy cardiac parameters • Percent reduction in serum vitamin A levels • PK profile of ALN-TTRSC02 and patisiran-LNP • Incidence and titers of ADA to ALN-TTRSC02 and patisiran-LNP
Safety	
• To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a global Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran-LNP, a reference comparator.

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, an 18-month Treatment Extension Period which will include collection of safety and efficacy in patients who switch from patisiran-LNP to ALN-TTRSC02 treatment, and up to a 1-year Follow-up Period after the last dose of study as shown in Figure 1.

After the Screening period at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as a SC injection on q3M or patisiran-LNP administered as an IV infusion q3w; patients in the patisiran-LNP arm will also receive premedications prior to each dose (see Section 5.2.2.2). During the 18-month Treatment Period, patients will undergo assessments for efficacy and/or safety (as outlined in the Schedule of Assessments), with key efficacy assessments being performed prior to first dose, at Month 9 (primary efficacy analysis time-point) and at Month 18; samples for TTR assessment will be collected more frequently throughout the 18-month Treatment Period.

All ALN-TTRSC02 doses will be administered at the clinic during scheduled study assessment visits through Month 18. For patients randomized to the ALN-TTRSC02 arm, after Month 9, non-dosing visits for routine assessments (eg, vital signs and blood collection) may be performed outside the clinic (eg, at home) by a trained healthcare professional where applicable country and local regulations and infrastructure allow.

All patisiran-LNP doses will be administered at the clinic during the scheduled study assessment visits through Month 9. After Month 9, visits for patisiran-LNP dosing, as well as routine assessments (eg, vital signs and blood collection), may be performed outside of the clinic (eg, at home) by a trained healthcare professional where applicable country and local regulations and infrastructure allow, with the exception of the patisiran-LNP dosing visits at Weeks 48, 60 and 72 which must be performed in the clinic.

For both ALN-TTRSC02 and patisiran-LNP treated patients, wherever possible, AE collection associated with visits performed outside of the clinic will be collected by a phone call from qualified site staff. In addition, ad hoc visits may be performed outside the clinic (eg, at home) throughout the study in cases where, for example, a blood sample needs to be redrawn. In all cases, the Month 9 and Month 18 efficacy visits will be performed in the clinic. Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

During the Treatment Extension Period, starting at Week 84/Month 19, patients who are tolerating their ALN-TTRSC02 injections as determined by the Investigator and where applicable country and local regulations allow, may have ALN-TTRSC02 administered outside the clinic (eg, home) by a healthcare professional trained on study drug administration. Also, starting at Week 84/Month 19, all patients on the patisiran-LNP arm will switch to treatment with ALN-TTRSC02 (first dose) and remain on ALN-TTRSC02 q3M treatment for the remainder of the study. For patients in the patisiran-LNP arm who transition to ALN-TTRSC02 during the Treatment Extension period,

ALN-TTRSC02 may be administered outside of the clinic (eg, at home) as outlined above after they have received, and tolerated, at least one dose in the clinic. During the Treatment Extension Period, patients will undergo safety assessments quarterly and efficacy assessments every 9 months at Month 27 and at Month 36.

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential will be followed until serum TTR levels return to ≥80% of baseline. Patients who discontinue treatment early while on patisiran-LNP will undergo a follow-up visit 30 days after the last dose of study drug.

The placebo arm of the APOLLO study will be used as an external control for the primary, most secondary, and most exploratory efficacy analysis. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, percent TTR reduction, and the composite of all-cause deaths and/or all-cause hospitalizations. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

3.2. Duration of Treatment

The treatment duration in this study is up to 36 months inclusive of the 18-month Treatment Period and the 18-month Treatment Extension Period.

Refer to Section 4.3.1 for information on early treatment discontinuation.

3.3. Duration of Study

The estimated time on study for each patient is approximately 3 years, inclusive of 42 days of Screening, and up to 36 months of open-label treatment (including the 18-month Treatment Period plus the 18-month Treatment Extension Period).

The Follow-up Period is until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if:

- the patient has completed the Month 36 Efficacy Visit, or
- the patient has completed the ALN-TTRSC02 Follow-up Period, until serum TTR levels return to ≥80% of baseline (for a maximum of up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

3.4. Number of Planned Patients

Approximately 160 patients are planned for enrollment in this study.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L at baseline.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 3:1 to the ALN-TTRSC02 or patisiran-LNP arm. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

Not applicable, this is an open-label, controlled study.

3.7. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will oversee the safety and overall conduct of this study through the Treatment Period (through Month 18), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC has the responsibility for reviewing safety data and analyses and making recommendations to the Sponsor. The DMC will perform periodic reviews of data during the course of the clinical trial through the Treatment Period, and on an ad hoc basis for review of emergent safety data. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and hospitalizations and will attribute a cause according to the responsible underlying disease process rather than the immediate mechanism. Deaths and hospitalizations will be classified as specified in the Adjudication Committee Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Each patient must meet all of the following eligibility criteria at Screening Visit 1 (except where specified) to be eligible for enrollment in the study.

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all of the following criteria apply:

Age and Sex

1. Male or female age 18 (or age of legal consent, whichever is older) to 85 years of age

Patient and Disease Characteristics

2. Have a diagnosis of hATTR amyloidosis with documented TTR mutation
3. Have an NIS of 5 to 130 (inclusive; this criterion must be met at the Screening Visit 2)
4. Have a PND score of ≤3b (this criterion must be met at the Screening Visit 2)
5. Have a Karnofsky Performance Status (KPS) of ≥60%

Informed Consent

6. Patient is willing and able to comply with the study requirements and to provide written informed consent

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Has had a liver transplant or is likely, in the opinion of the Investigator, to undergo liver transplantation during the 18-month Treatment Period of the study
2. Has known other (non-hATTR) forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis
3. Has a New York Heart Association heart failure classification >2

Laboratory Assessments

4. Has any of the following laboratory parameter assessments:
   a. ALT and/or AST >1.5× upper limit of normal reference range (ULN)
   b. Total bilirubin >ULN (>1.5 ULN in patients with Gilbert's Syndrome)
   c. International normalized ratio (INR) >1.2 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)

   (Note: ALT, AST, and total bilirubin laboratory criteria must be met at both Screening Visit 1 and Screening Visit 2)
5. Platelet count <50,000/µL
6. Absolute neutrophil count (ANC) <1500 cells/mm³
7. Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73m^2 (using the Modification of Diet in Renal Disease [MDRD] formula)
8. Has vitamin B12 levels below the lower limit of normal (LLN)
9. Has known human immunodeficiency virus (HIV) infection; or evidence of acute or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection

Prior/Concomitant Therapy

10. Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30

days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (Day 1)

11. Received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR amyloidosis
12. Is currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to dosing (Day 1)
13. Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to dosing (Day 1)

Medical Conditions

14. Has other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease, monoclonal gammopathy) that the treating physician believes to be contributing to the neuropathy
15. Had acute coronary syndrome within the past 3 months
16. Has uncontrolled clinically significant cardiac arrhythmia or unstable angina
17. Has known type 1 diabetes
18. Has had type 2 diabetes mellitus for ≥5 years
19. Has untreated hypo- or hyperthyroidism
20. Has had a major surgery within the past 3 months or has a major surgery planned during the study through Month 18
21. Has an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior dosing (Day 1)
22. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
23. Anticipated survival is less than 2 years, in the opinion of the Investigator
24. History of multiple drug allergies; or history of allergic reaction to an oligonucleotide or GalNAc; or had a prior severe reaction to a liposomal product or any component of patisiran-LNP (ALN-TTR02)
25. Is unable to take the required premedications (see Section 5.2.2.2)
26. History of intolerance to subcutaneous (SC) injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
27. Any condition (eg, medical concern), which in the opinion of the Investigator, would make the patient unsuitable for dosing or which could interfere with the study compliance, the patient's safety and/or the patient's participation through the Month 18 visit of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to hATTR identified by key laboratory abnormalities or medical history

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
29. Female patient is pregnant or breastfeeding

Alcohol Use

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])
31. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented and recorded in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse Event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-adverse event)
- Or, the study is terminated by the Sponsor

The Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing of the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.7.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 3), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians, or from review of medical records), including endpoints and adverse events, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including serious adverse events (SAEs), the event should be followed as described in Section 6.5.7. When a patient discontinues study drug dosing, the primary reason must be recorded in the electronic case report form (eCRF). Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue study drug early for any reason during the Treatment Period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month-18 assessments) should complete the Early Drug Discontinuation visit and will be encouraged to remain on the study to complete the modified Month 9 and Month 18 efficacy assessments visits, prioritizing the primary and secondary assessments, where possible so that their experience is captured in the final analyses. If a patient discontinues study drug and completes the Early Drug Discontinuation visit within 3 months of Month 9 or Month 18 and remains on the study, they will not be required to complete the modified Efficacy Assessments at Month 9 and/or Month 18, as applicable depending on the time they discontinue study drug (Table 3).

Patients who discontinue study drug, but who remain on study, may receive treatment consistent with local standard practice for their disease per Investigator judgment, as applicable. For patients who discontinue study drug and remain in the study, all AEs will be collected for 90 days after the last dose, thereafter, SAEs and AEs of clinical interest (see definition in Section 6.5.7.1) will be collected for the remainder of their participation in the study.

Patients who discontinue study drug during the Treatment Extension period will be asked to return for their next scheduled visit to complete the Early Drug Discontinuation visit.

All patients who discontinue study drug will also be asked to complete safety follow-up visits, per the Follow-up Period schedule (see Table 3) until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. Patients considering stopping their participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study

drug and stop participation in all follow-up, every effort should be made to conduct the Early Drug Discontinuation Visit assessments within 4 weeks of the last dose (Table 3).

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient's consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, use biological samples and as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.7.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study and/or should continue in the study.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-TTRSC02 and patisiran-LNP is provided in the Pharmacy Manual.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Description

ALN-TTRSC02 will be supplied as a sterile solution containing 50 mg/mL of siRNA ALN-65492 free acid (equivalent to 53 mg/mL sodium salt) in phosphate buffered saline for SC injection. The drug product does not contain preservatives and is intended for single use. See the Pharmacy Manual for further details of solution concentration and fill volume.

The comparator drug for this study will be patisiran-LNP that contains 2 mg/mL of drug substance ALN-18328 (siRNA) and lipid excipients DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG formulated as lipid nanoparticles (LNPs) in isotonic phosphate buffered saline for IV administration. Patisiran-LNP will be provided by the Sponsor.

5.2.2. Dose and Administration

5.2.2.1. ALN-TTRSC02

ALN-TTRSC02 25 mg SC injection will be administered q3M (12 weeks ±3 days during the Treatment Period and ±7 days during the Treatment Extension Period). Study drug SC injections will be administered under the supervision of the Investigator or healthcare professional.

All ALN-TTRSC02 doses will be administered at the clinic during scheduled study assessment visits during the Treatment Period on Day 1 through Month 18. During the Treatment Extension Period, starting at Week 84/Month 19, patients who are tolerating their ALN-TTRSC02 injections as determined by the Investigator and where applicable country and local regulations allow, may have ALN-TTRSC02 administered outside the clinic (eg, home) by a healthcare professional trained on study drug administration.

Method of Administration of ALN-TTRSC02

ALN-TTRSC02 is for SC use and should be administered by a healthcare professional.

The SC injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual.

Missed Doses of ALN-TTRSC02

If a patient does not receive a dose of ALN-TTRSC02 within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered with up to a 6-week delay (to be considered a delayed dose). Thereafter, the dose will be considered missed and not administered. If a dose is administered with a delay, the next dose will resume following the original schedule.

During the Treatment Period, every effort should be made to avoid missed doses of ALN-TTRSC02. During the Treatment Period, if a patients misses a dose, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study (see also Section 4.3).

5.2.2.2. Patisiran-LNP

Patisiran-LNP 0.3 mg/kg IV infusion will be administered once every 3 weeks (q3w) ±3 days. The amount (in mg) of study drug to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg.

All patisiran-LNP doses will be administered at the clinic during the scheduled study assessment visits through Month 9. After Month 9, patisiran-LNP dosing may be performed at home by a trained healthcare professional where applicable country and local regulations and infrastructure allow, with the exception of the patisiran-LNP dosing visits at Weeks 48, 60, and 72, which must be performed in the clinic during scheduled study assessment visits through Month 18.

Required premedication for patients in the patisiran-LNP arm

All patients should receive premedication prior to patisiran-LNP administration to reduce the risk of infusion-related reactions (IRRs). Each of the following medicinal products should be given on the day of patisiran-LNP infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally. Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

- If a patient is having difficulty tolerating the corticosteroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the corticosteroid premedication may be allowed for that patient after consultation with the medical monitor.
- If a patient has tolerated 3 or more infusions of patisiran-LNP with their current corticosteroid premedication regimen (ie, patient has not had IRRs during the past 3 or more infusions), then lowering of the corticosteroid premedication is recommended.

Corticosteroid tapering should be performed in the clinic. Steps to lower corticosteroid dosing are provided in the Pharmacy Manual.

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed. Guidelines for management of IRRs can be found in the Pharmacy Manual.

Method of Administration of patisiran-LNP

Patisiran-LNP is for IV use and should be administered by a healthcare professional.

Weight from previous visit may be used for calculating dose. Weight must be collected predose. The patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient will remain at the study site for 1 hour following completion of dosing for observation and completion of assessments.

Detailed instructions for study drug preparation and administration can be found in the Pharmacy Manual.

Missed Doses of patisiran-LNP

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

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study.

5.2.2.3. Switching from Patisiran-LNP to ALN-TTRSC02 After Month 18

On Week 84, patients in the patisiran-LNP arm will be switched to ALN-TTRSC02 treatment and will receive the first ALN-TTRSC02 dose. The last dose of patisiran-LNP will be at Week 81, and patients should receive treatment with ALN-TTRSC02 3 weeks later on Week 84 and thereafter q3M (12 weeks ±7 days) for the remainder of the study.

5.2.3. LFT Criteria for Withholding, Monitoring and Stopping ALN-TTRSC02 Dosing

1. LFT results (Table 7) are to be obtained within 28 days prior to ALN-TTRSC02 dosing and results are to be reviewed prior to each dose of ALN-TTRSC02. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 6.
3. For any ALT or AST elevation >3× ULN:
   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. Perform assessments per Table 6 and Table 8.
   c. If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3× ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 6 (below).

Table 6: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 8 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT and coagulation per Table 7
	• Monitor at least every two weeks (LFT and coagulation per Table 7)
	• If elevation persists for ≥2 months, must discuss with the medical monitor before continuing dosing

>5× to 8× ULN	• Hold ALN-TTRSC02 dosing until recovery to ≤1.5× ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 8 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 7
	• Monitor at least weekly (LFT and coagulation per Table 7) until ALT and/or AST is declining on two consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value at the central laboratory

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of ALN-TTRSC02 and patisiran-LNP doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately [5±3°C] until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 to Table 3). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use NSAIDs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins (including vitamin A supplementation) and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Prohibited medications during the study include inotersen, tafamidis, diflunisal, and doxycycline/TUDCA (see Section 4.2 for prior medication washout requirements before first dose of study drug). Use of patisiran-LNP outside of the protocol specified administration is also prohibited. Any investigational agent other than ALN-TTRSC02 is not permitted during the study.

For other permitted concomitant medications administered subcutaneously, do not administer in same injection site area as the study drug, for 2 weeks after the last dose of study drug.

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

If available, information from a cardiac technetium scan or liver biopsy prior to study enrollment or during the study (as part of standard of care) should be collected and recorded as part of concomitant procedure information.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use acceptable methods of contraception from 14 days before first ALN-TTRSC02 dose, throughout study participation, and for 90 days after last dose administration.

Females of child-bearing potential taking patisiran-LNP must use acceptable methods of contraception prior to dosing and for 12 weeks after the last dose of patisiran-LNP in this study if they do not switch and continue treatment with ALN-TTRSC02 starting at Day 337 (Week 48).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- 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).
- Established use of oral (except for low dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods, if they start heterosexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, contraception use by males should be consistent with local regulations as described in the corresponding patient informed consent forms.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.6.2).

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1 (Screening through Treatment Period Month 9), Table 2 (Treatment Period from Month 9 through Month 18), Table 3 (Treatment Extension Period, Other Visits, and Follow-up Period), Table 4 (ALN-TTRSC02 PK Time Points) and Table 5 (Patisiran-LNP PK Time Points). Additional information on the collection of study assessments will be detailed in the Study Reference Manual. In this study there are 2 types of study centers:

- Patient Care Sites (PCS) can screen, dose, and manage the well-being of patients and collect safety assessments, and can administer efficacy assessments that include, but are not limited to, completion of a questionnaire or collection of blood samples for assessment of TTR and other PD biomarkers, as well as cardiac biomarkers, but will not perform the following efficacy assessments: NIS, mNIS+7, HRdb, 10-MWT, FAP and PND, KPS, echocardiogram.
- Central Assessment Sites (CAS) can perform all efficacy assessments and perform the same assessments as at a PCS (as stated above). Efficacy assessments (NIS, mNIS+7, HRdb, 10-MWT, FAP and PND, KPS, echocardiogram) in this study may require special training as described further in Section 6.2; therefore, all patients must be sent to a CAS to collect these efficacy assessments during screening and predose baseline assessments, Month 9, Month 18, and during the Treatment Extension period at Month 27 and Month 36. Assessors who will perform efficacy assessments at a CAS will be different from site personnel who monitor the administration of study drug during the study and monitor the well-being of the patient during the study. This is instituted to minimize the influence patient management and AEs may have on efficacy assessment evaluation(s).

During the study, where applicable country and local regulations and infrastructure allow, assessments that may be conducted by a qualified home healthcare professional include but are not limited to: blood draws, vital signs, physical exam, collection of information regarding hospitalizations, urgent care visits, procedures and concomitant medications. Wherever possible, AE collection associated with visits outside of the clinic will be collected by a phone call from qualified site staff. Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

6.1. Screening Assessments

An informed consent form (ICF) or assent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF and/or assent form.

See Table 1 for a list of Screening visit assessments.

Patients will complete the following 3 visit types prior to randomization: the informed consent form (ICF) will be obtained at the Visit 1 (Screening), and all inclusion/exclusion criteria will be assessed except for the NIS and PND score criteria; see Section 4.1); the NIS and PND score inclusion criteria will be assessed at Visit 2 (Baseline first assessment); other baseline assessments will be completed at Visit 3 or at Day 1 prior to first dose. Visits 1, 2 and 3 may each occur over multiple days.

6.1.1. Retesting

If screening laboratory abnormalities, in the Investigator's judgement, are felt likely to be transient, then the laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility and randomized within the allowed Screening period. Qualifying LFTs (AST, ALT and bilirubin) are an exception to this rule and may not be repeated.

6.1.2. Rescreening

For patients who do not meet LFT or NIS eligibility criteria, rescreening patients once may be permitted with consultation of the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment.

6.1.3. Demographic and Medical History/Disease History

Medical history will be collected during screening Visit 1 (including any cardiac disorders, any eye disorders or previous ophthalmology test results, and prior medications). Documented technetium scintigraphy and/or tissue biopsy testing for amyloidosis performed prior to study enrollment should be collected and recorded as part of medical history. Information on prior medications, hospitalization, and procedures through 1 year prior to first dose should be collected and recorded.

At screening Visit 2 and Visit 3, only additional medical history changes since Visit 1 will be collected.

Also, technetium scintigraphy scans and/or tissue biopsy testing for amyloidosis performed as part of clinical care during the study should be collected and recorded as part of concomitant procedure information.

6.2. Efficacy Assessments

6.2.1. Neurologic Impairment Assessments

6.2.1.1. Modified Neurological Impairment Score +7 (mNIS+7)

The mNIS+7 assessment tool is a 304-point composite measure of neurologic impairment which includes the following measures and components (Suanprasert, Berk et al. 2014):

- Physical exam of lower limbs, upper limbs and cranial nerves to assess motor strength/weakness and determine the following component scores:
  - NIS-weakness (NIS-W)
  - NIS-reflexes (NIS-R)
- Electrophysiologic measures of small and large nerve fiber function to determine the Σ5 NCS component score that includes assessment of the ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, peroneal CMAP
- Sensory testing to determine the quantitative sensory testing (QST) score included assessing touch pressure by body surface area (QST-BSATP) and heat pain by body surface area (QST-BSAHP). A Computer Aided Sensory Evaluator (CASE) IV device will be used for this assessment.
- Postural blood pressure is measured to assess autonomic function. Postural blood pressure is measured sitting down and standing up. Points are assigned based on the change in blood pressure with standing.

A summary of the scoring of the components of the mNIS+7 is provided in Section 10.1.

6.2.1.2. Neurologic Impairment Score (NIS)

The NIS assessment is a 244-point composite measure of neurologic impairment which includes a physical exam of lower limbs, upper limbs and cranial nerves to assess motor strength/weakness and determine the following component scores:

- NIS-W
- NIS-R
- NIS-sensation (NIS-S)

6.2.1.3. Personnel and Procedures to Ensure Quality and Consistency of NIS and mNIS+7 Scoring

The NIS and mNIS+7 will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The NIS-W and NIS-R assessments obtained for NIS calculation do not need to be repeated for the mNIS+7 calculation.

As per the Schedule of Assessments, 2 independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have these assessments performed by the same assessor.

NIS and QST assessments will be performed by certified staff trained on the use of the CASE IV device. NCS studies will be performed by trained staff.

Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

All site staff performing the mNIS+7 will be trained and certified by the peripheral neuropathy laboratory at the [redacted], USA. The peripheral neuropathy laboratory at the [redacted] also serves as the central laboratory that will assess the mNIS+7 score. All data will be transmitted to the [redacted] where qualified personnel will assess the quality and acceptability of all test scores. The peripheral neuropathy laboratory at the [redacted] can request a site to repeat testing of mNIS+7 components per the [redacted] Standard Operating Procedures (SOP) if the quality was not acceptable at any time point.

Data acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

6.2.2. Heart Rate Response to Deep Breathing (HRdb)

The HRdb test evaluates small nerve fiber autonomic function by the cardio-vagal response. This assessment will be performed by a certified trained staff at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The average heart rate difference while taking eight deep breaths will be measured using a CASE IV device.

As per the Schedule of Assessments, 2 independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have this assessment performed by the same assessor.

6.2.3. Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life) (Vinik, Hayes et al. 2005; Vinik, Vinik et al. 2014).

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3).

6.2.4. Ten-meter Walk Test (10-MWT)

The time it takes for a patient to walk 10 meters (gait speed) will be assessed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The 10-MWT will be performed and recorded following procedures outlined in the Study Reference Manual. The test must be completed without assistance from another person; ambulatory aids such as canes and walkers are permitted.

As per the Schedule of Assessments, 2 independent assessments are to be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have this assessment performed by the same assessor.

6.2.5. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI; calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The site will not perform the calculation for mBMI.

6.2.6. Rasch-built Overall Disability Scale (R-ODS)

An assessment of the disability each patient experiences will be assessed through the R-ODS questionnaire at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

6.2.7. Deaths and Hospitalizations

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of adverse events (AEs) monitoring (see Section 6.5.7) according to the Schedule of Assessments (Table 1 to Table 3).

Reason for deaths and hospitalizations will be adjudicated by an Independent Clinical Adjudication Committee (see Section 3.8).

6.2.8. European Quality of Life-5 Dimensions 5-Levels (EQ-5D-5L) and EQ-Visual Analog Scale (EQ-VAS)

The EQ-5D index score is based on the response to questions evaluating 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Each dimension scored is based on 5 possible levels where level 1 reflects the best possible score for that dimension. As an example, the 5 levels for the dimension of self-care include: level 1: no problems with washing or dressing self, level 2: slight problems, level 3: moderate problems, level 4: severe problems, level 5: unable. The EQ-5D index score is derived based on scores from all 5 dimensions; score range is from 0 (worst QoL) to 1 (best QoL).

The EQ-VAS is a single question evaluating the patient's own global impression of their overall health and is evaluated on a scale of 0 (worst possible health) to 100 (best possible health).

The EQ-5D-5L and EQ-VAS questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3).

6.2.9. PND Score and FAP Stage

Ambulation and changes in disease stage will be evaluated through physician assessment of PND score and FAP stage (Coutinho, DeSilva et al. 1980; Yamamoto, Wilczek et al. 2007).

PND and FAP will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3).

PND scoring and FAP stages are described in Section 10.2.

6.2.10. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed through echocardiogram, as well as measurement of serum levels of the cardiac biomarkers NT-proBNP and troponin T and troponin I. The impact of heart failure on quality of life will also be assessed as described below.

Certified technicians will be required to administer cardiac imaging assessments as specified in the Study Reference Manual.

6.2.10.1. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

6.2.10.2. Cardiac Biomarkers

Cardiac biomarkers, including NT-proBNP, troponin T and troponin I, will be used to assess cardiac stress and heart failure severity. These biomarkers have also been shown to be prognostic of outcomes in heart failure including ATTR amyloidosis (Damy, Jaccard et al. 2016; Merlini, Lousada et al. 2016; Kristen, Maurer et al. 2017). Blood samples will be drawn to measure levels of NT-proBNP, troponin T and troponin I at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3).

At Screening Visit 1, only NT-proBNP will be assessed for eligibility purposes. Baseline cardiac biomarkers (NT-proBNP, troponin T, and troponin I) will be assessed at Screening Visit 3.

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

6.2.10.3. Technetium Scintigraphy Imaging

At select sites, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 to Table 3), as an exploratory imaging parameter to assess cardiac amyloid involvement. Based on local practice standards, either ^{99}Tc-Pyrophosphate (^{99}Tc-PYP), ^{99}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99}Tc-DPD) or ^{99}Tc-hydroxymethylene diphosphonate (^{99}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

At the select sites where technetium scintigraphy is being performed, patients may be exempt from baseline technetium scintigraphy assessment if a technetium scintigraphy has been performed prior to study entry as part of the patient clinical care within 6 months prior to the baseline assessment. In such cases, where possible, the historical technetium scintigraphy exam performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation.

6.2.10.4. New York Heart Association (NYHA) Class

NYHA class is a clinical assessment of symptoms resulting from heart failure and is assessed according to the table in Section 10.3. NYHA class will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The score collected at Screening will be used to determine eligibility and will also be collected on a regular basis during the study.

6.2.11. Karnofsky Performance Status (KPS)

The Karnofsky Performance Status (KPS) assessed according to Section 10.4 will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The score collected at Screening will be used to determine eligibility.

6.3. Pharmacodynamic Assessments

In this study serum TTR and vitamin A levels will be collected as measurements of PD effect. These measurements will be collected and analyzed centrally as specified in the Study Laboratory Manual.

Blood samples will be collected prior to dosing for the assessment of TTR and vitamin A levels according to the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). TTR levels will be determined by a validated enzyme-linked immunoassay (ELISA) assay.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma ALN-TTRSC02 and patisiran-LNP PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples for PK analysis at the timepoints specified in the Schedule of Assessments (Table 4 for ALN-TTRSC02 and Table 5 for patisiran-LNP).

Plasma concentration of ALN-TTRSC02 and patisiran-LNP will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Study Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication and measurements of vital signs, weight and height, physical examination, ECG findings and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by the Sponsor's Medical Monitors and Medical Monitors at the designated contract research organization in addition an independent DMC as described in Section 3.7.

During the study, where applicable country and local regulations and infrastructure allow, assessments that may be conducted by a qualified home healthcare professional include but are not limited to: blood draws, vital signs, physical exam, collection of information regarding hospitalizations, urgent care visits, procedures and concomitant medications. Wherever possible,

AE collection associated with visits outside of the clinic will be collected by a phone call from qualified site staff. Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

6.5.1. Vital Signs

Vital signs will be measured as specified at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3), and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated or supine position, after the patient has rested comfortably for 10 minutes. Blood pressure should be taken using the same arm during a single visit. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice (as applicable).

Vital signs results will be recorded in the eCRF.

6.5.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected at the timepoints specified in in the Schedule of Assessments (Table 1 to Table 3) and will be recorded in the eCRF.

For patients on the patisiran-LNP arm, weight must be collected prior to each dose.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1 to Table 3); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

A 12-lead ECG reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia corrected QT interval (QTcF) will be obtained locally as specified in the Schedule of Assessments (Table 1 to Table 3). Triplicate readings should be performed at Baseline and thereafter single readings can be performed. If the ECG machine does not calculate

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

If the investigator performs an ECG over-read per standard of care, over-reads should be conducted on each individual ECG performed.

Patients should be supine for at least 5 minutes before each ECG is obtained.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since baseline and to determine the clinical significance of the results. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

ECG recordings will be archived according to the Study Reference Manual.

6.5.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia–Suicide Severity Rating Scale (C-SSRS) will be used to assess patient's mental status as it relates to suicidal ideation and behavior. This questionnaire will be administered to the patient by trained and certified study personnel. The C-SSRS will be performed as specified in the Schedule of Assessments (Table 1 to Table 3).

6.5.6. Clinical Laboratory Assessments

Clinical laboratory assessments are listed in Table 7 will be collected as specified in the Schedule of Assessments (Table 1 to Table 3) and should be evaluated by a central laboratory. Clinical laboratory assessments may be collected at the clinical study center or outside the clinic (eg, home) by a trained healthcare professional.

For the ALN-TTRSC02 arm, LFTs must be obtained within 28 days and reviewed by the investigator prior to each dose of ALN-TTRSC02. LFTs can be analyzed locally, but if a local assessment is drawn, a sample must also be drawn for analysis at the central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.3.

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 7 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions.

For the patisiran-LNP arm, LFTs should be performed according to patisiran-LNP visit windows and do not need to be available prior to dosing.

For any other 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, or as per the Medical Monitor or DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 7: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the MDRD formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
B12 vitamin (at Screening only)	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Immunogenicity (see Section 6.5.6.1)	
Antidrug Antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.6.2)	
β-human chorionic gonadotropin Follicle stimulating hormone (FSH) (Only if applicable, to confirm postmenopausal status prior to dosing)	
Hepatic Tests (only at Screening)	

Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid MDRD=modification of diet in renal disease; WOCBP=women of child bearing potential.

6.5.6.1. Immunogenicity

Blood samples for anti-drug antibody (ADA) testing will be collected at the timepoints specified in Table 1 to Table 3. On dosing days, ADA sample collection is within 1 hour before dosing.

ADA will be assessed using a validated ELISA method. For the patisiran-LNP arm, ADA defined as serum immunoglobulin (Ig) G (IgG)/IgM antibodies specific to the PEG_{2000}-C-DMG component will be assessed.

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

6.5.6.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in Table 1 to Table 3.

A serum pregnancy test will be performed at Screening and urine or serum pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1 to Table 3) and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. More frequent pregnancy testing can be conducted according to country-specific regulations. In Argentina and Brazil, pregnancy testing should be performed prior to each dose.

Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.5.7.7 for follow-up instructions).

Follicle-stimulating hormone testing may be performed to confirm suspected post-menopausal status.

6.5.6.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.3. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 8 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 7, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring and dose modification will also be performed as outlined in Section 5.2.3.

Table 8: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBs Ag, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA= soluble liver antigen
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.7. Adverse Events

6.5.7.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject

administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

A serious adverse event (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 anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse)

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN)
- Severe or serious injection site reactions (ISRs), ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), recurrent ISRs that are increasing in severity, or ISRs that lead to temporary dose interruption or permanent discontinuation of ALN-TTRSC02

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR

For information on recording and reporting of AEs of clinical interest, see Section 6.5.7.2 and Section 6.5.7.3, respectively.

Adverse Event Severity

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

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

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).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, 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.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured

as medical history (see Section 6.1.3), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

For patients who discontinue study drug early and remain in the study, all AEs will be collected for 90 days after the last dose, thereafter, SAEs and AEs of clinical interest (see definition in Section 6.5.7.1) will be collected for the remainder of their participation in the study.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.7.1), the Sponsor or its designee should complete the supplemental AEs of Clinical Interest eCRF. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc.).

If patients develop ocular symptoms suggestive of vitamin A deficiency, for example reduced night vision or night blindness, the Investigator should consult with the Medical Monitor to determine if an ophthalmological assessment is needed. Any information collected during an ophthalmological assessment should be recorded in the eCRF and reports or images of ophthalmological assessments should be collected as well.

6.5.7.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.7.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.5.7.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.7.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. SAEs must be reported using the contact information provided in the Study Reference Manual.

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

6.5.7.5. Sponsor Safety Reporting to Regulatory Authorities

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

6.5.7.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee 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, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug.

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 results in a 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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hATTR amyloidosis, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/EC) approval, and patient consent (and assent, where applicable), samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-TTRSC02 and patisiran-LNP.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 through Table 5). Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

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

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

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

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

6.7. Pharmacoeconomic Assessments

6.7.1. Patient and Caregiver Impact Survey

To complement medical records, information about how hATTR amyloidosis impacts the lives of patients and their caregivers will be collected at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The Patient and Caregiver Impact Survey includes questions related to how hATTR amyloidosis affects patients, including their symptoms at the time of diagnosis, utilization of various healthcare providers, employment status, and need for government compensation/assistance. Questions will also be asked about how hATTR amyloidosis impacts the employment status of the patient's caregiver and patients' need for both informal and professional caregivers.

6.7.2. Hospitalization, Urgent Healthcare Visits, Surgeries, and Procedures

Hospitalization, urgent healthcare visits, surgeries, and procedure information will be collected on a separate eCRF for pharmacoeconomic evaluations, as specified in the Schedule of Assessments (Table 1 to Table 3).

Prior hospitalization, urgent healthcare visits, surgeries, and procedure information through 12 months prior to first dose should be collected at Screening.

6.7.3. Patient Experience Survey

The Patient Experience Survey will be administered to understand patients' level of satisfaction with their current hATTR amyloidosis therapy and their level of comfort using this therapy. This survey will be administered at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3).

6.7.4. Patient Preference Survey

This Patient Preference Survey will only be administered to patients who were randomized to the patisiran-LNP arm and switched to treatment with ALN-TTRSC02 in the Treatment Extension Period. The survey will be administered to understand patients' preferred method of administration and the primary reasons for their preference. This survey will be administered at the timepoints specified in the Schedule of Assessments (Table 3).

7. STATISTICS

The principal features of the planned analysis are presented in this section. A separate Statistical Analysis Plan (SAP) will be finalized prior to first patient dosed. The SAP will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

Approximately 160 patients will be enrolled in this study, with a 3:1 randomization ratio to either ALN-TTRSC02 or patisiran-LNP.

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of ALN-TTRSC02 in this patient population. For the co-primary efficacy endpoints mNIS+7 and Norfolk QoL-DN total scores, the ALN-TTRSC02 arm in the Phase 3 study will be compared to the placebo arm from the APOLLO study. For the mNIS+7 change from baseline at 9 months, the observed mean (±standard deviation [SD]) was 15 ± 17 points for the placebo arm from the APOLLO study. Assuming a mean change of 0 points for the ALN-TTRSC02 arm, there is >90% power to establish the superiority over placebo using a 2-sided t-test with a significance level of 0.05. For the Norfolk-QoL DN total score change from baseline at 9 months, the observed mean (±SD) was 11.5 ± 19.2 points for the placebo arm from the APOLLO study. Assuming a mean change of -4 points for the ALN-TTRSC02 arm, there is >90% power to establish the superiority over placebo using a 2-sided t-test with a significance level of 0.05.

For safety, a sample size of >100 patients on ALN-TTRSC02 can provide reasonable assurance that the true cumulative one-year incidence of adverse drug events (ADE) is no greater than 3% when no ADE is observed.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L.

7.2. Statistical Methodology

7.2.1. Populations to be Analyzed

The population analysis sets are defined as follows:

- Modified ITT (mITT) population: All randomized patients who received any amount of study drug. Patients will be grouped by their randomized treatment group.
- Safety Population: All randomized patients who received any amount of study drug, grouped according to the treatment actually received.
- PK Population: All randomized patients who received any amount of study drug and have at least 1 post dose blood sample for PK parameters and have evaluable PK data.
- Patients with cardiac involvement: All patients in the mITT population who had pre-existing evidence of cardiac amyloid involvement. Specific details will be provided in the SAP.

The primary population for efficacy analysis will be the mITT population. Safety analysis will be conducted in the safety population. PK analysis will be conducted in the PK population. Selected endpoints will be analyzed in the cardiac subpopulation.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

For efficacy assessments, if the scheduled visits (eg, 9-month) are not performed, the unscheduled and/or discontinuation visits performed within a 3-month window will be grouped with the scheduled assessments.

Sensitivity analyses for the co-primary endpoints, including different methods for handling of the missing data, will be conducted to assess the robustness of the primary analysis results.

More details of missing data handling will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively.

7.2.5. Efficacy Analyses

This Phase 3 study will use the placebo arm of the APOLLO study as an external control. Patient-level data from this study will be compared with patient-level data from APOLLO for efficacy analyses. For the co-primary and secondary clinical efficacy endpoints, the ALN-TTRSC02 arm in this study will be compared to the placebo arm from the APOLLO study. For the secondary endpoint of TTR percent reduction, the ALN-TTRSC02 arm in this study will be compared to the patisiran-LNP arm in this study. The treatment comparison will be conducted at Month 9 and/or Month 18. The efficacy endpoints beyond 18 months will be summarized descriptively.

The patisiran-LNP arm in this study will mainly serve as a reference arm. For the clinical efficacy endpoints at Month 9 and Month 18, the patisiran-LNP arm will be summarized descriptively and the treatment difference between ALN-TTRSC02 and patisiran-LNP arm in this study will not be tested. In addition, the efficacy assessments over time for patients before and after the switch to ALN-TTRSC02 will be summarized.

7.2.5.1. Co-Primary Endpoint

The co-primary endpoints are change from baseline at Month 9 for mNIS+7 and Norfolk QoL-DN total scores. The co-primary endpoints will be each be tested at a significant level of 0.05 and both must be significant to declare a positive trial. The primary comparison will be conducted at Month 9 and additional analyses will be performed at Month 18.

The co-primary endpoint mNIS+7 will compare change in mNIS+7 from baseline at Month 9 between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least-square (LS) means using an analysis of covariance (ANCOVA) model with baseline mNIS+7 score as a covariate and factors including treatment group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M) and age of disease onset (<50 vs ≥50 years old).

The other co-primary endpoint Norfolk QoL-DN total score will compare change at Month 9 between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least-square (LS) means using an analysis of covariance (ANCOVA) model with baseline score as a covariate and factors including treatment

group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M), age of disease onset (<50 vs ≥50 years old), and baseline NIS score (<50 vs ≥50).

Co-primary endpoint data that are missing will be multiply imputed separately for each treatment group using a regression procedure based on baseline covariates. The details will be specified in the SAP.

The co-primary endpoints for the patisiran-LNP group in this study will be summarized descriptively.

7.2.5.2. Secondary Endpoints

For the secondary clinical efficacy endpoints, the treatment comparison will be made between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. For the TTR percent reduction endpoint, the ALN-TTRSC02 group will be compared with the patisiran-LNP group in this study. To control the overall type I error, the secondary endpoints will be tested in the following hierarchical order:

- 10-MWT gait speed change from baseline at Month 9
- mBMI (BMI [kg/m^2] multiplied by serum albumin level [g/L]) change from baseline at Month 9
- R-ODS change from baseline at Month 9
- TTR percent reduction through 9 months
- All-cause hospitalization and death events over 18 months (overall population)
- All-cause hospitalization and death events over 18 months (patients with cardiac involvement)

For 10-MWT gait speed, mBMI, and R-ODS, the analysis will be based on an ANCOVA model similar to the model described for the analysis of Norfolk QoL-DN while adjusting for baseline value of the endpoint being modeled. In the APOLLO study, mBMI was not assessed at Month 9. The average values of Day 189 and Day 357 will be derived as Month 9. The primary comparison will be conducted at Month 9 and additional analyses will be performed at Month 18.

The TTR percent reduction through Month 9 will be derived as the average trough TTR percent reduction from Month 6 to 9 which is the steady state period for both ALN-TTRSC02 and patisiran-LNP. A Hodges-Lehmann method stratified by previous TTR stabilizer use (yes vs no) will be used to estimate the 95% CI for the median difference between the ALN-TTRSC02 and patisiran-LNP groups in this study. Non-inferiority will be declared if the lower limit of the 95% CI for the treatment difference is greater than –10%. A sensitivity analysis will be conducted to compare the TTR percent reduction between the ALN-TTRSC02 group from this study and the pooled patisiran-LNP groups from this Phase 3 study and the APOLLO study.

The composite endpoint of all-cause hospitalization and death events over 18 months will be analyzed using recurrent event method Andersen-Gill model with treatment group (ALN-TTRSC02 vs placebo) as an independent variable. The endpoint will be analyzed for both the overall population and in patients with cardiac involvement.

7.2.5.3. Exploratory Endpoints

Analysis of exploratory efficacy endpoints will be detailed in the SAP.

7.2.6. Pharmacodynamic Analysis

Summary tables and graphical displays of observed values, changes and percentage changes from baseline in PD biomarkers (TTR and vitamin A) will be presented.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted for ALN-TTRSC02 and patisiran-LNP using non-compartmental method. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

Population pharmacokinetic analysis will be performed to describe the plasma pharmacokinetics using Phoenix NLME (Version 1.1 or later) or a similar software, such as NONMEM. The impact of relevant covariates, such as, weight, gender, race, age, renal function, and hepatic function on plasma PK will be evaluated. Summary tables and figures and inferential statistics will be generated.

7.2.8. Safety Analyses

A summary of study drug exposure, including the durations of exposure and the proportions of patients with dose modifications will be produced.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System (ATC) and Preferred Term.

Adverse events will be summarized by MedDRA system organ class and preferred term. The number and percentage of patients experiencing AEs after the first dose of the study drug will be summarized. Separate tabulations will be produced for treatment-related AEs, 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, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time

Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

Incidence of ADA and titers will be summarized descriptively.

7.2.10. Other Analyses

For all the efficacy endpoints defined for Month 9, additional analyses will also be conducted at Month 18.

7.2.11. Interim Analysis

No interim analysis is planned.

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP 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.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF (assent form, if applicable), must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

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

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

The Investigator will submit reports of SAEs as outlined in Section 6.5.7. In addition, the Investigator agrees to submit progress reports to the 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.

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

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

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

8.1.3. Serious Breach of Protocol

Investigators must notify the medical monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. 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 Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

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.

To comply with local and/or regional regulations, this clinical study may be registered and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed 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.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The monitor will visit the Investigator and clinical study center periodically and will 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.

The monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published, or following the period of 18 months after completion of the study at all

centers. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

. "Mutations in Hereditary Amyloidosis - Mutations in Transthyretin Gene(TTR)." from http://amyloidosismutations.com/mut-attr.php.

Adams, D., T. Coelho, et al. (2015). "Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study." Neurology **85**(8): 675-682.

Adams, D., A. Gonzalez-Duarte, et al. (2018). "Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis." N Engl J Med **379**(1): 11-21.

Adams, D., O. B. Suhr, et al. (2017). "Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy." BMC Neurol **17**(1): 181.

Ando, Y., T. Coelho, et al. (2013). "Guideline of transthyretin-related hereditary amyloidosis for clinicians." Orphanet J of Rare Dis **8**(31).

Ashwell, G. and A. G. Morell (1974). "The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins." Adv Enzymol Relat Areas Mol Biol **41**(0): 99-128.

Baenziger, J. U. and D. Fiete (1980). "Galactose and N-acetylgalactosamine-specific endocytosis of glycopeptides by isolated rat hepatocytes." Cell **22**(2 Pt 2): 611-620.

Barroso, F. A., D. P. Judge, et al. (2017). "Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years." Amyloid **24**(3): 194-204.

Benson, M. and J. Kincaid (2007). "The molecular biology and clinical features of amyloid neuropathy." Muscle Nerve **36**(4): 411-423.

Berk, J., O. Suhr, et al. (2013). "Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial." JAMA **310**(24): 2658-2667.

Bumcrot, D., M. Manoharan, et al. (2006). "RNAi therapeutics: a potential new class of pharmaceutical drugs." Nat Chem Biol **2**(12): 711-719.

Carvalho, A., A. Rocha, et al. (2015). "Liver transplantation in transthyretin amyloidosis: issues and challenges." Liver Transpl **21**(3): 282-292.

Carvalho, M., M. Alves, et al. (1992). "Octreotide--a new treatment for diarrhoea in familial amyloidotic polyneuropathy." J Neurol Neurosurg Psychiatry **55**(9): 860-861.

Coelho, T., L. F. Maia, et al. (2012). "Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial." Neurology **79**(8): 785-792.

Connors, L., T. Yamashita, et al. (2004). "A rare transthyretin mutation (Asp18Glu) associated with cardiomyopathy." Amyloid **11**(1): 61-66.

Connors, L. H., A. Lim, et al. (2003). "Tabulation of human transthyretin (TTR) variants, 2003." Amyloid **10**(3): 160-184.

Coutinho, P., A. DeSilva, et al. (1980). Forty years of experience with type I amyloid neuropathy: review of 483 cases. Amyloid and Amyloidosis: Excerpta Medica. G. Glenner, P. Pinho, E. Costa and A. Falcao de Frietas. Amsterdam**:** 88-98.

Damy, T., A. Jaccard, et al. (2016). "Identification of prognostic markers in transthyretin and AL cardiac amyloidosis." Amyloid **23**(3): 194-202.

Dyck PJ, K. J., Dyck PJ et al (2017). "Assessing mNIS+7Ionis and international neurologists' proficiency in a familial amyloidotic polyneuropathy trial." Muscle Nerve **Jan 7. doi: 10.1002/mus.25563. [Epub ahead of print]**.

Ericzon, B. G., H. E. Wilczek, et al. (2015). "Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?" Transplantation **99**(9): 1847-1854.

Geffen, I. and M. Spiess (1992). "Asialoglycoprotein receptor." Int Rev Cytol **137B**: 181-219.

Hou, X., M. I. Aguilar, et al. (2007). "Transthyretin and familial amyloidotic polyneuropathy. Recent progress in understanding the molecular mechanism of neurodegeneration." FEBS J **274**(7): 1637-1650.

Jacobson, D., R. Pastore, et al. (1997). "Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans." N Engl J Med **336**(7): 466-473.

Kristen, A. V., M. S. Maurer, et al. (2017). "Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS)." PLoS One **12**(4): e0173086.

Liz, M. A., F. M. Mar, et al. (2010). "Aboard transthyretin: From transport to cleavage." IUBMB Life **62**(6): 429-435.

Maurer, M. S., P. Elliott, et al. (2017). "Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial)." Circ Heart Fail **10**(6).

Merlini, G., I. Lousada, et al. (2016). "Rationale, application and clinical qualification for NT-proBNP as a surrogate end point in pivotal clinical trials in patients with AL amyloidosis." Leukemia **30**(10): 1979-1986.

Nair, J. K., J. L. Willoughby, et al. (2014). "Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing." J Am Chem Soc **136**(49): 16958-16961.

Okamoto, S., J. Wixner, et al. (2009). "Liver transplantation for familial amyloidotic polyneuropathy: impact on Swedish patients' survival." Liver Transpl **15**: 1229-1235.

Parman, Y., D. Adams, et al. (2016). "Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP." Curr Opin Neurol **29 Suppl 1**: S3-S13.

Plante-Bordeneuve, V. and G. Said (2011). "Familial amyloid polyneuropathy." Lancet Neurol **10**(12): 1086-1097.

Ruberg, F. L. and J. L. Berk (2012). "Transthyretin (TTR) cardiac amyloidosis." Circulation **126**(10): 1286-1300.

Schwartz, A. L., D. Rup, et al. (1980). "Difficulties in the quantification of asialoglycoprotein receptors on the rat hepatocyte." J Biol Chem **255**(19): 9033-9036.

Soares, M. L., T. Coelho, et al. (2005). "Susceptibility and modifier genes in Portuguese transthyretin V30M amyloid polyneuropathy: complexity in a single-gene disease." Hum Mol Genet **14**(4): 543-553.

Solomon, S. A. D., Kristen A et al (2018). "Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients with Hereditary Transthyretin-Mediated Amyloidosis: An Analysis of the APOLLO Study." Circulation **10.1161/CIRCULATIONAHA.118.035831**.

Suanprasert, N., J. L. Berk, et al. (2014). "Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials." J Neurol Sci **344**(1-2): 121-128.

Swiecicki, P. L., D. B. Zhen, et al. (2015). "Hereditary ATTR amyloidosis: a single-institution experience with 266 patients." Amyloid **22**(2): 123-131.

Vinik, E. J., R. P. Hayes, et al. (2005). "The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy." Diabetes Technol Ther **7**(3): 497-508.

Vinik, E. J., A. I. Vinik, et al. (2014). "Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy." J Peripher Nerv Syst **19**(2): 104-114.

Wang et al. (2017). "Safety and Efficacy of Inotersen in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (NEURO-TTR)." ANA abstract.

Yamamoto, S., H. Wilczek, et al. (2007). "Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years." Am J Transplant **7**(11): 2597-2604.

Yazaki, M., T. Tokuda, et al. (2000). "Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin." Biochem Biophys Res Commun **274**(3): 702-706.

Ziegler, D., P. A. Low, et al. (2011). "Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial." Diabetes Care **34**(9): 2054-2060.

10. APPENDICES

10.1. mNIS+7 Components and Scoring

Refer to the Study Reference Manual for additional details.

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

10.2. PND Scores and FAP Stages

Polyneuropathy Disability (PND) Scores

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

Familial Amyloidotic Polyneuropathy (FAP) Stages

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

10.3. New York Heart Association (NYHA) Class

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.

10.4. Karnofsky Performance Status (KPS) 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

CLINICAL STUDY PROTOCOL
ALN-TTRSC02-002
DATED: 19 FEBRUARY 2021

Protocol Title:	HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)
Short Title:	HELIOS-A: A Phase 3 Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with hATTR Amyloidosis
Study Drug:	ALN-TTRSC02 (vutrisiran)
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Date:	Original protocol: 11 October 2018 Amendment 1: 10 October 2019 Amendment 2: 06 May 2020 Amendment 3: 17 July 2020 Amendment 4: 19 February 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

23 FEB 2021
Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-TTRSC02-002 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

Short Title

HELIOS-A: A Phase 3 Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with hATTR Amyloidosis

Study Drug

ALN-TTRSC02

Phase

3

Study Centers

The study will be conducted at up to 80 clinical study centers worldwide.

Objectives and Endpoints

The primary and most secondary and exploratory efficacy endpoints are in comparison to the placebo arm of the Phase 3 pivotal patisiran study (ALN-TTR02-004, also referred to as the APOLLO study) as specified in the statistical analysis section of the HELIOS-A protocol.

Objectives	Endpoints
Primary	
• To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment	• Change from baseline in the Modified Neurologic Impairment Score +7 (mNIS+7) compared to the placebo arm of the APOLLO study at Month 9
Secondary	
• To determine the efficacy of ALN-TTRSC02 on quality of life, gait speed, neurologic impairment, nutritional status, and disability • To demonstrate the noninferiority of ALN-TTRSC02 compared to patisiran with respect to serum TTR levels	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score at Month 9; – Timed 10-meter walk test (10-MWT) at Month 9; – mNIS+7 at Month 18; – Norfolk QoL-DN total score at Month 18; – 10-MWT at Month 18; – Modified body mass index (mBMI) at Month 18; – Rasch-built Overall Disability Scale (R-ODS) at Month 18

Objectives	Endpoints
	• Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran arm through Month 18
Exploratory	
• To determine the effect of ALN-TTRSC02 on: – Disability and nutritional status; – Manifestations of cardiac amyloid involvement; – Other assessment of neurologic impairment; – Other assessments of quality of life; – Disease stage; – Performance of daily activities • To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and patisiran on serum TTR and vitamin A levels • To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran • To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study at Month 9: – R-ODS; – mBMI • Change from baseline over time: – N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters, Troponin I and T levels, New York Heart Association (NYHA) class; – Neurologic Impairment Score (NIS); – EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQoL-Visual Analog Scale (EQ-VAS); – Familial Amyloidotic Polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score; – Karnofsky Performance Status (KPS) • Change from baseline in technetium scintigraphy cardiac parameters at Month 18 • Percent reduction in serum TTR and vitamin A levels over time • PK profile of ALN-TTRSC02 and patisiran • Incidence and titers of ADA to ALN-TTRSC02 and patisiran
Safety	
• To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

Study Design

This is a global Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran, a reference comparator. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, and an 18-month Randomized Treatment Extension Period (RTE) as of Amendment 4, in lieu of the 18-month Treatment Extension Period (hereafter referred to as the Legacy Treatment Extension Period). A Follow-up Period of up to 1 year will occur after the last dose of study drug.

18-Month Treatment Period

After the Screening period at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as an SC injection q3M or patisiran administered as an IV infusion q3w. During the 18-month Treatment Period, patients will undergo assessments for efficacy and/or safety (as outlined in the Schedule of Assessments), with key efficacy assessments being performed prior to first dose, at Month 9 (primary efficacy analysis timepoint), and at Month 18; samples for TTR assessment will be collected more frequently throughout the 18-month Treatment Period.

All efficacy visits must be conducted at the clinic (Month 9, Month 18, and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 or Month 18 efficacy assessments as applicable. After consultation with the Medical Monitor, the Month 9 or Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Month 15 or Month 24, respectively).

The placebo arm of the APOLLO study will be used as an external control for the primary, most secondary, and most exploratory efficacy analysis. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

Randomized Treatment Extension (RTE) Period

[redacted]

[redacted]

Follow-up Period

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

Number of Planned Patients

Approximately 160 patients are planned for enrollment in this study.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L at baseline.

Diagnosis and Main Eligibility Criteria

This study will include adults age 18 (or age of legal consent, whichever is older) to 85 years of age, with a documented TTR mutation, and a confirmed diagnosis of symptomatic hATTR amyloidosis with a NIS of 5 to 130 (inclusive), a PND score of ≤3b, and KPS ≥60%.

Study Drug, Dose, and Mode of Administration

ALN-TTRSC02 drug product is a subcutaneously (SC) administered N-acetyl galactosamine ligand (GalNAc)-conjugated small interfering RNA (siRNA) targeting liver-expressed transthyretin (TTR) messenger RNA (mRNA).

ALN-TTRSC02 will be administered as a 25 mg SC injection q3M (12 weeks).

[redacted]

Reference Treatment, Dose, and Mode of Administration

Patisiran drug product is an intravenously (IV) administered siRNA targeting liver-expressed TTR mRNA formulated with lipid excipients (DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG) in isotonic phosphate buffered saline.

Patisiran will be administered as a 0.3 mg/kg IV infusion once every 3 weeks (q3w) ± 3 days. All patients will receive premedication prior to patisiran infusions as described further in the protocol.

Duration of Treatment and Study

The estimated time on study for each patient is a maximum of 5 years, inclusive of 42 days of Screening, and up to 54 months of open-label treatment (including 18 months in the Treatment Period, 0 to 18 months in the Legacy Treatment Extension Period and 18 months in the Randomized Treatment Extension Period), plus a Follow-Up Period up to 1 year.

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

Statistical Methods

A full statistical analysis plan (SAP) will be finalized prior to first patient dosed.

The primary endpoint mNIS+7 will compare change in mNIS+7 from baseline at Month 9 between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least squares (LS) means using an analysis of covariance (ANCOVA) model with baseline mNIS+7 score as a covariate and factors including treatment group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M) and age of disease onset (<50 vs ≥50 years old). The primary endpoint will be tested at a significance level of 0.05 and must be significant to declare a positive trial.

For the key secondary endpoints of change in Norfolk QoL-DN total score and 10-MWT gait speed from baseline at Month 9, the analysis will be based on an ANCOVA model similar to the model described for the analysis of change in mNIS+7 from baseline at Month 9, while adjusting for baseline value of the

endpoint being modeled and including baseline NIS score (<50 vs ≥50) as an additional factor in the model. For these 2 endpoints, data that are missing will be multiply imputed separately for each treatment group using a regression procedure based on baseline covariates.

For change from baseline at Month 18 analyses, the analysis will be based on a mixed-effects model for repeated measures (MMRM), adjusting for a covariate (baseline value for the endpoint being modeled), categorical factors (treatment group, visit [Month 9 vs Month 18], genotype, age of disease onset, baseline NIS score), and an interaction term (treatment group by visit). For mNIS+7, baseline NIS score will not be included in the model.

The primary endpoint for the patisiran group in this study will be summarized descriptively.

The TTR percent reduction through Month 18 will be derived as the average trough TTR percent reduction from Month 6 to 18 which is the steady state period for both ALN-TTRSC02 and patisiran. A Hodges-Lehmann method stratified by previous TTR stabilizer use (yes vs no) will be used to estimate the 95% confidence interval (CI) for the median difference between the ALN-TTRSC02 and patisiran groups in this study. Non-inferiority will be declared if the lower limit of the 95% CI for the treatment difference is greater than –10%. A sensitivity analysis will be conducted to compare the TTR percent reduction between the ALN-TTRSC02 group from this study and the pooled patisiran groups from this Phase 3 study and the APOLLO study.

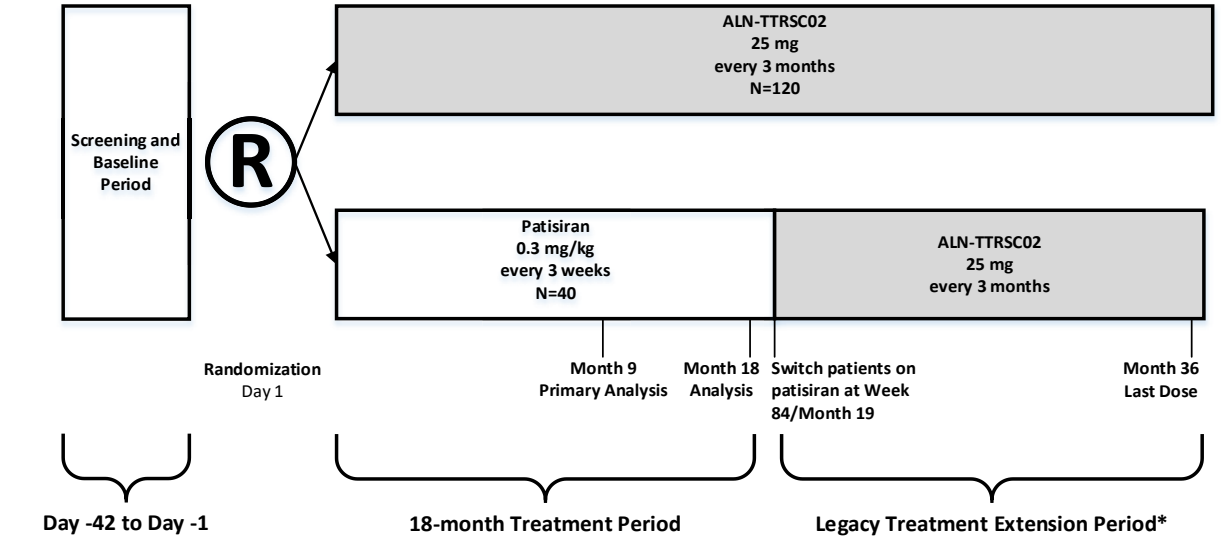
Overall type I error control for secondary endpoints will be achieved by a hierarchical testing procedure.

The analysis of exploratory efficacy endpoints will be described in the SAP.

Safety data will be summarized descriptively.

[redacted]

Figure 1: Study Design



[redacted]

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

		Scre e-ning	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window	**Note**					0	±3D	±3D	±3D	±3D	±3 D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA[a]
Informed Consent	Section 6.1	X																	
Medical Records Release Form (optional)	Section 6.1	X																	
Inclusion/Exclusion	Section 4.1; Section 4.2	X	X																
Demographics and Medical/Disease History	Section 6.1.3	X	X	X															
Physical Exam (PE)	Symptom-directed PE unless specified as Full see Section 6.5.3	X PE Full		X						X				X				X PE Full	
Vital signs; Weight	Section 6.5.1; Section 6.5.2	X	Vital signs only	X	X	Vital signs only	X[b]	X[b]	X[b]	X	X[b]	X[b]	X[b]	X	X[b]	X[b]	X[b]	X	X
Height	Section 6.5.2	X																	
mBMI; NYHA Class; KPS	Section 6.2.5; Section 6.2.11.4 Section 6.2.12	X								mBMI only				mBMI only					X
PND Score	Section 6.2.10		X	X															X
FAP Stage	Section 6.2.10		X – Single assessment at any of these visits																X
Serum Chemistry; Hematology; Urinalysis; Coagulation	Section 6.5.6	X			X					X				X					X

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Scre e-ning	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window						0	±3D	±3D	±3D	±3D	±3 D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA[a]
Hepatitis Tests	Section 6.5.6	X																	
LFT	See below Table 1 notes. Results from both V1 and V2 must meet eligibility criteria. Section 6.5.6; Section 6.5.6.3	X	X		X		X		X	X				X				**X**	
FSH (only to confirm postmenopausal status if applicable)	Section 6.5.6	X																	
Pregnancy Test	At V1 serum pregnancy test; after V1, either urine or serum pregnancy test; Section 6.5.6.2	X			X					X				X				X	
Cardiac Biomarker Samples	Section 6.2.11.2	NT-proBNP only		X						X				X					X
TTR Protein; Vitamin A	Section 6.3			X	X		X	X		X				X				X	X

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

		Scre e-ning	Baseline				Treatment Period												Month 9 Efficacy	
		V1	V2	V3	Pre-dose	Post-dose														
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273	
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39	
±Visit Window	**Note**					0	±3D	±3D	±3D	±3D	±3 D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA[a]	
ADA	On dosing days, collect ADA within 1 hour before dosing; Section 6.5.6.1				X		X			X				X				X		
ALN-TTRSC02 Arm PK Sampling	See Table 5 for detail timepoints				X	X				X				X				X		
Patisiran Arm PK Sampling	See Table 6 for detail timepoints				X	X	X					X						X		
Sample for Exploratory Analysis	Section 6.6			X				X						X				X	X	
Exploratory DNA sample (optional)	Section 6.6			X																
Norfolk QoL-DN; R-ODS	Section 6.2.3; Section 6.2.6		X– single at any of these visits																X	
EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact Survey	Section 6.2.9; Section 6.5.5; Section 6.7.1			X– single at any of these visits															X	
Patient Experience Survey	Section 6.7.3																		X	
NIS; mNIS+7; HRdb	See below Table 1 Notes; and Section 6.2.1; Section 6.2.2		X	X															X	X

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Scre e-ning	Baseline				Treatment Period												Month 9 Efficacy	
		V1	V2	V3	Pre-dose	Post-dose														
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273	
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39	
±Visit Window						0	±3D	±3D	±3D	±3D	±3 D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA[a]	
10-MWT	See below Table 1 Notes; and Section 6.2.4		X – Two assessments performed at any of these visits																X	X
Single (unless indicated) 12-Lead ECG	Section 6.5.4		X-Triplicate performed at any of these visits							X									X	
Echocardiogram	Section 6.2.11.1		X - Single performed at any of these visits																X	
Technetium scintigraphy imaging (select sites only)	Section 6.2.11.3		X - Single performed at any of these visits																	
Randomization	Window: -5D prior to Day 1				X															
ALN-TTRSC02 Study Drug Admin.	Section 5.2.2.1				X					X				X				X		

Table 1: Schedule of Assessments – Screening through Treatment Period Month 9

	Note	Scre e-ning	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window						0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA[a]
Patisiran Arm: Premedication Admin.	Section 5.2.2.2				X		X	X	X	X	X	X	X	X	X	X	X	X	
Patisiran Study Drug Admin.	Section 5.2.2.2				X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital status check	Section 6.2.8	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Review/Record Hospitalization; Urgent care visits; Procedures	Section 6.7.2		X - Collected through Day 1 predose			Continuous Monitoring													
Review/Record AEs, Con. Med.	Section 6.5.7; Section 5.3					Continuous Monitoring													

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Admin.=administration; Con. Med.=concomitant medications; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EQ-5D-5L= EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS=EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; FSH=follicle-stimulating hormone; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NT-proBNP= B-type natriuretic peptide; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN= Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin; V=visits

Table 1 Notes:

- The Screening and Baseline visits (V1, V2 and V3) will be performed on separate days and can each occur over multiple days. V2 (first Baseline NIS, mNIS+7, HRdb assessment) must be performed within 21 days prior to the first dose of study drug (Day 1). V3 (second Baseline NIS, mNIS+7, HRdb assessment) must be conducted within approximately 24 hours after Visit 2 but not more than 7 days after. See Section 6.1 for retesting and re-screening instructions.
- Pre-randomization 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart.
- Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2.1 and Section 5.2.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in the beginning of Section 6.
- LFT for screening: Day 1 predose LFT does not need to be performed if there are available LFT results within 28 days of first dose.
- LFT for after randomization: For the ALN-TTRSC02 cohort, dosing decisions may be made based on LFT results (Table 8) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. LFT monitoring details are provided in Section 5.2.3.
  For the patisiran cohort, LFTs should be performed according to patisiran visit windows and do not need to be available prior to dosing.

- Unless otherwise specified, assessments on dosing days are predose.
- For the Month 9, NIS, mNIS+7, HRdb and 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Components that are shared between the mNIS+7 and NIS will be performed once at each assessment (eg, the weakness component should not be performed more than once on any given day).

[a] In situations in which a Month 9 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 efficacy assessment. After consultation with the Medical Monitor, Month 9 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15).

[b] For the ALN-TTRSC02 cohort, collection of vital signs and weight may be deferred at this timepoint if issues related to the COVID-19 pandemic limit the patient's ability or willingness to access the study site.

Table 2: Schedule of Assessments –Treatment Period from Month 9 through Month 18

		Treatment Period														Month 18 Efficacy[a]
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**
±Visit Window	**Note**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**NA[a]**
Physical Exam (PE)	Symptom-directed PE Section 6.5.3				X				X				X			
Vital signs;	Section 6.5.1;	X[b]	X[b]	X[b]	X	X[b]	X[b]	X[b]	X	X[b]	X[b]	X[b]	X	X[b]	X[b]	X - vitals only
ALN-TTRSC02 Arm: Weight	Section 6.5.2				X				X				X			X
Patisiran Arm: Weight	Section 6.5.2.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class; KPS; PND and FAP; mBMI	Section 6.2.11.4; Section 6.2.12; Section 6.2.10; Section 6.2.5				mBMI only				mBMI only				mBMI only			X
Serum Chemistry; Hematology; Urinalysis; Coagulation	Section 6.5.6				X				X				X			X-Serum chemistry only
LFT	Section 6.5.6; Section 6.5.6.3				X				X				X			
Pregnancy Test	Section 6.5.6.2				X				X				X			X
Cardiac Biomarker Samples	Section 6.2.11.2				X				X				X			X
TTR Protein; Vitamin A	Section 6.3				X				X				X		X	X
ADA	On dosing days, collect ADA within 1 hour before dosing, Section 6.5.6.1				X								X			X

Table 2: Schedule of Assessments –Treatment Period from Month 9 through Month 18

		Treatment Period														Month 18 Efficacy[a]
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**
±Visit Window	**Note**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**NA[a]**
ALN-TTRSC02 Arm PK	See Table 5 for detail timepoints				X				X				X			
Patisiran Arm PK	See Table 6 for detail timepoints	X					X								X	
Samples for Exploratory Analysis	Plasma, serum, urine; Section 6.6				X				X							X
Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact Survey	Section 6.2.3; Section 6.2.6; Section 6.2.9; Section 6.5.5; Section 6.7.1															X
Patient Experience Survey	Section 6.7.3															X
NIS; mNIS+7; HRdb; 10-MWT	See below Table 2 Notes; Section 6.2.1; Section 6.2.2; Section 6.2.4															X X
Single 12-Lead ECG	Section 6.5.4				X											X
Echocardiogram	Section 6.2.11.1															X
Technetium scintigraphy imaging (select sites only)	Section 6.2.11.3															X
ALN-TTRSC02 Study Drug Administration	Section 5.2.2.1				X				X				X			

Table 2: Schedule of Assessments –Treatment Period from Month 9 through Month 18

		Treatment Period														Month 18 Efficacy[a]
Study Day		**D274**	**D295**	**D316**	**D337**	**D358**	**D379**	**D400**	**D421**	**D442**	**D463**	**D484**	**D505**	**D526**	**D547**	**D554-D561**
Study Week		**39**	**42**	**45**	**48**	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**79-80**
±Visit Window	**Note**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**NA[a]**
Patisiran: Premedication Administration	Section 5.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patisiran Study Drug Administration	Section 5.2.2.2	X – Dose after Month 9 efficacy assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status check	Section 6.2.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs; Con. Med.; Hospitalization; Urgent care visits; Procedures	Section 6.5.7; Section 5.3; Section 6.7.2	Continuous Monitoring														

Abbreviations: AE=adverse event; ADA=antidrug antibodies; Con. Med.=concomitant medications; C-SSRS= Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EQ-5D-5L=EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS=EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin

Table 2 Notes:

- Unless otherwise specified, assessments on dosing days are predose.
- For the Month 18 NIS; mNIS+7; HRdb and 10-MWT: Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Components that are shared between the mNIS+7 and NIS will be performed once at each assessment (eg, the weakness component should not be performed more than once on any given day).
- Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2.1 and Section 5.2.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in the beginning of Section 6.
- For the ALN-TTRSC02 cohort, dosing decisions may be made based on LFT results (Table 8) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. LFT monitoring details are provided in Section 5.2.3.
  For the patisiran cohort, LFTs should be performed according to patisiran visit windows and do not need to be available prior to dosing.

[a] In situations in which a Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18 efficacy assessment. After consultation with the Medical Monitor, Month 18 efficacy assessments may be completed within

6 months after the intended time point (ie, up to Study Month 24). [redacted]

[b] For the ALN-TTRSC02 cohort, collection of vital signs may be deferred at this timepoint if issues related to the COVID-19 pandemic limit the patient's ability or willingness to access the study site.

Table 3: Schedule of Assessments: Legacy Treatment Extension Period, Early Drug Discontinuation and Other Visits

		Legacy Treatment Extension Period[a,b,c]		Early Drug Discontinuation Visit		Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18			
		Last Patisiran Dosing Visit (ALN-TTRSC02 cohort exempt)	ALN-TTRSC02 Dosing Visits Every 12 Weeks	4 (+1) Weeks from Last Dose*		Month 9		Month 18	
Study Week	**Note**	**81**	**84, 96, 108, 120, 132, 144, and 156**	**-**		**36-39**		**79-80**	
±Visit Window		**±3D**	**±7D**	**-**		**-**		**-**	
Medical Records Release Form (optional)	Section 8.1.1 Recheck			X					
NYHA class; KPS; PND and FAP; mBMI	Section 6.2.11.4; Section 6.2.12; Section 6.2.10; Section 6.2.5			X		X		X	
Vital signs	Section 6.5.1	X	X						
Physical Examination (PE); Weight	Symptom-directed PE Section 6.5.3; Section 6.5.2	X	X	X		X		X	
NIS; mNIS+7; HRdb	See below Table 3 Notes; Section 6.2.1; Section 6.2.2			X	X	X	X	X	X
10-MWT	Section 6.2.4			X	X				
Questionnaires: Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact Survey	Section 6.2.3; Section 6.2.6; Section 6.2.9; Section 6.5.5; Section 6.7.1			X		X – No C-SSRS		X – No C-SSRS	
Single 12-Lead ECG	Section 6.5.4			X					
Echocardiogram	Section 6.2.11.1			X					
Technetium scintigraphy imaging (select sites only)	Section 6.2.11.3			X					
Serum Chemistry, Hematology, Urinalysis, Coagulation and Liver Function Tests	Section 6.5.6; Section 6.5.6.3	LFT only	X	X		Serum Chemistry and LFTs only		Serum Chemistry and LFTs only	

Table 3: Schedule of Assessments: Legacy Treatment Extension Period, Early Drug Discontinuation and Other Visits

		Legacy Treatment Extension Period[a,b,c]		Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18	
		Last Patisiran Dosing Visit (ALN-TTRSC02 cohort exempt)	ALN-TTRSC02 Dosing Visits Every 12 Weeks	4 (+1) Weeks from Last Dose*	Month 9	Month 18
Study Week	**Note**	**81**	**84, 96, 108, 120, 132, 144, and 156**	**-**	**36-39**	**79-80**
±Visit Window		**±3D**	**±7D**	**-**	**-**	**-**
Pregnancy Test	Section 6.5.6.2		X	X	X	X
Cardiac Biomarker Samples	Section 6.2.11.2		X - Week 96, Week 120, Week 144	X	X	X
TTR Protein; Vitamin A	Prior to each dose on dosing days; Section 6.3		X	X	X	X
ADA	On dosing days, collect within 1 hour before dosing; Section 6.5.6.1		X – Week 96, Week 120, Week 144	X		
ALN-TTRSC02 PK	Table 5 for PK collection timepoints			X	X	X
Samples for Exploratory Analysis	Section 6.6			X		
AEs; Con. Meds; Hospitalizations, Urgent care visits and Procedures	Section 6.5.7; Section 5.4; Section 6.7.2	Continuous monitoring				
ALN-TTRSC02 Study Drug Administration	Section 5.2.2.1		X – Every 12 weeks starting at Week 84 to EOT Week 156			
Patisiran: Premedication Administration	Section 5.2.2.2	X				
Patisiran Study Drug Administration	Section 5.2.2.2	X				
Vital status check	Section 6.2.8	X	X	X	X	X

Abbreviations: ADA=antidrug antibodies; AE=adverse event; Con. Med.=concomitant medications; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=End of Treatment; EQ-5D-5L=EuroQuality of Life 5-Dimensions 5-Levels; EQ-VAS= EuroQuality of Life-Visual Analog Scale; FAP=Familial Amyloidotic Polyneuropathy; FU=Follow-up; HRdb=heart rate variability with deep breathing; KPS= Karnofsky Performance Status; LFT=liver function test; mBMI=modified body mass

index; 10-MWT=10-meter walk test; mNIS+7=modified NIS+7; NIS=Neurologic Impairment Score; NYHA=New York Heart Association; PE=physical exam; PK=pharmacokinetics; PND=Polyneuropathy Disability; QoL-DN=Quality of Life-Diabetic Neuropathy; R-ODS=Rasch-built Overall Disability Scale; TTR=transthyretin

Table 3 Notes:

- Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2.1 and Section 5.2.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified in the beginning of Section 6.
- For the NIS; mNIS+7; HRdb;10-MWT performed as part of the Early Drug Discontinuation Visit and the Modified Month 9 and 18 Efficacy Visit(s): Two independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart.
- See Section 4.3 for instructions on early discontinuation of study drug procedures.
- SAE, AECI will be collected throughout the Follow-up Period; AEs will be collected until 3 months after the last dose of study drug.
- Dosing decisions may be made based on LFT results (Table 8) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases, the most recently available LFTs should be used. LFT monitoring details are provided in Section 5.2.3.
  For the patisiran cohort, LFTs should be performed according to patisiran visit windows and do not need to be available prior to dosing.

* The Early Discontinuation Visit applies to all periods of the study. [redacted].

[a] Previously referred to as the 18-month Treatment Extension Period (per Amendment 3 and earlier); [redacted]

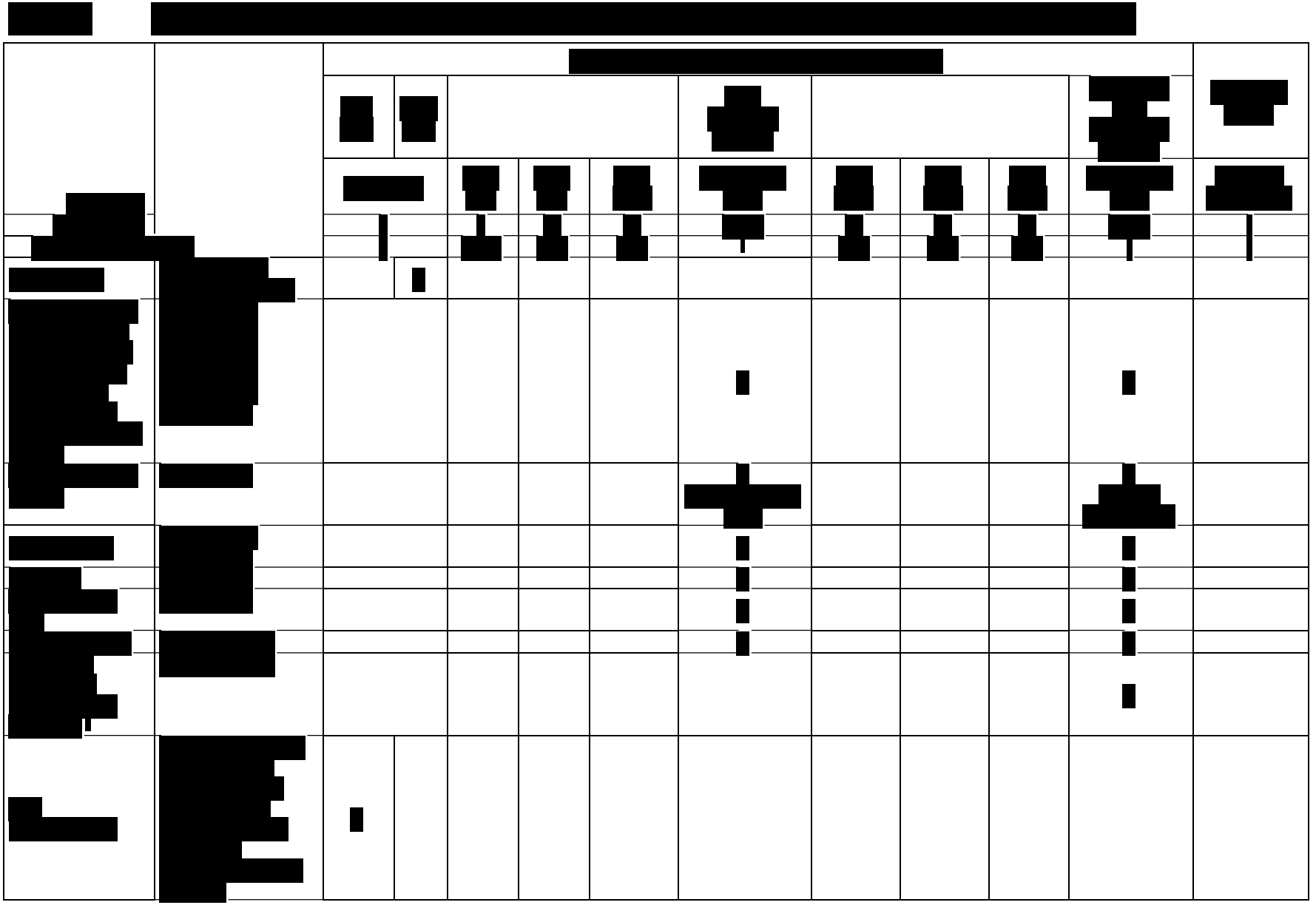


Table 5: Pharmacokinetic Time Points: ALN-TTRSC02

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
	06:00 (±1 hr) after dosing	X
	24:00 (±2 hr) after dosing	X
Day 85 and Day 169 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
Day 337, Day 421, and Day 505 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
[redacted]	[redacted]	[redacted]
Early Drug Discontinuation Visit	Collect any time within the visit window	X
Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18	Collect any time within the visit window	X

Abbreviations: [redacted]
PK sample collection timepoints at 6 and 24 hours after dosing are optional when samples are being collected outside the clinic (eg, the patient's home).

Table 6: Pharmacokinetic Time Points: Patisiran

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before the start of infusion)	X
	00:30 (±5 min) from the end of infusion	X
	06:00 (±1 hr) from the end of infusion	X
	24:00 (±2 hr) from the end of infusion	X
Day 22, Day 127, Day 274, Day 379, and Day 547 (±3 days)	Predose (within 60 minutes before the start of infusion)	X
	03:00 (±1 hr) from the end of infusion	X

PK sample collection timepoints at 6 and 24 hours after dosing are optional when samples are being collected outside the clinic (eg, the patient's home).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
AE	Adverse event
ALN-TTRSC02	Name of study drug product
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
APOLLO	Name of patisiran pivotal Phase 3 clinical study ALN-TTR02-004
ASGPR	Asialoglycoprotein receptor
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
BUN	Blood urea nitrogen
CAS	Central Assessment Sites
CASE	Computer Aided Sensory Evaluator
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
Con. Med	Concomitant medication
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency

Abbreviation	Definition
EOT	End of Treatment
EQ-5D-5L	EuroQoL 5-Dimensions 5-Levels
EQ-VAS	EuroQoL visual analogue scale
EU	European Union
FAC	Familial amyloidotic cardiomyopathy, also known as hATTR amyloidosis with cardiomyopathy
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
GalNAc	N-acetyl galactosamine ligand
GCP	Good Clinical Practice
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HRdb	Heart rate variability with deep breathing
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio
IRB	Institutional review board
IRR	Infusion related reaction
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
KPS	Karnofsky Performance Status
LFT	Liver function test
LLN	Lower limit of normal
LS	Least squares
LV	Left ventricle

Abbreviation	Definition
mBMI	Modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease Study
mITT	Modified Intent-to-Treat
10-MWT	10-meter walk test
mNIS+7	Modified Neurologic Impairment Score +7
mRNA	Messenger RNA
NCS	Nerve conduction studies
NCS Σ5	NCS sum of 5 attributes
NIS	Neurologic Impairment Score
NIS-R	NIS reflexes
NIS-S	NIS sensation
NIS-W	NIS weakness
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	B-type natriuretic peptide
NYHA	New York Heart Association
OLT	Orthotopic Liver Transplantation
Patisiran	Name of patisiran drug product; patisiran-lipid nanoparticles
PCS	Patient Care Sites
PD	Pharmacodynamics
PK	Pharmacokinetics
PND	Polyneuropathy Disability
PT	Prothrombin time
q3M	Once every 3 months
q3w	Once every 3 weeks
QoL or QOL	Quality of life
QST	Quantitative sensory testing
QST-BSA_{HP}	QST heat pain by body surface area
QST-BSA_{TP}	QST touch pressure by body surface area
QTc	Corrected QT interval
QTcF	QT obtained using Fridericia's formula

Abbreviation	Definition
RBC	Red blood cell
RBP	Retinol binding protein
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
R-ODS	Rasch-built Overall Disability Scale
RTE	Randomized Treatment Extension
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
siRNA	Small interfering ribonucleic acid
SNAP	Sensory nerve action potential
SOC	System organ class
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
T3	Triiodothyronine
T4	Thyroxine
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
TUDCA	Tauroursodeoxycholic acid
ULN	Upper limit of normal
US	United States
USA	United States of America
V30M	Valine to methionine mutation at position 30
V122I	Valine to isoleucine mutation at position 122
WHO	World Health Organization
Wt	Wild type

1. INTRODUCTION

1.1. Disease Overview

Hereditary ATTR amyloidosis (hATTR amyloidosis) is a rare, life-threatening, autosomal dominant, multi-systemic disease caused by mutations in the transthyretin (TTR) gene that results in rapidly progressive, debilitating morbidity and high mortality. The cardinal manifestations of hATTR amyloidosis are polyneuropathy and cardiomyopathy.

TTR, also known as prealbumin, is a tetrameric protein predominantly produced by hepatocytes (>95% of circulating TTR is liver-derived), with a smaller fraction produced by the choroid plexus and retina [Liz 2010]. The primary physiological role of TTR is to serve as a carrier of retinol (also known as vitamin A), which involves TTR binding to the retinol binding protein (RBP): vitamin A complex. TTR also serves as a minor carrier for thyroxine (T4).

In hATTR amyloidosis, inherited mutations in the TTR gene lead to destabilization of the tetrameric protein and disassociation of the TTR subunits into dimers and individual mutant and wild-type (wt) monomers, which subsequently misfold. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues [Hou 2007], including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system and eye, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Since almost all patients are heterozygous for the mutated TTR allele, the amyloid fibrils typically consist of both mutant and wtTTR. There are over 120 reported TTR genetic mutations associated with hATTR [Ando 2013; Brodsky 2008; Connors 2003]. The disease is most often caused by the valine to methionine mutation at position 30 in the human TTR gene (V30M)primarily in families with heritage from Portugal, Sweden, Japan, and Brazil [Parman 2016]. Another common genotype is the isoleucine substitution for valine at position 122 (V122I). This mutation occurs in up to 4% of African Americans and in over 5% of West African populations [Jacobson 1997].

Historically, due to incomplete understanding of etiology and pathogenesis, 2 clinical syndromes of hATTR amyloidosis have been described in the medical literature: hATTR amyloidosis with polyneuropathy (previously known as familial amyloidotic polyneuropathy, or FAP) and hATTR amyloidosis with cardiomyopathy (previously known as familial amyloidotic cardiomyopathy, or FAC), both of which are characterized by amyloid deposits comprised of both mutant and wt TTR [Yazaki 2000]. However, while patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease. Therefore, hATTR amyloidosis is increasingly viewed as a single hereditary disease with a spectrum of clinical manifestations rather than 2 distinct syndromes [Swiecicki 2015].

The clinical manifestations of the length-dependent, symmetrical polyneuropathy are the result of amyloid-mediated injury to large and small peripheral nerve fibers [Ando 2013; Benson and Kincaid 2007; Plante-Bordeneuve and Said 2011]. Sensory abnormalities include painful dysesthesias in the feet and hands, as well as loss of sensation leading to thermal burns in these areas and to joint injury in the lower limbs. Progressive muscle atrophy and motor weakness in both lower and upper limbs leads to impaired ambulation (progressing from the use of one stick

to two for ambulation, followed by needing to use a wheel chair and then becoming bed-ridden over just a few years), and inability to perform other activities of daily living. Autonomic dysfunction results in debilitating orthostatic hypotension, severe gastrointestinal symptoms, and bladder dysfunction with recurrent urinary tract infections.

Polyneuropathy stage or severity is classified by FAP stage or Polyneuropathy Disability (PND) score, both of which are based on ambulatory ability. The degree of neurologic impairment has historically been measured using the Neurologic Impairment Score (NIS), which has been shown to be correlated with FAP stage and PND score; an increase from baseline in NIS score signifies worsening in neurologic impairment, which in turn correlates with a higher FAP stage designation and PND score [Adams 2015]. The maximum impairment score for the NIS is 244 points, and a change from baseline of 10 to 14 points per year has been observed in untreated patients based on data from an hATTR amyloidosis clinical study and an observational natural history study [Adams 2015; Berk 2013]. This is in contrast to patients with diabetic polyneuropathy where NIS progression is <1 point/year [Ziegler 2011]. For clinical studies, the modified NIS+7 (mNIS+7) score, a more sensitive measure with a scale from 0 to 304 points, has been developed to provide a more comprehensive measure of polyneuropathy in patients with hATTR amyloidosis [Suanprasert 2014].

Cardiac infiltration with amyloid leads to heart wall thickening and cardiomyopathy characterized by clinical heart failure due to both diastolic and systolic dysfunction, as well as cardiac conduction disturbances and arrhythmias [Ando 2013; Benson and Kincaid 2007; Carvalho 1992; Connors 2004; Soares 2005]. Patients with symptomatic heart failure experience rapid progression of their amyloid cardiomyopathy, with substantial worsening of echocardiographic and biomarker measures of cardiac function, ambulation, and quality of life seen over a period of 18 months or less [Ruberg and Berk 2012].

1.2. Current Treatments

The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, gastroenterology, and cardiology specialties. Palliative/symptomatic therapies directed at specific symptoms such as pain, nausea/vomiting and diarrhea have been the mainstay of treatment.

Two treatment approaches that have historically been used for the treatment of hATTR amyloidosis are orthotopic liver transplantation (OLT), which serves to eliminate mutant TTR from the circulation, but does not affect the hepatic production of wt TTR [Carvalho 2015; Ericzon 2015; Okamoto 2009], and TTR tetramer stabilizers (including tafamidis and diflunisal), which have been shown in clinical studies to reduce neuropathy in patients with early stage polyneuropathy [Berk 2013; Coelho 2012]. However, these therapies are restricted to a small subset of patients with hATTR amyloidosis with early stage neuropathy. Furthermore, the majority of patients receiving tafamidis continue to experience neuropathy progression with a steady decline in quality of life, ability to walk, and to perform activities of daily living [Barroso 2017].

Recently, the antisense oligonucleotide inotersen and the short interfering ribonucleic acid (siRNA) patisiran were shown in randomized controlled studies to significantly reduce neurologic impairment and improve quality of life compared with placebo in patients with hATTR amyloidosis [Adams 2017; Dyck 2017; Wang et al. 2017]. Both novel therapies, albeit

through different mechanisms, aim at reducing the expression of TTR messenger RNA (mRNA), and the amount of circulating amyloidogenic protein in patients with hATTR amyloidosis.

1.3. RNAi Therapeutics to Reduce TTR Levels

Patisiran-LNP (ONPATTRO™; hereafter referred to as patisiran) developed by Alnylam, which targets the production of hepatic TTR, is approved in the US for the treatment of the polyneuropathy of hATTR amyloidosis in adults and in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 and stage 2 polyneuropathy. The recommended dose of patisiran is 0.3 mg/kg administered via intravenous (IV) infusion once every 3 weeks (q3w). To minimize the risk of infusion related reactions (IRRs), all patients must receive pre-medication including corticosteroids (10 mg dexamethasone IV), histamine 1 (H1) and histamine 2 (H2) blockers, and paracetamol or equivalents 60 minutes prior to the infusion.

Patisiran utilizes the mechanism of RNA interference to selectively degrade TTR mRNA and thereby reduce the expression of its corresponding protein [Bumcrot 2006]. Patisiran is an siRNA that is formulated as lipid nanoparticles (LNP) to target delivery to hepatocytes in the liver, the primary source of TTR protein in circulation. Following IV infusion, opsonization of the LNP by apolipoprotein E facilitates binding to the low-density lipoprotein receptor on hepatocytes and subsequent endocytosis. Fusion of the ionizable lipid component of the LNP with the endosomal membrane then leads to release of the siRNA into the cytoplasm where it can bind to and activate the RNA-induced silencing complex (RISC). Upon binding and activation of RISC in the cytoplasm within hepatocytes, the siRNA duplex unwinds and the antisense strand specifically binds to a genetically conserved sequence in the 3' untranslated region of wt and mutant TTR mRNA. The Argonaute-2 endonuclease within the RISC/siRNA enzyme complex catalytically degrades wt and mutant TTR mRNA, resulting in a reduction of wt and mutant TTR protein.

Alnylam had also developed another siRNA-conjugate therapeutic, revusiran, primarily for the treatment of patients with hATTR amyloidosis with cardiomyopathy; however, this program was discontinued as described further in the ALN-TTRSC02 Investigator's Brochure (IB).

ALN-TTRSC02 (also known as vutrisiran) is in clinical development for the treatment of ATTR amyloidosis. This molecule is designed to have greater potency and prolonged duration of action compared to current and previous siRNAs evaluated in the clinic for treatment of this disease. ALN-TTRSC02 has the same nucleotide sequence as revusiran but employs a different ratio of chemical modifications to confer increased stability of the siRNA.

ALN-TTRSC02 drug product comprises the drug substance ALN-65492, an siRNA targeting TTR mRNA that is conjugated to an N-acetyl galactosamine ligand (GalNAc) to facilitate delivery to the liver, formulated in 10 mM sodium phosphate, 110 mM sodium chloride at pH 7 for subcutaneous (SC) injection. Uptake of ALN-TTRSC02 occurs via the asialoglycoprotein receptor (ASGPR), a member of the C-type lectin family of receptors that recognizes and binds glycoproteins with terminal galactose (Gal) or GalNAc residues [Ashwell and Morell 1974; Nair 2014]. It is expressed on the cell surface of hepatocytes at a high copy number (0.5-1 million per cell) [Baenziger and Fiete 1980; Schwartz 1980], and facilitates clearance of desialylated glycoproteins from the blood [Geffen and Spiess 1992]. Binding of the carbohydrate ligand to the ASGPR leads to receptor-mediated endocytosis of the ligand-receptor complex followed by

release of its cargo in the endocytic pathway, and subsequent recycling of the receptor to the cell surface for successive rounds of uptake.

ALN-TTRSC02 has been shown to have increased potency and duration of TTR reduction in nonclinical species and in a clinical study in healthy volunteers described in Section 1.4.2, enabling a much lower dose, lower injection volume, and significantly less frequent dosing for patients compared to other TTR-lowering drugs.

1.4. Clinical Experience with Patisiran and ALN-TTRSC02

1.4.1. The APOLLO Study

The safety and efficacy of patisiran was shown in a Phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study (ALN-TTR02-004, APOLLO) that met the primary and all secondary endpoints [Adams 2018]. This study demonstrated that in patients with hATTR amyloidosis, who exhibited a broad range of disease severity and TTR genotypes, treatment with patisiran leads to a significant improvement in neuropathy (mNIS+7) relative to placebo at 18 months (primary analysis), as well as significant improvement in quality of life (Norfolk QoL-DN, key secondary analysis) relative to placebo at 18 months. Significant improvement in neuropathy and quality of life were also observed at Month 9. This study furthermore demonstrated that treatment with patisiran is associated with an improvement in overall health (gait speed, nutritional status, and disability), with improvement in these endpoints seen as early as at Month 9. Patisiran treatment was also associated with improvement compared to placebo in exploratory cardiac endpoints including key echocardiographic parameters and the biomarker NT-proBNP [Solomon 2018]. In post-hoc analyses, patisiran demonstrated a reduction in the composite event rate of hospitalization and mortality.

In the patisiran group, the mean TTR percent reduction from baseline was 82.6% and 84.3% at Month 9 and Month 18, respectively. TTR percent reduction was maintained over the duration of the study. A correlation (Pearson's r, 0.59; 95% CI, 0.49-0.68) was observed between the degree of TTR reduction from baseline and the change in the mNIS+7 at 18 months.

Patisiran showed an acceptable safety profile in the APOLLO study. Common adverse events (AEs) occurring more frequently with patisiran compared to placebo included peripheral edema (30% versus 22%) and infusion related reactions (IRRs) (19% versus 9%, respectively).

1.4.2. ALN-TTRSC02-001 Phase 1 Clinical Study

ALN-TTRSC02 has been evaluated in a recently completed Phase 1 study (study ALN-TTRSC02-001). ALN-TTRSC02-001 was a randomized, single-blind, placebo controlled single-ascending dose study to evaluate the safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ALN-TTRSC02 in healthy subjects and in healthy subjects of Japanese descent. Single doses of 5, 25, 50, 100, 200 or 300 mg ALN-TTRSC02 were administered by SC injection to cohorts of 8 subjects (6:2 ratio ALN-TTRSC02 to placebo). Subjects remained blinded to treatment assignment through Day 90. Eighty healthy volunteers were randomized in 10 cohorts and followed for up to 314 days.

ALN-TTRSC02 reduced serum TTR in a dose dependent fashion with higher doses of ALN-TTRSC02 achieving deeper and longer duration of serum TTR reduction. At the proposed dose of 25 mg ALN-TTRSC02, a single dose resulted in maximum TTR reduction of 94% and mean

maximum TTR reduction of 83% that was maintained for 90 days (n=12). Consistent with the expected PD effect, vitamin A levels were also reduced following a single dose of ALN-TTRSC02. Similar PD effects were observed in the subjects of Japanese descent, as compared to the subjects in the non-Japanese cohorts.

AEs were reported in 77% and 50% of ALN-TTRSC02 and placebo treated subjects, respectively. Among ALN-TTRSC02 treated patients, the majority of AEs were mild. ALN-TTRSC02 drug-related AEs included injection site reactions in 4 subjects that were mild and transient including bruising (50 mg), erythema (200 mg) and pain (200 mg and 300 mg); there were no drug-related AEs in patients receiving ALN-TTRSC02 doses ≤25 mg. There were no severe or serious AEs; no subject discontinued from the study due to an AE. A dose-dependent pattern in transaminase elevations was observed across the ALN-TTRSC02 doses tested, in particular at doses ≥100 mg; the majority were mild, transient, and none were reported as AEs. Most alanine transaminase (ALT) and aspartate transaminase (AST) elevations were ≤3 x upper limit of normal (ULN); 1 subject receiving ALN-TTRSC02 50 mg had AST >3 x ULN and 1 subject receiving ALN-TTRSC02 200 mg had ALT and AST >3 x ULN, which were asymptomatic and resolved to <ULN without intervention. There were no concurrent elevations in bilirubin or alkaline phosphatase. There were no clinically significant changes in renal function or hematologic parameters, including platelets and no clinically significant changes in electrocardiogram (ECG), vital signs or physical exam.

Further information on the chemistry, pharmacology, efficacy, and safety of ALN-TTRSC02 is provided in the current edition of the Investigator's Brochure.

1.5. Study Design Rationale

This is a global Phase 3 open-label study designed to evaluate the efficacy, safety, and PK/PD profile of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran. Patisiran is the reference comparator arm. All patients randomized to patisiran will be transitioned to ALN-TTRSC02 after completion of the 18-month Treatment Period.

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, and an 18-month Randomized Treatment Extension Period (RTE) as of Amendment 4, in lieu of the 18-month Treatment Extension Period (hereafter referred to as the Legacy Treatment Extension Period). A Follow-up Period of up to 1 year will occur after the last dose of study drug. See also Section 3.1.

The proposed development plan for ALN-TTRSC02 builds upon learnings from the previous development of another siRNA that targets TTR, patisiran (described in Section 1.4). The completed patisiran Phase 3 APOLLO study, which enrolled a similar patient population to the current study and incorporated similar endpoints to the current study, will be used as an external control for efficacy analysis. The primary endpoint in this study, change from baseline in mNIS+7 score at Month 9, and the key secondary endpoint of Norfolk QoL-DN total score at Month 9, will be compared with the placebo group from the APOLLO study at Month 9 as the primary analysis. The use of an external control for comparison is supported by the principles outlined in the EMA guideline on clinical trials in small populations (CHMP/EWP/83561/2005), ICH E10 guidance on control groups in clinical trials, as well as the USA's 21st Century Cures Act (Section 3012 Targeted Drugs for Rare Diseases). Based on these guidelines, an external

comparison is an appropriate clinical study design for diseases occurring in small populations, with well understood natural history of disease course. The natural history of hATTR amyloidosis has been well-characterized in several, large, randomized clinical trials, including the APOLLO study, as well as natural history studies. Importantly, these studies all demonstrate similar rates of disease progression despite having been conducted at substantially different points in time and in patients with different disease characteristics across different geographies [Adams 2015; Adams 2018; Berk 2013; Maurer 2017]. The patisiran reference comparator arm will help to validate the use of the external control for the primary and secondary efficacy analyses both by allowing descriptive comparison of the clinical efficacy endpoints between treatment arms within this study and by establishing similar (non-inferior) level of TTR reduction is achieved for ALN-TTRSC02 and patisiran.

Secondary and exploratory endpoints in this study assessing the clinical manifestations of hATTR amyloidosis are similar to those in the APOLLO study. Additional cardiac assessments are included in this study as exploratory endpoints. These endpoints will all be assessed in comparison to the placebo group in the APOLLO study.

Safety will be assessed by monitoring of AEs, laboratory data including liver function tests, changes in physical exam, vital signs, and ECG.

[redacted]

1.6. Dose Rationale

The proposed dose of ALN-TTRSC02 for this study is 25 mg SC given q3M. This dose was well-tolerated in the Phase 1 study (see Section 1.4.2) and is expected to provide efficacy similar to patisiran based on the anticipated magnitude of TTR lowering. [redacted]

Modeling and simulation predicted that the proposed 25 mg dose of ALN-TTRSC02 administered SC q3M will lead to substantial and persistent serum TTR reduction, comparable to TTR lowering observed with patisiran in the Phase 3 APOLLO study. At steady state, which is achieved by approximately 6 months, 25 mg SC q3M regimen of ALN-TTRSC02 is predicted to achieve median trough TTR reductions of 86%, which is similar to patisiran. This magnitude of TTR lowering is expected to lead to durable clinical benefit as evidenced by the statistically significant difference in mNIS+7 and all the secondary endpoints, including Norfolk QoL-DN, in the patisiran arm compared to placebo in the pivotal Phase 3 APOLLO study. Furthermore, on the Phase 3 APOLLO study, this magnitude of TTR lowering was associated with an acceptable safety profile.

[redacted]

Overall, available nonclinical and clinical data suggest the selected dose will appropriately balance safety and efficacy in the broad hATTR patient population.

1.7. Benefit-Risk Assessment

Based on available nonclinical and clinical data, with evidence of TTR reduction in the healthy subject study, TTR reduction by ALN-TTRSC02 is anticipated to beneficially impact disease progression in patients with hATTR amyloidosis, as has been shown with other available TTR lowering agents including patisiran and inotersen. The q3M and q6M SC regimens are infrequent, easy to administer, do not require premedication, and thus may maximize convenience and minimize overall burden of care. In the Phase 1 clinical study in healthy subjects, single SC doses up to the highest tested dose (300 mg) of ALN-TTRSC02 were well tolerated.

Patients with hATTR amyloidosis often suffer substantial loss in ambulation and mobility associated with other comorbidities that significantly impact activities of daily living and can make healthcare visits challenging. [redacted] aims to further minimize the need for frequent healthcare visits and further mitigate patient burden. This is consistent with global trends toward decreased healthcare encounters, the importance of which has been further highlighted by the COVID-19 pandemic.

Given the biological target of ALN-TTRSC02, the available nonclinical and clinical data, and the mode of administration, important potential risks for ALN-TTRSC02 are injection site reactions (ISRs), liver function test (LFT) abnormalities, and consequences of vitamin A deficiency. During the study, patients will be closely monitored, including evaluation of injections sites. As ALN-TTRSC02 is targeted for delivery to the liver, there is a potential for development of LFT abnormalities. Patients presenting with any laboratory result considered unacceptable as per exclusion criteria (see Section 4) at time of enrollment will be excluded from participation in this study, and LFTs will be routinely monitored throughout the study per the Schedule of Assessments. Criteria for dose withholding, modification and stopping ALN-TTRSC02 dosing due to LFT abnormalities are provided in Section 5.2.3. Detailed information about the known and expected benefits and risks of ALN-TTRSC02 and additional safety information may be found in the current edition of the ALN-TTRSC02 Investigator's Brochure.

For patisiran, important identified risks include infusion related reactions (IRRs). All patients must receive premedication with a corticosteroid, paracetamol/acetaminophen, and H1 and H2 blockers prior to patisiran administration to reduce the risk of IRRs (see Section 5.2.2.2). Potential risks include consequences of vitamin A deficiency and severe hypersensitivity (eg, anaphylaxis) to the active substance or any of the excipients. Detailed information about the known and expected benefits and risks of patisiran and additional safety information may be found in the current edition of the patisiran Investigator's Brochure or, where approved, in the ONPATTRO prescribing/product information.

Nonclinical and clinical data with ALN-TTRSC02 and patisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in severe vitamin A deficiency; transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. However, as the vitamin A content of the diet may vary between different individuals, all patients will be instructed to take the recommended daily allowance of vitamin A while on the study (see Section 5.2). Laboratory

tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation beyond the recommended daily dose during treatment with ALN-TTRSC02 and patisiran.

2. OBJECTIVES AND ENDPOINTS

The primary and most secondary and exploratory efficacy endpoints are in comparison to the placebo arm of the Phase 3 pivotal patisiran study (ALN-TTR02-004, also referred to as the APOLLO study) as specified in the statistical analysis section of this protocol.

Objectives	Endpoints
Primary	
• To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment	• Change from baseline in the Modified Neurologic Impairment Score +7 (mNIS+7) compared to the placebo arm of the APOLLO study at Month 9
Secondary	
• To determine the efficacy of ALN-TTRSC02 on quality of life, gait speed, neurologic impairment, nutritional status, and disability • To demonstrate the noninferiority of ALN-TTRSC02 compared to patisiran with respect to serum TTR levels	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score at Month 9; – Timed 10-meter walk test (10-MWT) at Month 9; – mNIS+7 at Month 18; – Norfolk QoL-DN total score at Month 18; – 10-MWT at Month 18; – Modified body mass index (mBMI) at Month 18; – Rasch-built Overall Disability Scale (R-ODS) at Month 18 • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran arm through Month 18
Exploratory	
• To determine the effect of ALN-TTRSC02 on: – Disability and nutritional status; – Manifestations of cardiac amyloid involvement; – Other assessment of neurologic impairment; – Other assessments of quality of life; – Disease stage; – Performance of daily activities	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study at Month 9: – R-ODS; – mBMI • Change from baseline over time: – N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters,

Objectives	Endpoints
• To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and patisiran on serum TTR and vitamin A levels • To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran • To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran	Troponin I and T levels, New York Heart Association (NYHA) class; – Neurologic Impairment Score (NIS); – EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQoL-Visual Analog Scale (EQ-VAS); – Familial Amyloidotic Polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score; – Karnofsky Performance Status (KPS) • Change from baseline in technetium scintigraphy cardiac parameters at Month 18 • Percent reduction in serum TTR and vitamin A levels over time • PK profile of ALN-TTRSC02 and patisiran • Incidence and titers of ADA to ALN-TTRSC02 and patisiran
Safety	
• To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

For submission of the marketing authorization to the European Union, formal hypothesis testing will be conducted at Month 18, with mNIS+7 compared to the placebo arm of the APOLLO study at Month 18 considered the primary endpoint. Details will be specified in the statistical analysis plan (SAP).

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a global Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran, a reference comparator. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, and an 18-month RTE Period in lieu of the 18-month Legacy Treatment Extension Period. A Follow-up Period of up to 1 year will occur after the last dose of study drug (Figure 2).

18-Month Treatment Period

After the Screening period at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as a SC injection q3M or patisiran administered as an IV infusion q3w; patients in the patisiran arm will also receive premedications prior to each dose (see Section 5.2.2.2). During the 18-month Treatment Period, patients will undergo assessments for efficacy and/or safety (as outlined in the Schedule of Assessments), with key efficacy assessments being performed prior to first dose, at Month 9 (primary efficacy analysis timepoint) and at Month 18; samples for TTR assessment will be collected more frequently throughout the 18-month Treatment Period.

All efficacy visits must be conducted at the clinic (Month 9, Month 18, and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 or Month 18 efficacy assessments as applicable. After consultation with the Medical Monitor, the Month 9 or Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Month 15 or Month 24, respectively).

Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2.1 and Section 5.2.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified at the beginning of Section 6.

The placebo arm of the APOLLO study will be used as an external control for the primary, most secondary, and most exploratory efficacy analysis. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

In order to allow for a robust cross study comparison, attempts will be made to minimize differences between the HELIOS-A and APOLLO study populations. As such, baseline disease characteristics will be monitored and may result in enrollment limitations based on certain characteristics (eg, genotype) to ensure comparability. Decisions around enrollment adjustments will be made by staff without access to primary efficacy results.

Randomized Treatment Extension (RTE) Period

[redacted]

Follow-up Period

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

3.2. Duration of Treatment

The treatment duration in this study is up to a maximum of 54 months inclusive of the 18-month Treatment Period, potential time on the Legacy Treatment Extension Period prior to transition to the RTE Period, and an 18-month RTE Period.

Refer to Section 4.3.1 for information on early treatment discontinuation.

3.3. Duration of Study

The estimated time on study for each patient is a maximum of 5 years, inclusive of 42 days of Screening and up to 54 months of open-label treatment (including 18 months in the Treatment Period, 0 to 18 months as applicable in the Legacy Treatment Extension Period, and 18 months in the Randomized Treatment Extension Period), plus the Follow-up Period of up to 1 year.

The Follow-up Period is until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if:

- [redacted]
- the patient has completed the ALN-TTRSC02 Follow-up Period, until serum TTR levels return to ≥80% of baseline (for a maximum of up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

3.4. Number of Planned Patients

Approximately 160 patients are planned for enrollment in this study.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L at baseline.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 3:1 to the ALN-TTRSC02 or patisiran arm. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

Not applicable, this is an open-label, controlled study.

3.7. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will oversee the safety and overall conduct of this study through the Treatment Period (through Month 18), providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC has the responsibility for reviewing safety data and analyses and making recommendations to the Sponsor. The DMC will perform periodic reviews of data during the course of the clinical trial through the Treatment Period, and on an ad hoc basis for review of emergent safety data. Details are provided in the DMC Charter.

3.8. Adjudication Committee

An independent Adjudication Committee will review deaths and will attribute a cause according to the responsible underlying disease process rather than the immediate mechanism. Deaths will be classified as specified in the Adjudication Committee Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Each patient must meet all of the following eligibility criteria at Screening Visit 1 (except where specified) to be eligible for enrollment in the study.

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all of the following criteria apply:

Age and Sex

1. Male or female age 18 (or age of legal consent, whichever is older) to 85 years of age

Patient and Disease Characteristics

2. Have a diagnosis of hATTR amyloidosis with documented TTR mutation
3. Have a NIS of 5 to 130 (inclusive; this criterion must be met at the Screening Visit 2)
4. Have a PND score of ≤3b (this criterion must be met at the Screening Visit 2)
5. Have a Karnofsky Performance Status (KPS) of ≥60%

Informed Consent

6. Patient is willing and able to comply with the study requirements and to provide written informed consent

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Disease-specific Conditions

1. Has had a liver transplant or is likely, in the opinion of the Investigator, to undergo liver transplantation during the 18-month Treatment Period of the study
2. Has known other (non-hATTR) forms of amyloidosis or clinical evidence of leptomeningeal amyloidosis
3. Has a New York Heart Association heart failure classification >2

Laboratory Assessments

4. Has any of the following laboratory parameter assessments:
   a. ALT and/or AST >1.5× upper limit of normal reference range (ULN)
   b. Total bilirubin >ULN (>1.5 ULN in patients with Gilbert's Syndrome)
   c. International normalized ratio (INR) >1.2 (patients on anticoagulant therapy with an INR of ≤3.5 will be allowed)

   (Note: ALT, AST, and total bilirubin laboratory criteria must be met at both Screening Visit 1 and Screening Visit 2)
5. Platelet count <50,000/μL
6. Absolute neutrophil count (ANC) <1500 cells/mm^3
7. Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73m^2 (using the Modification of Diet in Renal Disease [MDRD] formula)
8. Has vitamin B12 levels below the lower limit of normal (LLN)

9. Has known human immunodeficiency virus (HIV) infection; or evidence of acute or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection

Prior/Concomitant Therapy

10. Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to dosing (Day 1)
11. Received prior TTR-lowering treatment or participated in a gene therapy trial for hATTR amyloidosis
12. Is currently taking tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 14-day wash-out prior to dosing (Day 1)
13. Is currently taking diflunisal; if previously on this agent, must have at least a 3-day wash-out prior to dosing (Day 1)

Medical Conditions

14. Has other known causes of sensorimotor or autonomic neuropathy (eg, autoimmune disease, monoclonal gammopathy) that the treating physician believes to be contributing to the neuropathy
15. Had acute coronary syndrome within the past 3 months
16. Has uncontrolled clinically significant cardiac arrhythmia or unstable angina
17. Has known type 1 diabetes
18. Has had type 2 diabetes mellitus for ≥5 years
19. Has untreated hypo- or hyperthyroidism
20. Has had a major surgery within the past 3 months or has a major surgery planned during the study through Month 18
21. Has an active infection requiring systemic antiviral, antiparasitic or antimicrobial therapy that will not be completed prior dosing (Day 1)
22. Had a malignancy within 2 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
23. Anticipated survival is less than 2 years, in the opinion of the Investigator
24. History of multiple drug allergies; or history of allergic reaction to an oligonucleotide or GalNAc; or had a prior severe reaction to a liposomal product or any component of patisiran (ALN-TTR02)
25. Is unable to take the required premedications (see Section 5.2.2.2)
26. History of intolerance to subcutaneous (SC) injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
27. Any condition (eg, medical concern), which in the opinion of the Investigator, would make the patient unsuitable for dosing or which could interfere with the study

compliance, the patient's safety and/or the patient's participation through the Month 18 visit of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to hATTR identified by key laboratory abnormalities or medical history

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.6.1.
29. Female patient is pregnant or breastfeeding

Alcohol Use

30. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])
31. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented and recorded in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse Event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-adverse event)
- Or, the study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing of the patient. Patients who are pregnant will be discontinued from study

drug dosing immediately (see Section 6.5.7.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience (including, at a minimum, information on vital status, cardiac transplant procedures, LVAD placement and hospitalizations for the duration of the study) is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 3), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians, or from review of medical records), including endpoints and adverse events, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including serious adverse events (SAEs), the event should be followed as described in Section 6.5.7. When a patient discontinues study drug dosing, the primary reason must be recorded in the electronic case report form (eCRF). Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue study drug early for any reason during the Treatment Period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 18 assessments) should complete the Early Drug Discontinuation visit and will be encouraged to remain on the study to complete the modified Month 9 and Month 18 efficacy assessments visits, prioritizing the primary and secondary assessments, where possible so that their experience is captured in the final analyses. If a patient discontinues study drug and completes the Early Drug Discontinuation visit within 3 months of Month 9 or Month 18 and remains on the study, they will not be required to complete the modified efficacy assessments at Month 9 and/or Month 18, as applicable depending on the time they discontinue study drug (Table 3).

Patients who discontinue study drug during the Legacy Treatment Extension Period or the RTE Period will be asked to return to complete the Early Drug Discontinuation visit (Table 3).

Patients who discontinue study drug, but who remain on study, may receive treatment consistent with local standard practice for their disease per Investigator judgment, as applicable. For patients who discontinue study drug and remain in the study, all AEs will be collected for 90 days after the last dose, thereafter, SAEs and AEs of clinical interest (see definition in Section 6.5.7.1) will be collected for the remainder of their participation in the study.

All patients who discontinue study drug will also be asked to complete safety follow-up visits, per the Follow-up Period schedule (see Table 4) until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed

for a minimum of 3 months. Female patients of child-bearing potential who discontinue ALN-TTRSC02 will be followed until serum TTR levels return to ≥80% of baseline.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. Patients considering stopping their participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the Early Drug Discontinuation Visit assessments in Table 3 within 4 weeks of the last dose during the Treatment Period, and at any time during the Legacy Treatment Extension Period or the RTE Period.

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient's consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, use biological samples and as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the

observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.7.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient misses a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. Attempts should also be made to collect information related to cardiac transplant procedures, left-ventricular assist device placement and hospitalizations from other sources for the duration of the study. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of ALN-TTRSC02 and patisiran is provided in the Pharmacy Manual. Detailed Instructions for Use for the ALN-TTRSC02 pre-filled syringe will also be provided.

All patients will be instructed to take the recommended daily allowance of vitamin A while on the study.

5.2.1. Description

ALN-TTRSC02 will be supplied as a vial of sterile solution containing 50 mg/mL of siRNA ALN-65492 free acid (equivalent to 53 mg/mL sodium salt) in phosphate buffered saline for SC injection. The drug product does not contain preservatives and is intended for single use. See the Pharmacy Manual for further details of solution concentration and fill volume.

ALN-TTRSC02 will also be supplied as a pre-filled syringe and a needle safety device. The pre-filled syringe will be filled with ALN-TTRSC02 (25 mg dose) with a volume of 0.5 mL. [redacted] The pre-filled syringe is a single-use injection device, and after injection the needle safety device will engage to cover the exposed needle.

ALN-TTRSC02 will initially be administered using injections prepared from vials. Patients may be transitioned from vial-based injections to the pre-filled syringe-based injections at any study time point as this presentation becomes available.

The comparator drug for this study will be patisiran that contains 2 mg/mL of drug substance ALN-18328 (siRNA) and lipid excipients DLin-MC3-DMA, DSPC, cholesterol, and PEG_{2000}-C-DMG formulated as lipid nanoparticles (LNPs) in isotonic phosphate buffered saline for IV administration. Patisiran will be provided by the Sponsor.

5.2.2. Dose and Administration

5.2.2.1. ALN-TTRSC02

ALN-TTRSC02 25 mg SC injection will be administered q3M (12 weeks ±3 days during the Treatment Period [redacted]. Study drug SC injections in the clinic will be administered under the supervision of the Investigator or a trained healthcare professional. ALN-TTRSC02 may be administered at a location other than the study center (eg, the patient's home) as specified below.

If a patient has tolerated at least 1 dose of ALN-TTRSC02 in the clinic, subsequent dosing may be administered outside the study site (eg, the patient's home) at all time points where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator. If the patient is unable to come to the study center, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, ALN-TTRSC02 25 mg SC q3M may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on ALN-TTRSC02 administration. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing. [redacted]

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. In addition, instructions and procedures related to administration of ALN-TTRSC02 (25 mg q3M only) by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

Method of Administration of ALN-TTRSC02

ALN-TTRSC02 is for SC use.

The SC injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. Detailed Instructions for Use for the pre-filled syringe will also be provided.

Missed Doses of ALN-TTRSC02

If a patient does not receive a dose of ALN-TTRSC02 within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose [redacted] may be administered with up to an 8-week delay or as determined by the Medical Monitor (to be considered a delayed dose). If a dose is administered with a delay, the next dose will resume following the original schedule. In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required unless the dose cannot be administered within the 8-week delay, then the Medical Monitor must be consulted. In all cases, the dose should be administered as close as possible to the scheduled timepoint. If a dose is delayed, all assessments associated with the originally scheduled dose may also be delayed to coincide with the delayed dose.

During the Treatment Period, every effort should be made to avoid missed doses of ALN-TTRSC02. During the Treatment Period, if a patient misses a dose for reasons unrelated to the COVID-19 pandemic, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study (see also Section 4.3).

5.2.2.2. Patisiran

Patisiran 0.3 mg/kg IV infusion will be administered once every 3 weeks (q3w) ±3 days. The amount (in mg) of study drug to be administered should be determined based on the patient's weight (kg). Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg.

If a patient has tolerated at least 2 doses of patisiran administered in the clinic, dosing may be administered outside the study site (eg, the patient's home) at all timepoints where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator.

Required premedication for patients in the patisiran arm

All patients should receive premedication prior to patisiran administration to reduce the risk of infusion-related reactions (IRRs). Each of the following medicinal products should be given on the day of patisiran infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

Oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.

Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

1. If a patient is having difficulty tolerating the corticosteroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the corticosteroid premedication may be allowed for that patient after consultation with the medical monitor.
2. If a patient has tolerated 3 or more infusions of patisiran with their current corticosteroid premedication regimen (ie, patient has not had IRRs during the past 3 or more infusions), then lowering of the corticosteroid premedication is recommended.

Steps to lower corticosteroid dosing are provided in the Study Manual. Corticosteroid tapering may be performed in the clinic or, at the discretion of the investigator, may be performed outside of the clinic (eg, in the patient's home) after consultation with the Medical Monitor.

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed. Guidelines for management of IRRs can be found in the Pharmacy Manual.

Method of Administration of patisiran

Patisiran is for IV use and should be administered by a healthcare professional.

Weight from previous visit may be used for calculating dose. Weight must be collected predose. The patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient should be observed for 1 hour following completion of dosing for observation and completion of assessments.

Detailed instructions for study drug preparation and administration can be found in the Pharmacy Manual.

Missed Doses of patisiran

If a patient does not receive a dose of patisiran within the dosing window (±3 days) due to the COVID-19 pandemic, the dose may be administered with up to 7 days delay after the scheduled visit, after consultation with the Medical Monitor (to be considered a delayed dose). If a dose is administered with a delay, the next dose will resume following the original schedule per the

Schedule of Assessments. In all cases, the dose should be administered as close as possible to the scheduled time point. If a dose is delayed, all assessments associated with the originally scheduled dose may also be delayed to coincide with the delayed dose.

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses for reasons unrelated to the COVID-19 pandemic, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study.

5.2.2.3. Switching from Patisiran to ALN-TTRSC02 After Month 18

After the Treatment Period, patients in the patisiran arm will switch to ALN-TTRSC02 treatment [redacted]

Patients who enter the Legacy Treatment Extension Period [redacted] (as of Amendment 4) will receive the 25 mg q3M dose and complete visits in the Legacy Treatment Extension Period. [redacted] If a patient receiving patisiran is unable to complete the Month 18 efficacy visit at the study center due to the COVID-19 pandemic before Week 84 [redacted] they may transition to treatment with ALN-TTRSC02 at Week 84 [redacted]; the patient should still complete the Month 18 efficacy assessment as soon as possible (see also Section 3.1).

5.2.3. LFT Criteria for Withholding, Monitoring and Stopping ALN-TTRSC02 Dosing

1. For the ALN-TTRSC02 cohort, dosing decisions may be made based on LFT results (Table 8) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory collection is not possible, then a local laboratory may be used. These local laboratory results must be sent to the site for review by the Investigator and entry into the clinical database.
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 7.
3. For any ALT or AST elevation >3× ULN:
    a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days. If a central laboratory result is not possible due to the COVID-19 pandemic, a local laboratory may be used for monitoring in consultation with the Medical Monitor; all local laboratory results must be sent to the clinical site for entry into the clinical database.
    b. Perform assessments per Table 7 and Table 9.

c. If an alternative cause is found, provide appropriate care.

4. For any ALT or AST elevation >3× ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 7 (below).

Table 7: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action
>3× to 5× ULN	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 9 (all assessments to be performed once) – Hematology, serum chemistry, LFT and coagulation per Table 8 • Monitor at least every two weeks (LFT and coagulation per Table 8) • If elevation persists for ≥2 months, must discuss with the medical monitor before continuing dosing
>5× to 8× ULN	• Hold ALN-TTRSC02 dosing until recovery to ≤1.5× ULN; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments: – Table 9 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 8 • Monitor at least weekly (LFT and coagulation per Table 8) until ALT and/or AST is declining on two consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing
>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value at the central laboratory

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center**,** or the home healthcare professional, will be responsible for preparation of ALN-TTRSC02 and patisiran doses, according to procedures detailed in the Pharmacy Manual. In cases where ALN-TTRSC02 is administered outside the study center, dosing may be prepared by the home healthcare professional or patient/caregiver (patient/caregiver is applicable to only the 25 mg q3M dose) according to procedures detailed in

the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 5±3°C until dose preparation.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage and preparation details will be provided in the Pharmacy Manual and Patient/Caregiver Storage and Administration Instructions.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Product Complaints

5.3.1. Definition

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product and its packaging after it is released for distribution.

A PC may be detected prior to use of study drug, during use, or after use. A PC is typically non-medical in nature; however, it is possible that complaints could be associated with an AE. Examples of a PC include, but are not limited to: illegible label, missing label, damaged vial/syringe, empty vial/syringe, contamination of product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For PCs, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. PCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.7. Detailed instructions on reporting PCs will also be detailed in the Pharmacy Manual.

In situations where a dose is being administered by a patient or caregiver, instructions to report to the study site any issues that could fall under a PC are outlined in the Patient/Caregiver Storage and Administration Instructions. The study site should then notify the Sponsor or designee within 24 hours of being informed per above instructions.

5.4. Concomitant Medications

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 to Table 4). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use NSAIDs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins (including vitamin A supplementation) and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Prohibited medications during the study include inotersen, tafamidis, diflunisal, and doxycycline/TUDCA (see Section 4.2 for prior medication washout requirements before first dose of study drug). Use of patisiran outside of the protocol specified administration is also prohibited. Any investigational agent other than ALN-TTRSC02 is not permitted during the study.

For other permitted concomitant medications administered subcutaneously, do not administer in same injection site area as the study drug, for 2 weeks after the last dose of study drug.

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

If available, information from a cardiac technetium scan and/or any tissue biopsy used to support the diagnosis of hATTR amyloidosis performed prior to study enrollment or during the study (as part of standard of care) should be collected and recorded as part of concomitant procedure information.

5.5. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.6. Other Requirements

5.6.1. Contraception

Females of child-bearing potential must be willing to use acceptable methods of contraception from 14 days before first ALN-TTRSC02 dose, throughout study participation, and for 90 days after last dose administration.

Females of child-bearing potential taking patisiran must use acceptable methods of contraception prior to dosing and for 12 weeks after the last dose of patisiran in this study if they do not switch and continue treatment with ALN-TTRSC02 starting at Day 337 (Week 48).

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- 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).
- Established use of oral (except for low dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods, if they start heterosexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, contraception use by males should be consistent with local regulations as described in the corresponding patient informed consent forms.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.6.2).

5.6.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1 (Screening through Treatment Period Month 9), Table 2 (Treatment Period from Month 9 through Month 18), Table 3 (Legacy Treatment Extension Period, Early Drug Discontinuation, and Other Visits), Table 4 (Randomized Treatment Extension Period), Table 5 (ALN-TTRSC02 PK Time Points) and Table 6 (Patisiran PK Time Points). Additional information on the collection of study assessments will be detailed in the Study Reference Manual. In this study there are 2 types of study centers:

- Patient Care Sites (PCS) can screen, dose, and manage the well-being of patients and collect safety assessments, and can administer efficacy assessments that include, but are not limited to, completion of a questionnaire or collection of blood samples for assessment of TTR and other PD biomarkers, as well as cardiac biomarkers, but will not perform the following efficacy assessments: NIS, mNIS+7, HRdb, 10-MWT, FAP and PND, KPS, echocardiogram.
- Central Assessment Sites (CAS) can perform all efficacy assessments and perform the same assessments as at a PCS (as stated above). Efficacy assessments (NIS, mNIS+7, HRdb, 10-MWT, FAP and PND, KPS, echocardiogram) in this study may require special training as described further in Section 6.2; therefore, all patients must be sent to a CAS to collect these efficacy assessments during screening and predose baseline assessments, Month 9 and Month 18 of the Treatment Period and the RTE Period, and modified efficacy visits for patients who discontinue early during the Treatment Period.

Where applicable country and local regulations and infrastructure allow, routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include the following: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory assessments are not possible, then a local laboratory may be used. These local lab results must be sent to the site for review by the Investigator and entry into the clinical database. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient.

With the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center, at a minimum, patients must visit the site for scheduled dosing and assessments at the Treatment Period Week 12 and Week 60 visits within the study visit windows and for efficacy assessments as detailed below.

If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must, at a minimum, verbally contact the patient within the expected window for each study visit to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

All efficacy visits must be conducted at the clinic (Month 9, Month 18, [redacted], and modified efficacy visits for those who discontinue early during the Treatment Period). In situations in which an efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to receive their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the efficacy assessment. After consultation with the Medical Monitor, efficacy assessments may be completed within 6 months after the intended time point (ie, up to Month 15 or Month 24) during [redacted] the Treatment Period [redacted] as necessary.

Further details regarding visits performed outside of the clinic are provided in the Study Reference Manual.

6.1. Screening Assessments

See Table 1 for a list of Screening visit assessments.

An informed consent form (ICF) or assent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated (Table 1) and before any procedures are performed in the RTE Period (Table 4). All patients (or their legal guardians) will be given a copy of the signed and dated ICF and/or assent form.

In addition of the ICF, patients will be asked to sign a Medical Records Release Form (where allowed by local regulations) at Screening for the purpose of obtaining information on vital status, cardiac transplant procedures, left-ventricular assist device placement (Section 6.2.8), and hospitalizations (Section 6.2.7) from patients for the duration of the study. This information will be obtained by the patient's physician through contacting the patient or family or from death registries.

Signing the Medical Records Release Form will be optional and will apply if the patient discontinues from the study early. Every effort should be made to collect the Medical Records Release Form from all patients enrolled in the study. Also see Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

Patients will complete the following 3 visit types prior to randomization for the Treatment Period: the ICF and Medical Records Release Form will be obtained at the Visit 1 (Screening), and all inclusion/exclusion criteria will be assessed except for the NIS and PND score criteria; see Section 4.1); the NIS and PND score inclusion criteria will be assessed at Visit 2 (Baseline first assessment); other baseline assessments will be completed at Visit 3 or at Day 1 prior to first dose. Visits 1, 2 and 3 may each occur over multiple days.

6.1.1. Retesting

If screening laboratory abnormalities, in the Investigator's judgement, are felt likely to be transient, then the laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility and randomized within the allowed Screening period. Qualifying LFTs (AST, ALT and bilirubin) are an exception to this rule and may not be repeated.

6.1.2. Rescreening

For patients who do not meet all study eligibility requirements, due to a transient clinical condition during screening or who fail to complete screening activities due to unforeseen and unavoidable circumstances, rescreening once may be permitted after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment. In this case, a patient will be re-consented and all screening procedures must be repeated.

6.1.3. Demographic and Medical History/Disease History

Medical history will be collected during screening Visit 1 (including any cardiac disorders, any eye disorders or previous ophthalmology test results, and prior medications). Documented technetium scintigraphy and/or tissue biopsy testing for amyloidosis performed prior to study enrollment should be collected and recorded as part of medical history. Information on prior use of tetramer stabilizers at any time prior to first dose should be collected and recorded. Information on other prior medications, hospitalization, and procedures through 1 year prior to first dose should be collected and recorded.

At screening Visit 2 and Visit 3, only additional medical history changes since Visit 1 will be collected.

Also, technetium scintigraphy scans and/or tissue biopsy testing for amyloidosis performed as part of clinical care during the study should be collected and recorded as part of concomitant procedure information.

6.2. Efficacy Assessments

See the beginning of Section 6 for procedures to follow in situations in which an efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center.

6.2.1. Neurologic Impairment Assessments

6.2.1.1. Modified Neurological Impairment Score +7 (mNIS+7)

The mNIS+7 assessment tool is a 304-point composite measure of neurologic impairment which includes the following measures and components [Suanprasert 2014]:

- Physical exam of lower limbs, upper limbs and cranial nerves to assess motor strength/weakness and determine the following component scores:
  - NIS-weakness (NIS-W)
  - NIS-reflexes (NIS-R)
- Electrophysiologic measures of small and large nerve fiber function to determine the Σ5 NCS component score that includes assessment of the ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, peroneal CMAP
- Sensory testing to determine the quantitative sensory testing (QST) score included assessing touch pressure by body surface area (QST-BSATP) and heat pain by body

surface area (QST-BSAHP). A Computer Aided Sensory Evaluator (CASE) IV device will be used for this assessment.

- Postural blood pressure will be measured to assess autonomic function as described in the Study Manual. Points are assigned based on the change in blood pressure with standing.

A summary of the scoring of the components of the mNIS+7 is provided in Section 10.1.

6.2.1.2. Neurologic Impairment Score (NIS)

The NIS assessment is a 244-point composite measure of neurologic impairment which includes a physical exam of lower limbs, upper limbs and cranial nerves to assess motor strength/weakness and determine the following component scores:

- NIS-W
- NIS-R
- NIS-sensation (NIS-S)

6.2.1.3. Personnel and Procedures to Ensure Quality and Consistency of NIS and mNIS+7 Scoring

The NIS and mNIS+7 will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The NIS-W and NIS-R assessments obtained for NIS calculation do not need to be repeated for the mNIS+7 calculation.

As per the Schedule of Assessments for the 18-month Treatment Period, 2 independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have these assessments performed by the same assessor. [redacted]

NIS and QST assessments will be performed by certified staff trained on the use of the CASE IV device. NCS studies will be performed by trained staff.

Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

All site staff performing the mNIS+7 will be trained and certified by the peripheral neuropathy laboratory at the [redacted], USA. The peripheral neuropathy laboratory at the [redacted] also serves as the central laboratory that will assess the mNIS+7 score. All data will be transmitted to the [redacted] where qualified personnel will assess the quality and acceptability of all test scores. The peripheral neuropathy laboratory at the [redacted] can request a site to repeat testing of mNIS+7 components per the [redacted] Standard Operating Procedures (SOP) if the quality was not acceptable at any time point.

Data acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

6.2.2. Heart Rate Response to Deep Breathing (HRdb)

The HRdb test evaluates small nerve fiber autonomic function by the cardio-vagal response. This assessment will be performed by a certified trained staff during the Treatment Period at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). The average heart rate difference while taking eight deep breaths will be measured using a CASE IV device.

As per the Schedule of Assessments, 2 independent assessments will be performed on separate days (1 assessment on each day); the 2 assessments should be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have this assessment performed by the same assessor.

6.2.3. Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that assesses 5 domains: physical function, large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. The total score ranges from -4 (best possible quality of life) to 136 points (worst possible quality of life) [Vinik 2005; Vinik 2014].

The Norfolk QoL-DN questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4).

6.2.4. Ten-meter Walk Test (10-MWT)

The time it takes for a patient to walk 10 meters (gait speed) will be assessed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The 10-MWT will be performed and recorded following procedures outlined in the Study Reference Manual. The test must be completed without assistance from another person; ambulatory aids such as canes and walkers are permitted.

As per the Schedule of Assessments for the 18-month Treatment Period, 2 independent assessments are to be performed approximately 24 hours apart from each other but not more than 7 days apart. Each site should make every effort to have this assessment performed by the same assessor. [redacted]

6.2.5. Modified Body Mass Index (mBMI)

The nutritional status of patients is evaluated using the mBMI; calculated as the product of body mass index (BMI) (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

Weight, height, and serum albumin (collected as part of the serum chemistry panel) will be collected at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The site will not perform the calculation for mBMI.

6.2.6. Rasch-built Overall Disability Scale (R-ODS)

An assessment of the disability each patient experiences will be assessed through the R-ODS questionnaire at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4).

The R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

6.2.7. Deaths and Hospitalizations

All deaths and hospitalizations will be recorded at Day 1 post dose and throughout the study as specified as part of adverse events (AEs) monitoring (see Section 6.5.7) according to the Schedule of Assessments (Table 1 to Table 4).

Reason for deaths will be adjudicated by an Independent Clinical Adjudication Committee (see Section 3.8).

6.2.8. Vital Status Check

Vital status checks will be performed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). Vital status checks should include checking for the occurrence of heart transplantation or left-ventricular assist device implantation procedures.

Also see Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

6.2.9. European Quality of Life-5 Dimensions 5-Levels (EQ-5D-5L) and EQ-Visual Analog Scale (EQ-VAS)

The EQ-5D index score is based on the response to questions evaluating 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Each dimension scored is based on 5 possible levels where level 1 reflects the best possible score for that dimension. As an example, the 5 levels for the dimension of self-care include: level 1: no problems with washing or dressing self, level 2: slight problems, level 3: moderate problems, level 4: severe problems, level 5: unable. The EQ-5D index score is derived based on scores from all 5 dimensions; score range is from 0 (worst QoL) to 1 (best QoL).

The EQ-VAS is a single question evaluating the patient's own global impression of their overall health and is evaluated on a scale of 0 (worst possible health) to 100 (best possible health).

The EQ-5D-5L and EQ-VAS questionnaire will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4).

6.2.10. PND Score and FAP Stage

Ambulation and changes in disease stage will be evaluated through physician assessment of PND score and FAP stage [Coutinho 1980; Yamamoto 2007].

PND and FAP will be completed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4).

PND scoring and FAP stages are described in Section 10.2.

6.2.11. Cardiac Assessments

Manifestations of cardiac amyloid involvement will be assessed through echocardiogram, as well as measurement of serum levels of the cardiac biomarkers NT-proBNP and troponin T and troponin I. The impact of heart failure on quality of life will also be assessed as described below.

Certified technicians will be required to administer cardiac imaging assessments as specified in the Study Reference Manual.

6.2.11.1. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Echocardiograms will be performed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4), and analyzed at a central cardiac imaging core lab.

Image acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

6.2.11.2. Cardiac Biomarkers

Cardiac biomarkers, including NT-proBNP, troponin T and troponin I, will be used to assess cardiac stress and heart failure severity. These biomarkers have also been shown to be prognostic of outcomes in heart failure including ATTR amyloidosis [Damy 2016; Kristen 2017; Merlini 2016]. Blood samples will be drawn to measure levels of NT-proBNP, troponin T and troponin I at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4).

At Screening Visit 1, only NT-proBNP will be assessed for eligibility purposes. Baseline cardiac biomarkers (NT-proBNP, troponin T, and troponin I) will be assessed at Screening Visit 3.

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

6.2.11.3. Technetium Scintigraphy Imaging

At select sites, technetium scintigraphy will be collected according to the Schedule of Assessments (Table 1 to Table 4), as an exploratory imaging parameter to assess cardiac amyloid involvement. Based on local practice standards, either ^{99}Tc-Pyrophosphate (^{99}Tc-PYP), ^{99}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99}Tc-DPD) or ^{99}Tc-hydroxymethylene diphosphonate (^{99}Tc-HMDP) can be used as the tracer. Technetium scintigraphy images will be interpreted at a central imaging core laboratory. Image acquisition, storage, and transfer guidelines will be provided in the Study Reference Manual.

At the select sites where technetium scintigraphy is being performed, patients may be exempt from baseline technetium scintigraphy assessment if a technetium scintigraphy has been performed prior to study entry as part of the patient clinical care within 6 months prior to the baseline assessment. In such cases, where possible, the historical technetium scintigraphy exam performed prior to study entry as part of the patient's clinical care should be collected and transferred to the central imaging core laboratory for interpretation.

6.2.11.4. New York Heart Association (NYHA) Class

NYHA class is a clinical assessment of symptoms resulting from heart failure and is assessed according to the table in Section 10.3. NYHA class will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The score collected at Screening will be used to determine eligibility and will also be collected on a regular basis during the study.

6.2.12. Karnofsky Performance Status (KPS)

The Karnofsky Performance Status (KPS) assessed according to Section 10.4 will be evaluated at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The score collected at Screening will be used to determine eligibility.

6.3. Pharmacodynamic Assessments

In this study serum TTR and vitamin A levels will be collected as measurements of PD effect. These measurements will be collected and analyzed centrally as specified in the Study Laboratory Manual.

Blood samples will be collected prior to dosing for the assessment of TTR and vitamin A levels according to the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). TTR levels will be determined by a validated enzyme-linked immunoassay (ELISA) assay.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of plasma ALN-TTRSC02 and patisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples for PK analysis at the timepoints specified in the Schedule of Assessments (Table 5 for ALN-TTRSC02 and Table 6 for patisiran).

Plasma concentration of ALN-TTRSC02 and patisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Study Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication and measurements of vital signs, weight and height, physical examination, ECG findings and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by the Sponsor's Medical Monitors and Medical Monitors at the designated contract research organization in addition to an independent DMC as described in Section 3.7.

Routine safety assessments and collection of relevant safety information may be collected outside of the study center where applicable country and local regulations and infrastructure allow (as described at the beginning of Section 6).

6.5.1. Vital Signs

Vital signs will be measured as specified at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4), and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured predose in the seated or supine position, after the patient has rested comfortably for 10 minutes. Blood pressure should be taken using the same arm during a single visit. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medially indicated, may be added at the discretion of the Investigator, or as per DMC advice (as applicable).

Vital signs results will be recorded in the eCRF.

6.5.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected at the timepoints specified in in the Schedule of Assessments (Table 1 to Table 4) and will be recorded in the eCRF.

For patients on the patisiran arm, weight must be collected prior to each dose.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1 to Table 4); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. In situations where the patient has a home visit, symptom-directed physical examinations may be deferred until the next in-clinic visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

A 12-lead ECG reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval will be obtained locally as specified in the Schedule of Assessments (Table 1 to Table 4).

Triplicate readings should be performed at Baseline and thereafter single readings can be performed.

If the investigator performs an ECG over-read per standard of care, over-reads should be conducted on each individual ECG performed.

Patients should be supine for at least 5 minutes before each ECG is obtained.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs, including those collected by a healthcare professional outside of the study center, to assess whether the results have changed since baseline and to determine the clinical significance of the results. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

ECG recordings will be archived according to the Study Reference Manual.

6.5.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia–Suicide Severity Rating Scale (C-SSRS) will be used to assess patient's mental status as it relates to suicidal ideation and behavior. This questionnaire will be administered to the patient by trained and certified study personnel. The C-SSRS will be performed as specified in the Schedule of Assessments (Table 1 to Table 4).

6.5.6. Clinical Laboratory Assessments

Clinical laboratory assessments are listed in Table 8 will be collected as specified in the Schedule of Assessments (Table 1 to Table 4) and should be evaluated by a central laboratory. Clinical laboratory assessments may be collected at the clinical study center or outside the clinic (eg, the patient's home) by a trained healthcare professional within the study visit window as described at the beginning of Section 6**.**

For the ALN-TTRSC02 arm, ALN-TTRSC02 dosing decisions may be made based on LFT results (Table 8) collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used. Specific instructions for transaminase elevations are provided in Section 5.2.3.

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the assessments, all laboratory assessments specified in Table 8 which are performed at the clinic or outside the study center (eg, the patient's home) should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions. The only exception for central laboratory testing is related to the COVID-19 pandemic as described in the beginning of Section 6.

For the patisiran arm, LFTs should be performed according to patisiran visit windows and do not need to be available prior to dosing.

For any other 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, or as per the Medical Monitor or DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 8: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the MDRD formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
B12 vitamin (at Screening only)	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Immunogenicity (see Section 6.5.6.1)	
Antidrug Antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.6.2**)**	
β-human chorionic gonadotropin	

Follicle stimulating hormone (FSH) (Only if applicable, to confirm postmenopausal status prior to dosing)	
Hepatitis Tests (only at Screening)	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid MDRD=modification of diet in renal disease; WOCBP=women of child bearing potential.

6.5.6.1. Immunogenicity

Blood samples for anti-drug antibody (ADA) testing will be collected at the timepoints specified in Table 1 to Table 4. On dosing days, ADA sample collection is within 1 hour before dosing.

ADA will be assessed using a validated ELISA method. For the patisiran arm, ADA defined as serum immunoglobulin (Ig) G (IgG)/IgM antibodies specific to the PEG_{2000}-C-DMG component will be assessed.

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

6.5.6.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential at the timepoints specified in Table 1 to Table 4.

A serum pregnancy test will be performed at Screening and urine or serum pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1 to Table 4) and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. More frequent pregnancy testing can be conducted according to country-specific regulations. In Brazil, pregnancy testing should be performed prior to each dose.

Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.5.7.7 for follow-up instructions).

In situations where a study visit is unable to be completed at the site due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, pregnancy testing may be performed by a healthcare professional or the patient/caregiver (and confirmed by the site) where applicable country and local regulations and infrastructure allow.

Follicle-stimulating hormone testing will be performed in all post-menopausal women to confirm suspected post-menopausal status.

6.5.6.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.3. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 9 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 8, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring and dose modification will also be performed as outlined in Section 5.2.3.

Table 9: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBs Ag, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA= soluble liver antigen
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.7. Adverse Events

6.5.7.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

A serious adverse event (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 anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse)

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN)
- Severe or serious injection site reactions (ISRs), ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), recurrent ISRs that are increasing in severity, or ISRs that lead to temporary dose interruption or permanent discontinuation of ALN-TTRSC02
- An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR

For information on recording and reporting of AEs of clinical interest, see Section 6.5.7.2 and Section 6.5.7.3, respectively.

Adverse Event Severity

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

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

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).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, 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.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study.

Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1.3), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

For patients who discontinue study drug early and remain in the study, all AEs will be collected for 90 days after the last dose, thereafter, SAEs and AEs of clinical interest (see definition in Section 6.5.7.1) will be collected for the remainder of their participation in the study.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.7.1), the Sponsor or its designee should complete the supplemental AEs of Clinical Interest eCRF. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc.).

If patients develop ocular symptoms suggestive of vitamin A deficiency, for example reduced night vision or night blindness, the Investigator should consult with the Medical Monitor to determine if an ophthalmological assessment is needed. Any information collected during an ophthalmological assessment should be recorded in the eCRF and reports or images of ophthalmological assessments should be collected as well.

6.5.7.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.7.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.5.7.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.7.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. SAEs must be reported using the contact information provided in the Study Reference Manual.

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

6.5.7.5. Sponsor Safety Reporting to Regulatory Authorities

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

6.5.7.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) 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.

6.5.7.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, or through their last visit in the study (whichever is later), the Investigator must report the pregnancy to the Sponsor or designee 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, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug.

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 results in a 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 6.5.7.4.

6.5.7.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. When an overdose is suspected, the Investigator should inform the Medical Monitor.

6.5.8. COVID-19 Data Collection

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hATTR amyloidosis, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/EC) approval, and patient consent (and assent, where applicable), samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of ALN-TTRSC02 and patisiran.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 through Table 6). Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

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

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

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

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

6.7. Pharmacoeconomic Assessments

6.7.1. Patient and Caregiver Impact Survey

To complement medical records, information about how hATTR amyloidosis impacts the lives of patients and their caregivers will be collected at the timepoints specified in the Schedule of Assessments (Table 1 to Table 4). The Patient and Caregiver Impact Survey includes questions related to how hATTR amyloidosis affects patients, including their symptoms at the time of diagnosis, utilization of various healthcare providers, employment status, and need for government compensation/assistance. Questions will also be asked about how hATTR amyloidosis impacts the employment status of the patient's caregiver and patients' need for both informal and professional caregivers.

6.7.2. Hospitalization, Urgent Healthcare Visits, Surgeries, and Procedures

Hospitalization, urgent healthcare visits, surgeries, and procedure information will be collected on a separate eCRF for pharmacoeconomic evaluations, as specified in the Schedule of Assessments (Table 1 to Table 4). As described in the beginning Section 6, in situations where a study visit is unable to be completed at the study center, the study physician (or delegate) may verbally contact the patient within the expected study visit window to assess hospitalizations, urgent healthcare visits, surgeries, and procedures.

Prior hospitalization, urgent healthcare visits, surgeries, and procedure information through 12 months prior to first dose should be collected at Screening.

6.7.3. Patient Experience Survey

The Patient Experience Survey will be administered to understand patients' level of satisfaction with their current hATTR amyloidosis therapy and their level of comfort using this therapy. This survey will be administered at the timepoints specified in the Schedule of Assessments (Table 1, Table 2, and Table 4).

6.7.4. Patient Preference Survey

[redacted] The survey aims to understand patients' preferred method of treatment administration and the primary reasons for their preference. This survey will be administered at the timepoints specified in the Schedule of Assessments (Table 4).

7. STATISTICS

The principal features of the planned analysis are presented in this section. A separate SAP will be finalized prior to first patient dosed. The SAP will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

Approximately 160 patients will be enrolled in this study, with a 3:1 randomization ratio to either ALN-TTRSC02 or patisiran.

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of ALN-TTRSC02 in this patient population. For the primary efficacy endpoint of mNIS+7 and the key secondary endpoint of Norfolk QoL-DN total scores, the ALN-TTRSC02 arm in the Phase 3 study will be compared to the placebo arm from the APOLLO study. For the mNIS+7 change from baseline at 9 months, the observed mean (±standard deviation [SD]) was 15 ± 17 points for the placebo arm from the APOLLO study. Assuming a mean change of 0 points for the ALN-TTRSC02 arm, there is >90% power to establish the superiority over placebo using a 2-sided t-test with a significance level of 0.05. For the Norfolk-QoL DN total score change from baseline at 9 months, the observed mean (±SD) was 11.5 ± 19.2 points for the placebo arm from the APOLLO study. Assuming a mean change of -4 points for the ALN-TTRSC02 arm, there is >90% power to establish the superiority over placebo using a 2-sided t-test with a significance level of 0.05.

For safety, a sample size of >100 patients on ALN-TTRSC02 can provide reasonable assurance that the true cumulative one-year incidence of adverse drug events (ADE) is no greater than 3% when no ADE is observed.

To match the cardiac disease severity with the APOLLO study population, the study plans to enroll no more than 15% of patients with NT-proBNP values greater than 3000 ng/L.

7.2. Statistical Methodology

Additional data summaries to help understand any impact of the COVID-19 pandemic and any descriptive comparison of [redacted] on efficacy, PD and safety assessments will be outlined in the SAP.

7.2.1. Populations to be Analyzed

The population analysis sets are defined as follows:

- Modified ITT (mITT) population: All randomized patients who received any amount of study drug. Patients will be grouped by their randomized treatment group.
- TTR Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment associated with adequate treatment compliance between Month 6 and Month 18. Specific details will be provided in the SAP.
- Safety Population: All randomized patients who received any amount of study drug, grouped according to the treatment actually received.
- PK Population: All randomized patients who received any amount of study drug and have at least 1 post dose blood sample for PK parameters and have evaluable PK data.
- Patients with cardiac involvement: All patients in the mITT population who had pre-existing evidence of cardiac amyloid involvement. Specific details will be provided in the SAP.

The primary population for efficacy analysis will be the mITT population, except TTR percent reduction analysis, which will be conducted in the TTR PP population. Safety analysis will be conducted in the safety population. PK analysis will be conducted in the PK population. Selected endpoints will be analyzed in the cardiac subpopulation.

7.2.2. Examination of Subgroups

Subgroup analyses will be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

For efficacy assessments, if the scheduled visits (eg, 9-month) are not performed, the unscheduled and/or discontinuation visits performed within a 3-month window will be grouped with the scheduled assessments. For patients impacted by the COVID-19 pandemic, efficacy visits delayed up to 6 months will be included in the analysis.

Sensitivity analyses for the primary efficacy endpoint of mNIS+7 and the key secondary endpoint of Norfolk QoL-DN total scores, including different methods for handling of the missing data, will be conducted to assess the robustness of the primary analysis results.

More details of missing data handling will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively.

7.2.5. Efficacy Analyses

This Phase 3 study will use the placebo arm of the APOLLO study as an external control. Patient-level data from this study will be compared with patient-level data from APOLLO for efficacy analyses. For the primary and secondary clinical efficacy endpoints, the ALN-TTRSC02 arm in this study will be compared to the placebo arm from the APOLLO study. For the secondary endpoint of TTR percent reduction, the ALN-TTRSC02 arm in this study will be compared to the patisiran arm in this study. The treatment comparison will be conducted at Month 9 and/or Month 18. The efficacy endpoints beyond 18 months will be summarized descriptively.

The patisiran arm in this study will mainly serve as a reference arm. For the clinical efficacy endpoints at Month 9 and Month 18, the patisiran arm will be summarized descriptively and the treatment difference between ALN-TTRSC02 and patisiran arm in this study will not be tested.

[redacted]

7.2.5.1. Primary Endpoint

The primary endpoint mNIS+7 will compare change in mNIS+7 from baseline at Month 9 between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study. The treatment effect will be estimated based on the least squares (LS) means using an analysis of

covariance (ANCOVA) model with baseline mNIS+7 score as a covariate and factors including treatment group (ALN-TTRSC02 vs placebo), genotype (V30M vs non-V30M) and age of disease onset (<50 vs ≥50 years old). The primary endpoint will be tested at a significance level of 0.05 and must be significant to declare a positive trial.

Primary endpoint data that are missing will be multiply imputed separately for each treatment group using a regression procedure based on baseline covariates. The details will be specified in the SAP.

The mNIS+7 score for the patisiran group in this study will be summarized descriptively.

7.2.5.2. Secondary Endpoints

For the secondary clinical efficacy endpoints, the treatment comparison will be made between the ALN-TTRSC02 group in this study and the placebo group in the APOLLO study at Month 9 or Month 18 as specified. For the TTR percent reduction endpoint, the ALN-TTRSC02 group will be compared with the patisiran group in this study. To control the overall type I error, the secondary endpoints will be tested in the following hierarchical order:

- Norfolk QoL-DN total score change from baseline at Month 9
- 10-MWT gait speed change from baseline at Month 9
- mNIS+7 change from baseline at Month 18
- Norfolk QoL-DN total score change from baseline at Month 18
- 10-MWT gait speed change from baseline at Month 18
- mBMI (BMI [kg/m^2] multiplied by serum albumin level [g/L]) change from baseline at Month 18
- R-ODS change from baseline at Month 18
- TTR percent reduction through 18 months

For change in Norfolk QoL-DN total score and 10-MWT gait speed from baseline at Month 9, the analysis will be based on an ANCOVA model similar to the model described for the analysis of change in mNIS+7 from baseline at Month 9, while adjusting for baseline value of the endpoint being modeled and including baseline NIS score (<50 vs ≥50) as an additional factor in the model. For these 2 endpoints, data that are missing will be multiply imputed separately for each treatment group using a regression procedure based on baseline covariates. The details will be specified in the SAP.

For change from baseline at Month 18 analyses, the analysis will be based on a mixed-effects model for repeated measures (MMRM), adjusting for a covariate (baseline value for the endpoint being modeled), categorical factors (treatment group, visit [Month 9 vs Month 18], genotype, age of disease onset, baseline NIS score), and an interaction term (treatment group by visit). For mNIS+7, baseline NIS score will not be included in the model.

In the APOLLO study, mBMI was not assessed at Month 9 or Month 18. The average values of Day 189 and Day 357 will be derived as Month 9, and the Day 546 value will be substituted as Month 18.

The TTR percent reduction through Month 18 will be derived as the average trough TTR percent reduction from Month 6 to 18 which is the steady state period for both ALN-TTRSC02 and patisiran. A Hodges-Lehmann method stratified by previous TTR stabilizer use (yes vs no) will be used to estimate the 95% CI for the median difference between the ALN-TTRSC02 and patisiran groups in this study. Non-inferiority will be declared if the lower limit of the 95% CI for the treatment difference is greater than –10%. A sensitivity analysis will be conducted to compare the TTR percent reduction between the ALN-TTRSC02 group from this study and the pooled patisiran groups from this Phase 3 study and the APOLLO study.

7.2.5.3. Exploratory Endpoints

Analysis of exploratory efficacy endpoints will be detailed in the SAP.

7.2.6. Pharmacodynamic Analysis

Summary tables and graphical displays of observed values, changes and percentage changes from baseline in PD biomarkers (TTR and vitamin A) will be presented.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted for ALN-TTRSC02 and patisiran using non-compartmental method. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

Population pharmacokinetic analysis will be performed to describe the plasma pharmacokinetics using Phoenix NLME (Version 1.1 or later) or a similar software, such as NONMEM. The impact of relevant covariates, such as, weight, sex, race, age, renal function, and hepatic function on plasma PK will be evaluated. Summary tables and figures and inferential statistics will be generated.

7.2.8. Safety Analyses

A summary of study drug exposure, including the durations of exposure and the proportions of patients with dose modifications will be produced.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System (ATC) and Preferred Term.

Adverse events will be summarized by MedDRA system organ class and preferred term. The number and percentage of patients experiencing AEs after the first dose of the study drug will be summarized. Separate tabulations will be produced for treatment-related AEs, 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, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time

Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

Incidence of ADA and titers will be summarized descriptively.

7.2.10. Other Analyses

Not applicable.

7.2.11. Interim Analysis

No interim analysis is planned.

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP 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.

8.1.1. Informed Consent and Medical Records Release Form

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

In addition of the ICF, patients will be asked to sign a Medical Records Release Form (where allowed by local regulations) at Screening for the purpose of obtaining information on vital status, cardiac transplant procedures, left-ventricular assist device placement (Section 6.2.8), and hospitalizations (Section 6.2.7) from patients for the duration of the study. This information will be obtained by the patient's physician through contacting the patient or family or from death registries.

Signing the Medical Records Release Form will be optional and will apply if the patient discontinues from the study early. The form should be checked at the Early Treatment

Discontinuation Visit and a new form will be signed if the information needs updating. Every effort should be made to collect the Medical Records Release Form from all patients enrolled in the study.

8.1.2. Ethical Review

The study protocol, including the ICF (assent form, if applicable), must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

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

The Investigator will submit reports of SAEs as outlined in Section 6.5.7. In addition, the Investigator agrees to submit progress reports to the 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.

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

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

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

8.1.3. Serious Breach of Protocol

Investigators must notify the medical monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to

review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. 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 Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

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.

To comply with local and/or regional regulations, this clinical study may be registered and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

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, IRB/IEC 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.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site

personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The monitor will visit the Investigator and clinical study center periodically and will 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.

The monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed/received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Adams D, Coelho T, Obici L, Merlini G, Mincheva Z, Suanprasert N, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology. 2015 Aug 25;85(8):675-82.

Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):11-21.

Adams D, Suhr OB, Dyck PJ, Litchy WJ, Leahy RG, Chen J, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017 Sep 11;17(1):181.

Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013 Feb 20;8:31.

Ashwell G,Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Adv Enzymol Relat Areas Mol Biol. 1974;41(0):99-128.

Baenziger JU,Fiete D. Galactose and N-acetylgalactosamine-specific endocytosis of glycopeptides by isolated rat hepatocytes. Cell. 1980 Nov;22(2 Pt 2):611-20.

Barroso FA, Judge DP, Ebede B, Li H, Stewart M, Amass L, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017 Sep;24(3):194-204.

Benson MD,Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007 Oct;36(4):411-23.

Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013 Dec 25;310(24):2658-67.

Brodsky RA, Young NS, Antonioli E, Risitano AM, Schrezenmeier H, Schubert J, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008 Feb 15;111(4):1840-7.

Bumcrot D, Manoharan M, Koteliansky V,Sah DW. RNAi therapeutics: a potential new class of pharmaceutical drugs. Nat Chem Biol. 2006 Dec;2(12):711-9.

Carvalho A, Rocha A,Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. Liver Transpl. 2015 Mar;21(3):282-92.

Carvalho M, Alves M,Luis ML. Octreotide--a new treatment for diarrhoea in familial amyloidotic polyneuropathy. J Neurol Neurosurg Psychiatry. 1992 Sep;55(9):860-1.

Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Plante-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012 Aug 21;79(8):785-92.

Connors LH, Lim A, Prokaeva T, Roskens VA,Costello CE. Tabulation of human transthyretin (TTR) variants, 2003. Amyloid. 2003 Sep;10(3):160-84.

Connors LH, Yamashita T, Yazaki M, Skinner M,Benson MD. A rare transthyretin mutation (Asp18Glu) associated with cardiomyopathy. Amyloid. 2004 Mar;11(1):61-6.

Coutinho P, DeSilva A, Lima J,Barbosa A. Forty years of experience with type I amyloid neuropathy: review of 483 cases. In: Glenner G,Pinho P,Costa E,Falcao de Frietas A, editors. Amyloid and Amyloidosis: Excerpta Medica. Amsterdam1980. p. 88-98.

Damy T, Jaccard A, Guellich A, Lavergne D, Galat A, Deux JF, et al. Identification of prognostic markers in transthyretin and AL cardiac amyloidosis. Amyloid. 2016 Sep;23(3):194-202.

Dyck PJ, Kincaid JC, Dyck PJB, Chaudhry V, Goyal NA, Alves C, et al. Assessing mNIS+7Ionis and international neurologists' proficiency in a familial amyloidotic polyneuropathy trial. Muscle Nerve. 2017 Nov;56(5):901-11.

Ericzon BG, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR, et al. Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative? Transplantation. 2015 Sep;99(9):1847-54.

Geffen I,Spiess M. Asialoglycoprotein receptor. Int Rev Cytol. 1992;137B:181-219.

Hou X, Aguilar MI,Small DH. Transthyretin and familial amyloidotic polyneuropathy. Recent progress in understanding the molecular mechanism of neurodegeneration. FEBS J. 2007 Apr;274(7):1637-50.

Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Buck FS, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. N Engl J Med. 1997 Feb 13;336(7):466-73.

Kristen AV, Maurer MS, Rapezzi C, Mundayat R, Suhr OB,Damy T. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). PLoS One. 2017;12(4):e0173086.

Liz MA, Mar FM, Franquinho F,Sousa MM. Aboard transthyretin: From transport to cleavage. IUBMB Life. 2010 Jun;62(6):429-35.

Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, et al. Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Circ Heart Fail. 2017 Jun;10(6).

Merlini G, Lousada I, Ando Y, Dispenzieri A, Gertz MA, Grogan M, et al. Rationale, application and clinical qualification for NT-proBNP as a surrogate end point in pivotal clinical trials in patients with AL amyloidosis. Leukemia. 2016 Oct;30(10):1979-86.

Nair JK, Willoughby JL, Chan A, Charisse K, Alam MR, Wang Q, et al. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. J Am Chem Soc. 2014 Dec 10;136(49):16958-61.

Okamoto S, Wixner J, Obayashi K, Ando Y, Ericzon BG, Friman S, et al. Liver transplantation for familial amyloidotic polyneuropathy: impact on Swedish patients' survival. Liver Transpl. 2009 Oct;15(10):1229-35.

Parman Y, Adams D, Obici L, Galan L, Guergueltcheva V, Suhr OB, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A

European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016 Feb;29 Suppl 1:S3-S13.

Plante-Bordeneuve V,Said G. Familial amyloid polyneuropathy. Lancet Neurol. 2011 Dec;10(12):1086-97.

Ruberg FL,Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012 Sep 04;126(10):1286-300.

Schwartz AL, Rup D,Lodish HF. Difficulties in the quantification of asialoglycoprotein receptors on the rat hepatocyte. J Biol Chem. 1980 Oct 10;255(19):9033-6.

Soares ML, Coelho T, Sousa A, Batalov S, Conceicao I, Sales-Luis ML, et al. Susceptibility and modifier genes in Portuguese transthyretin V30M amyloid polyneuropathy: complexity in a single-gene disease. Hum Mol Genet. 2005 Feb 15;14(4):543-53.

Solomon S, Adams D, Coelho T, Karsten V, Sweetser M, Chen J, et al., editors. APOLLO, a phase 3 study of patisiran for the treatment of hereditary transthyretin-mediated amyloidosis: 18-month safety and efficacy in subgroup of patients with cardiac involvement. 2018 XVIIth International Symposium of Amyloidosis; 2018; Kumamoto, Japan.

Suanprasert N, Berk JL, Benson MD, Dyck PJ, Klein CJ, Gollob JA, et al. Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials. J Neurol Sci. 2014 Sep 15;344(1-2):121-8.

Swiecicki PL, Zhen DB, Mauermann ML, Kyle RA, Zeldenrust SR, Grogan M, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 2015;22(2):123-31.

Vinik EJ, Hayes RP, Oglesby A, Bastyr E, Barlow P, Ford-Molvik SL, et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technol Ther. 2005 Jun;7(3):497-508.

Vinik EJ, Vinik AI, Paulson JF, Merkies IS, Packman J, Grogan DR, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2014 Jun;19(2):104-14.

Wang et al. Safety and Efficacy of Inotersen in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (NEURO-TTR). ANA abstract. 2017.

Yamamoto S, Wilczek H, Nowak G, Larsson M, Oksanen A, Iwata T, et al. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. Am J Transplant. 2007;7(11):2597-604.

Yazaki M, Tokuda T, Nakamura A, Higashikata T, Koyama J, Higuchi K, et al. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. Biochem Biophys Res Commun. 2000 Aug 11;274(3):702-6.

Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, et al. Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care. 2011 Sep;34(9):2054-60.

10. APPENDICES

10.1. mNIS+7 Components and Scoring

Refer to the Study Reference Manual for additional details.

[redacted]

10.2. PND Scores and FAP Stages

Polyneuropathy Disability (PND) Scores

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

Familial Amyloidotic Polyneuropathy (FAP) Stages

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

10.3. New York Heart Association (NYHA) Class

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.

10.4. Karnofsky Performance Status (KPS) 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

ALN-TTRSC02-002 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 10 OCTOBER 2019

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

Rationale for Protocol Amendment

The primary purpose of this protocol amendment is to introduce the use of a vutrisiran (ALN-TTRSC02) in single-use, pre-filled syringes after completion of a patient's Month 9 efficacy assessments. After the Week 36 dose (last dose prior to the Month 9 efficacy assessments), patients will be transitioned from vial-based injections to the pre-filled syringes as this presentation becomes available.

Several additional changes are being implemented as outlined below.

The following secondary objective/endpoint has been added:

- A new objective has been added to determine the efficacy of ALN-TTRSC02 on improvement in neurologic impairment and quality of life. This will be assessed by analyzing the change at Month 18 compared to baseline in mNIS+7 and Norfolk QoL-DN total score in ALN-TTRSC02-treated patients.

A Medical Records Release form has been added:

- All patients will be asked to sign an optional Medical Records Release Form (where allowed by local regulations) in addition to the informed consent form. This form will ensure collection of vital status data, cardiac transplant procedures, left-ventricular assist device placement, and hospitalizations from patients who discontinue early from the study.

The following additional assessment timepoints or clarification have been made to the Schedule of Assessments:

- Vital status assessments have been added to reflect collection of this information at every visit throughout the study.
- Collection of Polyneuropathy Disability (PND) score and Familial Amyloid Polyneuropathy (FAP) stage assessments at the Month 9 efficacy visit to ensure consistency in the timing of the collection of disease stage information with the ALN-TTR02-004 (APOLLO) study.
- Clarified the timing of hepatitis tests, exploratory biomarkers (urine, plasma, serum), optional exploratory DNA sample, and pharmacoeconomic assessments (Patient and Caregiver Impact Survey; Patient Experience Survey; Patient Preference Survey)
- Added an additional check of serum TTR and vitamin A at Week 42.
- Clarified that treatment administration and efficacy visits during the Extension Period at Month 27 and Month 36 are expected to be distinct visits, consistent with the

efficacy visits at Month 9 and Month 18. Also clarified the safety assessments to be conducted at the administration and efficacy visits.

- Added a clarification to indicate the predose and postdose patisiran pharmacokinetic blood draws will be timed based on the start and end of patisiran infusion.
- Clarified that that LFTs must be obtained with results available within 28 days before the clinic visit on which ALN-TTRSC02 dosing is scheduled during treatment from Month 9 to Month 18 and during the treatment extension period.

Additional protocol modifications or clarifications have been added for the following:

- The study design description was updated to clarify that the Sponsor will be making efforts to enroll a population in this study that is comparable to the APOLLO study population to enable robust cross-study comparisons.
- Under female contraception requirements, clarified that use of oral, implantable, injectable, or transdermal hormonal methods of contraception must be associated with the inhibition of ovulation.
- When recording medical history, clarified that information on prior tetramer stabilizer use anytime should be recorded and not only the use within the 1 year prior to the first dose of study drug.
- Clarified that follicle-stimulating hormone testing will be performed in all post-menopausal women to confirm suspected post-menopausal status.
- Additional requirements for study termination were implemented in line with ICH E6 (R2) Guideline, and the publication policy details were updated to match language in the Clinical Trial Agreement.
- Added the international non-proprietary name (INN), vutrisiran, of the drug product ALN-TTRSC02; updated the comparator name “patisiran-LNP” to “patisiran” throughout the protocol.
- Rescreening criteria limited previously to LFT and NIS eligibility requirements have broadened to allow more flexibility.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes) are not detailed.

Table 1: Protocol Amendment 1 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 1 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated the version and date of the protocol.

The primary change occurs in the Title Page

The Title Page now reads:

Original protocol: 11 October 2018

Amendment 1: 10 October 2019

Sections also containing this change:

All headers at the top of all protocol pages

Purpose: All patients will be asked to sign an optional Medical Records Release Form (where allowed by local regulations) in addition to the informed consent form. This form will ensure collection of vital status data, cardiac transplant procedures, left-ventricular assist device placement, and hospitalizations from patients who discontinue early from the study.

The primary change occurs in Section 6.1, Screening Assessments

Section 6.1 now reads:

An informed consent form (ICF) or assent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF and/or assent form.

In addition of the ICF, patients will be asked to sign a Medical Records Release Form (where allowed by local regulations) at Screening for the purpose of obtaining information on vital status, cardiac transplant procedures, left-ventricular assist device placement (Section 6.2.8), and hospitalizations (Section 6.2.7) from patients for the duration of the study. This information will be obtained by the patient's physician through contacting the patient or family or from death registries.

Signing the Medical Records Release Form will be optional and will apply if the patient discontinues from the study early. Every effort should be made to collect the Medical Records Release Form from all patients enrolled in the study. Also see

Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

Patients will complete the following 3 visit types prior to randomization: the ICF **and Medical Records Release Form** will be obtained at the Visit 1 (Screening), and all inclusion/exclusion criteria will be assessed except for the NIS and PND score criteria; see Section 4.1); the NIS and PND score inclusion criteria will be assessed at Visit 2 (Baseline first assessment); other baseline assessments will be completed at Visit 3 or at Day 1 prior to first dose. Visits 1, 2 and 3 may each occur over multiple days.

Sections also containing this change:

- Table 1 (Schedule of Assessments, Screening through Treatment Period Month 9)
- Table 3 (Schedule of Assessments, Treatment Extension Period, Other Visits, and Follow-up Period)
- Section 4.3.3. Lost to Follow-Up
- Section 8.1.1. Informed Consent and Medical Records Release Form

---

Purpose: The collection of Vital Status information has been expanded. Vital status assessments have been added throughout the study rather than just at the Month 18 efficacy or discontinuation visits.

The primary change occurs in newly added Section 6.2.8, Vital Status Check

6.2.8. Vital Status Check

Vital status checks will be performed at the timepoints specified in the Schedule of Assessments (Table 1 to Table 3). Vital status checks should include checking for the occurrence of heart transplantation or left-ventricular assist device implantation procedures.

Also see Section 4.3.2.1 for the collection of vital status after withdrawal of consent and Section 4.3.3 for patients who are lost to follow-up.

Sections also containing this change:

- Table 1 (Schedule of Assessments, Screening through Treatment Period Month 9),
- Table 2 (Schedule of Assessments, Treatment Period from Month 9 through Month 18),
- Table 3 (Schedule of Assessments, Treatment Extension Period, Other Visits, and Follow-up Period),

- Section 4.3.1, Discontinuation of Study Drug or Declining Procedural Assessments
- Section 4.3.3, Lost to Follow-Up
- Section 8.1.1, Informed Consent and Medical Records Release Form

---

Purpose: Added additional assessments of Polyneuropathy Disability (PND) score and Familial Amyloid Polyneuropathy (FAP) stage at the Month 9 efficacy visit to ensure consistency in the timing of the collection of disease stage information with the ALN-TTR02-004 (APOLLO) study.

The primary change occurs in Table 1, Schedule of Assessments (Screening through Treatment Period Month 9)

The Table 1 now reads:

		Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week	Note					0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window	See Section/Table for details					0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
PND Score	Section 6.2.10		X	X															**X**
FAP Stage	Section 6.2.10		X – Single assessment at any of these visits																**X**

Purpose: Row added for "hepatitis tests" with an assessment at Screening. This is mentioned in Section 6.5.6, but is not clearly indicated in Table 1. Also clarified in Section 6.5.6/Table 7, that these are hepatitis tests and not hepatic tests.

The primary change occurs in Table 1, Schedule of Assessments (Screening through Treatment Period Month 9)

The Table 1 now reads:

		Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window	Note					0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Hepatitis Tests	**Section 6.5.6**	**X**																	

This part of Table 7 now reads:

~~Hepatic~~ **Hepatitis** Tests (only at Screening)	
Hepatitis A, including: HAV antibody IgM and IgG	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Hepatitis C, including: HCV antibody HCV RNA PCR – qualitative and quantitative assays	Hepatitis E, including: HEV antibody IgM and IgG

Purpose: Row added for "Exploratory DNA sample (optional)" with an assessment at Baseline. This is to clarify this to be an optional single sample obtained during baseline visit 3 and distinguish this from the sample for exploratory analysis that will be assessed at Baseline and several post-baseline time points.

The primary change occurs in Table 1, Schedule of Assessments (Screening through Treatment Period Month 9)

The Table 1 now reads:

		Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window	Note					0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Sample for Exploratory Analysis	Section 6.6			X				X				X						X	X
Exploratory DNA sample (optional)	**Section 6.6**			**X**															

Purpose: Removed "Patient Experience Survey" from the rows in which it was combined with other assessments or surveys as it is administered using a different schedule.

The primary changes occur in Schedule of Assessments Table 1 (Screening through Treatment Period Month 9) and Table 2 (Treatment Period from Month 9 through Month 18)

The Table 1 now reads:

		Screening	Baseline				Treatment Period												Month 9 Efficacy
		V1	V2	V3	Pre-dose	Post-dose													
Study Day					Day 1		D22	D43	D64	D85	D106	D127	D148	D169	D190	D211	D232	D253	D254-D273
Study Week						0	3	6	9	12	15	18	21	24	27	30	33	36	36-39
±Visit Window	Note					0	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver Impact **Survey** ~~and Patient Experience Surveys~~	Section 6.2.9; Section 6.5.5; Section 6.7.1			X– single at any of these visits															X
Patient Experience Survey	**Section 6.7.3**																		**X**

Table 2 now reads:

		Treatment Period														Month 18 Efficacy
Study Day		D274	D295	D316	D337	D358	D379	D400	D421	D442	D463	D484	D505	D526	D547	D554-D561
Study Week		39	42	45	48	51	54	57	60	63	66	69	72	75	78	79-80
±Visit Window	Note	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; Patient and Caregiver **Survey** ~~and Patient Experience Surveys~~	Section 6.2.3; Section 6.2.6; Section 6.2.9; Section 6.5.5; Section 6.7.1															X
Patient Experience Survey	**Section 6.7.3**															**X**

Purpose: Additional assessment of serum TTR and vitamin A added at Week 42. To avoid a prolonged gap in PD assessment between the previous and subsequent visits.

The primary change occurs in Table 2, Schedule of Assessments (Treatment Period from Month 9 through Month 189)

The Table 2 now reads:

		Treatment Period														Month 18 Efficacy
Study Day		D274	D295	D316	D337	D358	D379	D400	D421	D442	D463	D484	D505	D526	D547	D554-D561
Study Week		39	42	45	48	51	54	57	60	63	66	69	72	75	78	79-80
±Visit Window	Note	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	±3D	NA
TTR Protein; Vitamin A	Section 6.3		**X**		X		X		X		X		X		X	X

Purpose: Modified the assessments under the Month 27 and Month 36 visit columns to clarify that treatment administration and efficacy visits are expected to be distinct visits, consistent with the efficacy visits at Month 9 and 18. Also clarified the windows for these visits. In addition to these changes, several additional minor changes are detailed in the following table:

Several other additional edits are also summarized below:

- *Full physical examinations (PEs) changed to symptom-directed PEs. Additional symptom-directed PEs added as indicated*
- *Replaced the reference to "all Pharmacoeconomic assessments" and each individual survey (Patient and Caregiver Impact Survey; Patient Experience Survey; Patient Preference Survey) to be consistent with how these were presented in Table 1 and Table 2. Clarified the schedules of each survey during the Early Discontinuation and modified efficacy visits for patients who discontinued treatment before Month 18.*
- *Medical Records Release Form recheck added (as described earlier)*

Changes to column headers and relevant rows in Table 3 (Schedule of Assessments: Treatment Extension Period, Other Visits, and Follow-up Period) are indicated below:

		Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**	-	36-39	79-80	-
±Visit Window	Note	±3D	±7D	~~±2 weeks~~**±7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~	-	-	-	-
Medical Records Release Form (optional)	**Section 8.1.1 Recheck**					**X**			

		Treatment Extension Period					Early Drug Discontinuation Visit		Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18				FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**		4 (+1) Weeks from Last Dose		Month 9		Month 18		See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**		-		36-39		79-80		-
±Visit Window		±3D	±7D	~~±2 weeks±~~**7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~		-		-		-		-
	Note												
NYHA class; KPS; PND and FAP; mBMI	Section 6.2.11.4; Section 6.2.12; Section 6.2.10; Section 6.2.5				X		X		X		X		
Vital Signs	Section 6.5.1	X	X	X	X								
~~Full~~ Physical Examination (PE); Weight	**Symptom-directed PE** Section 6.5.3; Section 6.5.2	**X**	**X**	**X**	~~X~~**Weight only**		X		X		X		X
NIS; mNIS+7; HRdb	See below Table 3 Notes; Section 6.2.1; Section 6.2.2			~~X~~	X	X	X	X	X	X	X	X	

		Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**	-	36-39	79-80	-
±Visit Window	Note	±3D	±7D	~~±2 weeks±~~**7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~	-	-	-	-
10-MWT	Section 6.2.4			~~X~~	X X	X X			
Questionnaires: Norfolk QoL-DN; R-ODS; EQ-5D-5L and EQ-VAS; C-SSRS; ~~all Pharmacoeconomic assessments~~ **Patient and Caregiver Impact Survey; Patient Experience Survey; Patient Preference Survey**	~~Section 6.7;~~ Section 6.2.3; Section 6.2.6; Section 6.2.9; Section 6.5.5; Section 6.7.1; **Section** 6.7.3; **Section** 6.7.4			~~X~~	X	X - **No Patient Experience Survey;** No Patient Preference Survey	X – No C-SSRS**; No Patient Experience Survey; No Patient Preference Survey**	X – No C-SSRS**; No Patient Experience Survey; No Patient Preference Survey**	
Single 12-Lead ECG	Section 6.5.4					X			
Echocardiogram	Section 6.2.11.1			~~X~~	X	X			

		Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**	-	36-39	79-80	-
±Visit Window		±3D	±7D	~~±2 weeks±~~**7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~	-	-	-	-
	Note								
Technetium scintigraphy imaging (select sites only)	Section 6.2.11.3			~~X~~	X	X			
Serum Chemistry, Hematology, Urinalysis, Coagulation and Liver Function Tests	Section 6.5.6; Section 6.5.6.3	LFT only; applies to both arms	X	~~X~~**LFTs only**	~~X~~ **No LFTs**	X	Serum Chemistry and LFTs only	Serum Chemistry and LFTs only	X
Pregnancy Test	Section 6.5.6.2		X	X	~~X~~	X	X	X	X
Cardiac Biomarker Samples	Section 6.2.11.2		~~X - Every 24 weeks starting at Week 96~~ **X - Week 96, Week 120, Week 144**		~~X~~	X	X	X	
TTR Protein; Vitamin A	Prior to each dose on dosing days; 6.3		X	X	X	X	X	X	X

		Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**	-	36-39	79-80	-
±Visit Window	Note	±3D	±7D	~~±2 weeks±~~**7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~	-	-	-	-
ADA	On dosing days, collect within 1 hour before dosing; Section 6.5.6.1		X **- Week 96, Week 120, Week 144-** ~~Every 24 weeks starting at Week 96~~		~~X~~	X			
ALN-TTRSC02 PK	~~See~~ Table 4 for PK collection timepoints					X	X	X	
Samples for Exploratory Analysis	Section 6.6			~~X~~	X	X			
AEs; Con. Meds; Hospitalizations, Urgent care visits and Procedures	Section 6.5.7; Section 5.3; Section 6.7.2	**Continuous monitoring** ~~X~~							X - Through week 12 after

		Treatment Extension Period				Early Drug Discontinuation Visit	Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18		FU Period
		Last Patisiran Dosing Visit	ALN-TTRSC02 Dosing Visits Every 12 Weeks	**ALN-TTRSC02 Dosing Visits at Months 27 and 36** ~~Month 27 Efficacy and Dosing Visit~~	Month **27 and** 36 Efficacy Visit**s**	4 (+1) Weeks from Last Dose	Month 9	Month 18	See Notes below Table 3
Study Week		81	84, 96, 108, ~~120,~~ 132, **and** 144~~, and 156~~	120**, 156**	~~160~~**120, 156**	-	36-39	79-80	-
±Visit Window		±3D	±7D	~~±2 weeks~~±**7D**	**+14D (≥1D after W120 and W156 doses, respectively)** ~~±2 weeks~~	-	-	-	-
	Note								
ALN-TTRSC02 Study Drug Administration	Section 5.2.2.1		X - Every 12 weeks starting at Week 84 to EOT Week 156						
Patisiran: Premedication Administration	Section 5.2.2.2	X							
Patisiran Study Drug Administration	Section 5.2.2.2	X							
Vital status check	~~See note below Table 3~~ **Section 6.2.8**	**X**	**X**	**X**	**X**	**X**	**X**	X	**X**

Purpose: Added footnotes to the schedules of assessments in Table 2 and Table 3 to clarify that LFT results must be available within 28 days before the clinic visit at which ALN-TTRSC02 dosing is scheduled. This is consistent with the guidance already indicated in Table 1, Section 5.2.3, and Section 6.5.6.

The primary changes occur in Table 2 (Treatment Period from Month 9 through Month 18) and Table 3 (Treatment Extension Period, Other Visits, and Follow-up Period)

The following footnote was added to Table 2:

For the ALN-TTRSC02 cohort, LFTs must be obtained with results available within 28 days before the clinic visit on which ALN-TTRSC02 dosing is scheduled. LFTs can be analyzed locally, but if a local assessment is drawn, a sample must also be drawn for analysis at the central laboratory. For the patisiran-cohort, LFTs should be performed according to patisiran visit windows and do not need to be available prior to dosing.

The following footnote was added to Table 3:

LFTs must be obtained with results available within 28 days before the clinic visit on which ALN-TTRSC02 dosing is scheduled. LFTs can be analyzed locally, but if a local assessment is drawn, a sample must also be drawn for analysis at the central laboratory.

Purpose: Clarified that predose and postdose patisiran pharmacokinetic blood draws will be timed based on the start and end of patisiran infusion in Table 5.

The primary change occurs in Table 5 (Pharmacokinetic Time Points: Patisiran)

Table 5 now reads:

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before ~~dosing~~**the start of infusion**)	X
	00:30 (±5 min) **from the end of infusion**	X
	06:00 (±1 hr) **from the end of infusion**	X

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
	24:00 (±2 hr) **from the end of infusion**	X
Day 22, Day 127, Day 274, Day 379, and Day 547 (±3 days)	Predose (within 60 minutes before ~~dosing~~**the start of infusion**)	X
	03:00 (±1 hr) **from the end of infusion**	X

Purpose: "Patisrian -LNP" drug product was changed to "patisiran" throughout the protocol.

These changes are not listed individually.

Purpose: "Vutrisiran" drug product has been added as the associated International Nonproprietary Name of ALN-TTRSC02.

These changes are not listed individually.

Purpose: Added additional secondary endpoints to evaluate the efficacy of ALN-TTRSC02 on improvement in neurologic impairment and quality of life.

The primary change occurs in Section 2, Objectives and Endpoint

This section now reads:

Objectives	Endpoints
Secondary	
• To determine the efficacy of ALN-TTRSC02 on gait speed, nutritional status, and disability • To characterize the effect of ALN-TTRSC02 on serum TTR levels • To evaluate patient mortality and hospitalization • **To determine the efficacy of ALN-TTRSC02 on improvement in neurologic impairment and on quality of life**	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Timed 10-meter walk test (10-MWT); – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R-ODS) • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran arm

Objectives	Endpoints
	• Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study • Composite events of all-cause deaths and/or all-cause hospitalizations in patients with cardiac involvement (over 18 months) compared to patients with cardiac involvement in the placebo arm of the APOLLO study • **Change at Month 18 compared to baseline in mNIS+7 in ALN-TTRSC02-treated patients** • **Change at Month 18 compared to baseline in Norfolk QoL-DN total score in ALN-TTRSC02-treated patients**

Sections also containing this change:

- Protocol Synopsis
- Section 7.2.5.2, Secondary Endpoints

Purpose: Language was added to more explicitly indicate how the Sponsor will maintain comparable populations between this study and the ALN-TTR02-004 (APOLLO) study to enable cross-study comparisons; consistent with our original intent based on the study design.

The primary change occurs in Section 3.1, Summary of Study Design

The following paragraph has been added:

In order to allow for a robust cross study comparison, attempts will be made to minimize differences between the HELIOS-A and APOLLO study populations. As such, baseline disease characteristics will be monitored and may result in enrollment

limitations based on certain characteristics (eg, genotype) to ensure comparability. Decisions around enrollment adjustments will be made by staff without access to primary efficacy results.

Purpose: As part of the introduction of ALN-TTRSC02 in pre-filled syringes, details of the addition of the pre-filled syringe and needle safety device have been added.

The primary change occurs in Section 5.2.1, Description

The relevant paragraphs in Section 5.2.1 now read:

5.2.1. Description

ALN-TTRSC02 will be supplied as a **vial of** sterile solution containing 50 mg/mL of siRNA ALN-65492 free acid (equivalent to 53 mg/mL sodium salt) in phosphate buffered saline for SC injection. The drug product does not contain preservatives and is intended for single use. See the Pharmacy Manual for further details of solution concentration and fill volume.

ALN-TTRSC02 will also be supplied as a pre-filled syringe and a needle safety device. The pre-filled syringe will be filled with ALN-TTRSC02 (25 mg dose) with a volume of 0.5 mL. The pre-filled syringe is a single-use injection device, and after injection the needle safety device will engage to cover the exposed needle.

ALN-TTRSC02 will be administered using injections prepared from vials up to and including at least the Week 36 dose (the last dose prior to the Month 9 efficacy assessments). After the Week 36 dose, patients will be transitioned from vial-based injections to the pre-filled syringes as this presentation becomes available.

Sections also containing this change:

- Section 5.2, Study Drug
- Section 5.2.2.1, ALN-TTRSC02

Purpose: As part of the introduction of ALN-TTRSC02 in pre-filled syringes, a new section on product complaints has been added to facilitate communication about issues related to study drug products provided in the study

The primary change occurs in newly added Section 5.3. Product Complaints

5.3. Product Complaints

5.3.1. Definition

A product complaint (PC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product and its packaging after it is released for distribution.

A PC may be detected prior to use of study drug, during use, or after use. A PC is typically non-medical in nature; however, it is possible that complaints could be associated with an AE. Examples of a PC include, but are not limited to: illegible label, missing label, damaged vial/syringe, empty vial/syringe, contamination of product, and malfunction of syringe needle safety device.

5.3.2. Reporting

For PCs, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. PCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.7. Detailed instructions on reporting PCs will also be detailed in the Pharmacy Manual.

Purpose: Under female contraception requirements, clarified that use of oral, implantable, injectable, or transdermal hormonal methods of contraception must be associated with the inhibition of ovulation.

In Section 5.6.1, the fifth bullet under birth control methods which are considered highly effective now reads:

- Established use of oral (except for low dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception **associated with the inhibition of ovulation**. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).

Purpose: Clarified that follicle-stimulating hormone testing will be performed in all post-menopausal women.

The primary change occurs in Section 6.5.6.2, Pregnancy Testing

The last paragraph in this section not reads:

Follicle-stimulating hormone testing ~~may~~ **will** be performed **in all post-menopausal women** to confirm suspected post-menopausal status.

Purpose: Rescreening criteria for LFT and NIS eligibility requirements have been broadened to allow more flexibility.

The primary change occurs in Section 6.1.2, Rescreening

This section now reads:

For patients who do not meet all study eligibility requirements, due to a transient clinical condition during screening or who fail to complete screening activities due to unforeseen and unavoidable circumstances, rescreening once may be permitted after consultation with the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment. In this case, a patient will be re-consented and all screening procedures must be repeated. ~~For patients who do not meet LFT or NIS eligibility criteria, rescreening patients once may be permitted with consultation of the Medical Monitor after a minimum of 5 days have elapsed from a patient's last screening assessment.~~

Purpose: Clarified that, when recording medical history, information on prior tetramer stabilizer use anytime should be recorded and not only the use within the 1 year prior to the first dose of study drug.

The primary change occurs in Section 6.1.3, Demographic and Medical History/Disease History

The first paragraph in this section now reads:

Medical history will be collected during screening Visit 1 (including any cardiac disorders, any eye disorders or previous ophthalmology test results, and prior medications). Documented technetium scintigraphy and/or tissue biopsy testing for amyloidosis performed prior to study enrollment should be collected and recorded as part of medical history. **Information on prior use of tetramer stabilizers at any time prior to first dose should be collected and recorded. Information on other** prior medications, hospitalization, and procedures through 1 year prior to first dose should be collected and recorded.

Purpose: Additional requirements for study termination were implemented in line with ICH E6 (R2) Guideline.

The primary change occurs in Section 8.1.6, Termination of the Clinical Study or Site Closure

This section now reads:

The Sponsor**, or designee,** reserves the right to terminate the study **or a clinical study site** ~~for clinical or administrative reasons~~ at any time. ~~If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site.~~
Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

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**/IEC** 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.

Purpose: Publication policy details were updated to match details that are provided in the Clinical Trial Agreement.

The primary change occurs in Section 8.3, Publication Policy

This section now reads:

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 separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published, or following the period of 18 months after completion of the study at all centers.~~ A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement ~~among the institution, Investigator, and Alnylam~~ will detail the procedures for ~~Alnylam's review of~~ publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

ALN-TTRSC02-002 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 06 MAY 2020

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

1. RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter dated 31 March 2020 to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. These changes were to be immediately adopted by the investigator site per the Dear Investigator Letter dated 31 March 2020 and are in line with guidance from both the European Medicines Agency and the United States Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic.[EMA 2020; FDA 2020] The USM modifications and new procedures are summarized in Section 1.1 and a detailed summary of protocol changes is provided in Section 2.1.

This protocol amendment also incorporates removal of the secondary endpoint all-cause hospitalization and death events over 18 months in patients with cardiac involvement. This change is summarized in Section 1.2 and a detailed summary of protocol changes is provided in Section 2.2. These changes will not be implemented until appropriate Health Authority and Ethics Committee (EC) and/or Institutional Review Board (IRB) approval.

1.1. Urgent Safety Measures due to the Impact of the COVID-19 Pandemic

Urgent Safety Measures were implemented by the Sponsor, as mentioned above, to ensure the safety of study participants and the integrity of study data in response to the impact of the COVID-19 pandemic. The changes are outlined below, and a detailed summary of the USMs is provided in Section 2.1.

- **Expanded ALN-TTRSC02 Dosing Outside the Study Center**

  Administration of ALN-TTRSC02 will be permitted outside the study center by a home healthcare professional (eg, the patient's home) at all time points provided the patient has tolerated at least 1 dose of ALN-TTRSC02 administered in the study center (previously allowed after Month 18).

- **Expanded use of Pre-filled Syringes for ALN-TTRSC02 Administration**

  ALN-TTRSC02 may be administered via pre-filled syringes at any time point during the study as this presentation becomes available (previously allowed after Week 36).

- **ALN-TTRSC02 Dosing Outside the Study Center by Patient or Caregiver**

  Following appropriate training on ALN-TTRSC02, dosing will be permitted by the patient or caregiver at all timepoints under the oversight of the Investigator and following consultation with the Medical Monitor. This measure is intended to remain

in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing. In addition, added references to patient/caregiver instructions for administration, storage of study drug, and reporting of product complaints.

- **Expanded Window After Which a ALN-TTRSC02 Dose Will be Considered Delayed**

  If a patient does not receive a dose of ALN-TTRSC02 within the specified dosing window, the dose may be administered with up to an 8-week delay (previously 6 weeks) to be considered a delayed dose. In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled time point.

  Given the long activity of the drug resulting in sustained suppression of TTR as observed in Phase 1 study, an occasional delay of 8 weeks in dosing is expected to have minimal impact on the TTR suppression (decrease of only 7% in TTR suppression relative to vutrisiran original scheduled dosing) as predicted by the Sponsor's PK/PD modeling. Resumption of dosing as per original dosing schedule is expected to be tolerated based on the safety from Phase 1 study which evaluated doses as high as 300 mg (12× higher than the therapeutic dose of 25 mg administered quarterly). Accordingly, this change has been implemented to provide greater flexibility amid travel and other restrictions related to the COVID-19 pandemic, in order to minimize the number of missed doses on study.

- **Expanded Patisiran Dosing Outside the Study Center**

  Administration of patisiran will be permitted outside the study center by a home healthcare professional (eg, the patient's home) at all timepoints (previously allowed after Month 9), provided the patient has tolerated at least 2 doses of patisiran administered in the study center.

  These changes were implemented to reduce the frequency of patient visits to the study center, and therefore reduce potential exposure to COVID-19, while maintaining continuity of study drug dosing. Based on the overall safety profile of patisiran, the frequency of infusion-related reactions (IRRs) decreases over time and IRRs do not increase in severity. When IRRs have occurred, most have been mild or moderate in severity, have not required any treatment and have not resulted in interruption during the infusion or a change in administration. When infusions have been interrupted due to an IRR, these have primarily been reported in patients during the first 2 infusions. Thus, for patients who tolerate infusions, these data support home administration following 2 doses administered at the study center. Home dosing of study drug will be performed by a healthcare professional, with oversight of the Investigator, allowing for ongoing appropriate monitoring of the patient.

- **Premedication Equivalents may be Administered Orally**

  Clarified that oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional. There have been no increases in IRR frequency with oral steroids compared to IV steroids for pre-medication.

- **Corticosteroid Tapering Outside the Study Center**

  Corticosteroid tapering may be performed in the clinic or, at the discretion of the Investigator, may be performed outside of the clinic (eg, in the patient's home) after consultation with the Medical Monitor.

  This change was implemented to allow for reduction of steroids, where it is deemed in the best interest of the patient by the investigator, in the context of expanded home dosing necessitated by the COVID-19 pandemic as outlined above. Patisiran dosing, and thus steroid tapering, will be performed by a healthcare professional, with oversight of the investigator, allowing for appropriate monitoring of the patient. Support for this approach comes from a review of data from the patisiran treated patients who have tapered steroids in the global-label extension studies (ALN-TTR02-003, ALN-TTR02-004 and ALN-TTR02-006) where IRRs were infrequent, mild, and tapering of steroids was not associated with an increase in the rate of IRRs.

- **Expanded the Patisiran Administration Window**

  Expanded the patisiran administration window. If a patient does not receive a dose of patisiran within the dosing window (±3 days) due to COVID-19, the dose may be administered with up to 7 days delay after the scheduled visit, after consultation with the Medical Monitor (to be considered a delayed dose). Previously the dose was to be considered missed if received outside the dosing window (±3 days).

  Based on Phase 1 data with patisiran (ALN-TTR02-001), an occasional 7-day delay in dosing for patisiran is expected to have a minimal impact on TTR suppression (ie, a decrease of ~10% in TTR suppression relative to patisiran original scheduled dosing). Resumption of dosing as per the original dosing schedule is expected to be tolerated based on the safety results from earlier patisiran studies. Accordingly, this change has been implemented to provide greater flexibility amid travel and other restrictions related to the COVID-19 pandemic, in order to minimize the number of missed doses on study.

- **Assessments Performed Outside the Study Center**

  Routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include the following: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient.

All laboratory samples should be sent to the central laboratory however, an exception has been added that local laboratory assessments are permitted in cases when assessment at central laboratory is not possible due to complications related to the COVID-19 pandemic.

Added that with the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center, at a minimum, patients must visit the site for scheduled dosing and assessments at the Week 12 and Week 60 visits within the study visit windows and for efficacy assessments as detailed below.

If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must verbally contact the patient to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

- **Liver Function Tests (LFTs)**

  The timing of LFT assessments was updated to coincide with ALN-TTRSC02 dosing visits (which are every 12 weeks). Thus, starting at Week 12, patients on ALN-TTRSC02 will have LFT results done every 12 weeks, instead of the current schedule of assessments, where LFT were assessed every 6 weeks until Month 9 and then every 12 weeks after Month 9. Additionally, the requirement for additional LFT results within 28 days prior to each ALN-TTRSC02 dose has been removed. Dosing decisions may will be based on the LFTs collected at the previous dosing visit (up to 14 weeks prior to dosing).

  These changes were implemented in order to limit the number of times a patient needs to visit the site/interact with home healthcare professionals and reduce potential exposure to COVID-19. The changes are based on the available safety data from the prior Phase 1 study (ALN-TTRSC02-001) and from this study (HELIOS-A), which have shown that ALN-TTRSCO2 continues to have an acceptable safety profile.

  In HELIOS-A, as of 08 April 2020, 120 patients had received a total of 305 doses of vutrisiran 25 mg every 3 months (mean 2.5 doses, range: 1-5 doses). This provides a mean exposure of 130.4 days (range: 1 to 339 days) and most patients (101 out of 120) have had at least 2 doses of vutrisiran. No subjects in the ongoing HELIOS-A study have had laboratory elevations of >3xULN for ALT or AST and no subjects have required interruption of study drug due to elevations in liver transaminases, bilirubin or adverse hepatic events. Thus, with increasing exposure in HELIOS-A, vutrisiran continues to have an acceptable hepatic safety profile.

  The Sponsor acknowledges that liver transaminase elevations remain an important potential risk based on the mechanism of action of vutrisiran, as well as findings in pre-clinical studies and early-phase clinical trials. The specific rules for monitoring and dosing in the setting of transaminase elevations outlined in the protocol are unchanged (Section 5.2.3 Table 6 [Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified]).

Given the available safety data for vutrisiran, the degree of risk of COVID-19 exposure related to the additional visits is considered in excess of the degree of risk mitigation obtained by more frequent LFT monitoring. With the current changes, a robust LFT monitoring schedule of every 12 weeks, is maintained and the results will be regularly reviewed by the Medical Monitor and the Data Monitoring Committee (DMC). Continuous monitoring of adverse events will also allow for detection of any clinically relevant events and additional LFTs may be obtained at any time at the discretion of the investigator.

- **Efficacy Assessments at Month 9**

  Clarified that all efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits). Specified that for situations in which a Month 9 efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 efficacy assessment. After consultation with the Medical Monitor, Month 9 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15).

  This change was implemented to allow for collection of critical efficacy data while limiting unnecessary patient exposure to COVID 19 and to ensure, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic. It is anticipated that the estimated treatment effects at Months 9 and 18 on vutrisiran treatment will be similar to the treatment effects observed on patisiran treatment in Study ALN-TTR02-004 (APOLLO). For these endpoints in the APOLLO study, treatment differences between patisiran and placebo-treated patients increased from Month 9 to Month 18. These increasing treatment differences were attributable largely to continued progression between Months 9 and 18 among placebo-treated patients. Based on these data, the delayed Month 9 efficacy assessments up to Month 15 would be similar to unobserved Month 9 efficacy assessments that would have been missed without this delayed assessment allowance, if not slightly worse considering potentially missed doses. Therefore, it is expected that this missing data minimization strategy will yield similar if not conservative estimated treatment effects on vutrisiran compared to what may have been observed had the COVID-19 pandemic not occurred during the course of this study.

- **Transthyretin (TTR)/Vitamin A Assessments**

  After Week 12, TTR/Vitamin A sample collections between ALN-TTRSC02 dosing visits have been removed for all patients.

  This change has been made as part of the overall strategy of reducing visits and assessments during the COVID-19 pandemic. Removal of these assessments is not expected to have a meaningful impact on the TTR efficacy endpoint at Month 18 as our modeling data support that there are minimal fluctuations in TTR levels over the dosing interval following Week 12; ie, following 2nd dose of ALN-TTRSC02.

- **Timing of other assessments**

  Reduced the frequency of select assessments or combined assessments from different visits to align with dosing visits in order to limit the number of times a patient needs to visit the site/interact with home healthcare professionals and reduce potential exposure to COVID-19.

- **Secondary Endpoint of TTR percent reduction**

  Changed the secondary endpoint related to comparison of TTR percent reduction in the ALN-TTRSC02 arm compared to patisiran through 9 months to 18 months.

  This change is being implemented to address concerns with regard to missed doses related to COVID-19 during critical time periods preceding the Month 9 assessment with potential impact to the integrity of this endpoint. TTR percent reduction through Month 9 was planned to be evaluated for noninferiority compared to the within-study randomized patisiran arm. This endpoint was specified in the SAP to be evaluated on the Per-protocol (PP) Population. With dosing flexibility adopted due to the COVID-19 pandemic, it is expected that the number of patients qualifying for the PP Population will be substantially reduced, thus greatly reducing power for the originally planned Month 9 analysis of TTR percent reduction. Changing TTR percent reduction from Month 9 to Month 18 is anticipated to allow for a more viable noninferiority comparison with sufficient power.

- **Collection of Information Related to COVID-19**

  Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient in order to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to Study Administration Text**

  Text was updated to provide clarification of Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

1.2. Changes Not Related to Urgent Safety Measures

Several additional changes are being implemented, which are outlined below and a detailed summary is provided in Section 2.2.

- **Secondary Endpoint of all-cause hospitalization and death events over 18 months in Patients with Cardiac Involvement**

  The secondary endpoint all-cause hospitalization and death events over 18 months in patients with cardiac involvement was removed. This change was implemented based on review of baseline data which suggests that a minority of patients are likely to meet pre-specified criteria for the cardiac subpopulation thus limiting the value of this analysis.

  Initial projections of sample size was based upon the ALN-TTR02-004 Study (APOLLO), which enrolled 90/148 (60.8%) patisiran-treated patients into the Cardiac Subpopulation. In the current study, only 36/122 (29%) vutrisiran-treated patients

qualified for the Cardiac Subpopulation, which is anticipated to result in an under-powered endpoint.

The following changes are not detailed: administrative changes, corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. PROTOCOL AMENDMENT 2 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

2.1. Urgent Safety Measure COVID-19-related Changes to be Adopted Immediately

Purpose: The following changes were made related to administration of ALN-TTRSC02:

- *Expanded ALN-TTRSC02 Dosing Outside the Study Center*
- *Expanded use of Pre-filled Syringes for ALN-TTRSC02 Administration*
- *ALN-TTRSC02 Dosing Outside the Study Center by Patient or Caregiver*
- *Expanded Window After Which a Dose Will be Considered Delayed*
- *Modified other dose, administration, and product complaint sections to match new administration strategy*

The primary changes occur in Section 5.2.2.1 (ALN-TTRSC02) and Section 5.2.1 (Description)

5.2.2.1. ALN-TTRSC02

Revised text:

ALN-TTRSC02 25 mg SC injection will be administered q3M (12 weeks ±3 days during the Treatment Period and ±7 days during the Treatment Extension Period). Study drug SC injections **in the clinic** will be administered under the supervision of the Investigator or **a trained** healthcare professional. **ALN-TTRSC02 may be administered at a location other than the study center (eg, the patient's home) as specified below.**

~~All ALN-TTRSC02 doses will be administered at the clinic during scheduled study assessment visits during the Treatment Period on Day 1 through Month 18. During the Treatment Extension Period, starting at Week 84/Month 19, patients who are tolerating their ALN-TTRSC02 injections as determined by the Investigator and where applicable country and local regulations allow, may have ALN-TTRSC02 administered outside the clinic (eg, home) by a healthcare professional trained on study drug administration.~~

If a patient has tolerated at least 1 dose of ALN-TTRSC02 in the clinic, subsequent dosing may be administered outside the study site (eg, the patient's home) at all time points where allowed by applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator. If the patient is unable to come to the study center, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, ALN-TTRSC02 may be administered by the patient or the caregiver under the oversight of the

Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on ALN-TTRSC02 administration. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.
Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. In addition, instructions and procedures related to administration of ALN-TTRSC02 by a patient or caregiver will be provided in the ALN-TTRSC02 Patient/Caregiver Storage and Administration Instructions.

Method of Administration of ALN-TTRSC02

ALN-TTRSC02 is for SC use ~~and should be administered by a healthcare professional~~.

The SC injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Additional details, including detailed instructions for study drug administration, can be found in the Pharmacy Manual. Detailed Instructions for Use for the pre-filled syringe will also be provided.

Missed Doses of ALN-TTRSC02

If a patient does not receive a dose of ALN-TTRSC02 within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered with up to ~~a 6~~**an 8**-week delay (to be considered a delayed dose). Thereafter, the dose will be considered missed and not administered. If a dose is administered with a delay, the next dose will resume following the original schedule. **In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled timepoint.**

During the Treatment Period, every effort should be made to avoid missed doses of ALN-TTRSC02. During the Treatment Period, if a patient misses a dose **for reasons unrelated to the COVID-19 pandemic**, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study (see also Section 4.3).

5.2.1. Description (relevant text only)

Revised text:

ALN-TTRSC02 will **initially** be administered using injections prepared from vials ~~up to and including at least the Week 36 dose (the last dose prior to the Month 9 efficacy assessments). After the Week 36 dose, patients will~~**. Patients may** be transitioned from vial-based injections to the pre-filled ~~syringes~~**syringe-based injections at any study time point** as this presentation becomes available.

Sections also reflecting this change:

- Table 1, Table 2 Schedules of Assessments
- Section 3.1 Summary of Study Design
- Section 5.2.4, Preparation, Handling, and Storage
- Section 5.3.2, Reporting

Purpose: The following changes were made related to administration of patisiran:

- *Expanded Patisiran Dosing Outside the Study Center*
- *Premedication Equivalents may be Administered Orally*
- *Corticosteroid Tapering Outside the Study Center*
- *Expanded the Patisiran Administration Window*
- *Modified other dose, administration, and product complaint sections to match new administration strategy*

The primary changes occur in Section 5.2.2.2 (Patisiran)

5.2.2.2. Patisiran

Revised text:

~~All patisiran doses will be administered at the clinic during the scheduled study assessment visits through Month 9. After Month 9, patisiran dosing may be performed at home by a trained healthcare professional where applicable country and local regulations and infrastructure allow, with the exception of the patisiran dosing visits at Weeks 48, 60, and 72, which must be performed in the clinic during scheduled study assessment visits through Month 18.~~ **If a patient has tolerated at least 2 doses of patisiran administered in the clinic, dosing may be administered outside the study site (eg, the patient's home) at all timepoints where allowed by**

applicable country and local regulations. In these cases, dosing should be administered by a trained healthcare professional, with oversight by the Investigator.

Required premedication for patients in the patisiran arm

All patients should receive premedication prior to patisiran administration to reduce the risk of infusion-related reactions (IRRs). Each of the following medicinal products should be given on the day of patisiran infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

~~For premedications not available or not tolerated intravenously, equivalents may be administered orally.~~ **Oral premedication equivalents are permitted, but must be administered in the presence of a healthcare professional.**

Modifications to lower the corticosteroid dose may be made to the premedication regimen for either of the following 2 reasons:

1. If a patient is having difficulty tolerating the corticosteroid premedication regimen (eg, patient develops uncontrolled hyperglycemia, altered mental status, or other complication), then lowering of the corticosteroid premedication may be allowed for that patient after consultation with the medical monitor.
2. If a patient has tolerated 3 or more infusions of patisiran with their current corticosteroid premedication regimen (ie, patient has not had IRRs during the past 3 or more infusions), then lowering of the corticosteroid premedication is recommended.

~~Corticosteroid tapering should be performed in the clinic.~~ Steps to lower corticosteroid dosing are provided in the Study Manual ~~Pharmacy Manual~~. **Corticosteroid tapering may be performed in the clinic or, at the discretion of the investigator, may be performed outside of the clinic (eg, in the patients home) after consultation with the Medical Monitor.**

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed. Guidelines for management of IRRs can be found in the Pharmacy Manual.

Method of Administration of patisiran

Patisiran is for IV use and should be administered by a healthcare professional.

Weight from previous visit may be used for calculating dose. Weight must be collected predose. The patient's infusion site should be assessed for signs of any localized reaction during the infusion and for 30 minutes after the end of the infusion. The patient ~~will~~

~~remain at the study site~~ **should be observed** for 1 hour following completion of dosing for observation and completion of assessments.

Detailed instructions for study drug preparation and administration can be found in the Pharmacy Manual.

Missed Doses of patisiran

If a patient does not receive a dose of patisiran within the dosing window (±3 days) **due to COVID-19** ~~the dose will be considered missed and not administered~~ **the dose may be administered with up to 7 days delay after the scheduled visit, after consultation with the Medical Monitor (to be considered a delayed dose). If a dose is administered with a delay, the next dose will resume following the original schedule per the Schedule of Assessments. In all cases, the dose should be administered as close as possible to the scheduled timepoint.**

A dose will be considered completed if 80% or more of the total volume of the IV solution has been administered to the patient. Patients will be permitted to miss an occasional dose of study drug. However, if a patient misses 2 consecutive doses **for reasons unrelated to the COVID-19 pandemic**, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue in the study.

Sections also reflecting this change:

- Table 1, Table 2 Schedules of Assessments
- Section 3.1 Summary of Study Design
- Section 5.2.4, Preparation, Handling, and Storage
- Section 5.3.2, Reporting

Purpose: The following changes have been made relating to expanding the ability to perform assessments outside of the study center:

- *Clarified and expanded on language already in the protocol related to performing routine assessments outside of the clinic (eg, at home) at all timepoints. These include: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications.*
- *Clarified that all laboratory samples should be sent to the central laboratory, however, an exception has been added that local laboratory assessments are permitted in cases when assessment at central laboratory is not possible due to complications related to the COVID-19 pandemic.*

- *If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must verbally contact the patient to collect relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).*
- *Clarified that in even if ECGs are conducted outside the clinic, the Investigator or qualified designee will review them.*
- *Added option for pregnancy testing by the patient or caregiver in situations a study visit is unable to be completed at the site due to the COVID-19 pandemic*

The primary changes occur in Section 6 (Study Assessments), Section 6.5.4 (Electrocardiogram), and Section 6.5.6.2 (Pregnancy Testing)

6. STUDY ASSESSMENTS *(applicable text only)*

Revised text:

~~During the study, where applicable country and local regulations and infrastructure allow, assessments that may be conducted by a qualified home healthcare professional include but are not limited to: blood draws, vital signs, physical exam, collection of information regarding hospitalizations, urgent care visits, procedures and concomitant medications. Wherever possible, AE collection associated with visits outside of the clinic will be collected by a phone call from qualified site staff.~~

Where applicable country and local regulations and infrastructure allow, routine assessments may be performed outside of the study center (eg, the patient's home) by a trained healthcare professional at all timepoints. These assessments include to the following: vital signs, physical exam, weight, ECGs, pregnancy tests, urine collection, blood draws (clinical laboratory assessments, ADA, PK; ATTR/vitamin A; exploratory samples), collection of information regarding vital status, hospitalizations, urgent care visits, procedures, and concomitant medications. All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory assessments are not possible, then a local laboratory may be used. These local lab results must be sent to the site for review by the Investigator and entry into the clinical database. Wherever possible, AE collection associated with visits outside of the clinic will be collected by qualified site staff through verbal contact with the patient.

With the exception of patients unable to come to the site due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center, at a minimum, patients must visit the site for scheduled dosing and assessments at the Week 12 and Week 60 visits within the study visit windows and for efficacy assessments as detailed below.

If any study assessments are not able to be completed at the site or at home within the study visit window, the study physician (or delegate) must, at a minimum, verbally contact the patient within the expected window for each study visit to collect

relevant safety information (including, but not limited to, AEs, concomitant medications, hospitalizations/procedures, and vital status).

Further details with regard to visits performed outside of the clinic are provided in the Study Reference Manual.

6.5.4. Electrocardiogram *(applicable text only)*

Revised text:

The Investigator or qualified designee will review all ECGs, **including those collected by a healthcare professional outside of the study center,** to assess whether the results have changed since baseline and to determine the clinical significance of the results. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.5.6.2. Pregnancy Testing *(applicable text only)*

Added text:

In situations where a study visit is unable to be completed at the site due to the COVID-19 pandemic impacting activities at the study center or patient ability or willingness to access the study center, pregnancy testing may be performed by a healthcare professional or the patient/caregiver (and confirmed by the site) where applicable country and local regulations and infrastructure allow.

Sections also reflecting this change:

- Table 1, Table 2, Table 3 Schedules of Assessments
- Section 3.1 Summary of Study Design
- Section 4.3.3. Lost to Follow-Up
- Section 6.2. Efficacy Assessments
- Section 6.5. Safety Assessments
- Section 6.5.6. Clinical Laboratory Assessments

Purpose: The following changes were made related to performance of liver function tests:

- *The timing of LFT assessments was updated to coincide with ALN-TTRSC02 dosing visits (which are every 12 weeks).*

- *The requirement for additional LFT results within 28 days prior to each ALN-TTRSC02 dose has been removed. Dosing decisions may will be based on the LFTs collected at the previous dosing visit*

The primary changes occur in Table 1 and Section 5.2.3 (LFT Criteria for Withholding, Monitoring and Stopping ALN-TTRSC02 Dosing)

Table 1 (Schedule of Assessments – Screening through Treatment Period Month 9)

The LFT assessments previously indicated on Week 15, Week 21, Week 27, and Week 33 have been removed for all patients and LFT assessments have been added for all patients at Week 12, Week 24, and Week 36.

5.2.3. LFT Criteria for Withholding, Monitoring and Stopping ALN-TTRSC02 Dosing

Revised text (relevant text only)

1. **For the ALN-TTRSC02 cohort, dosing decisions may be made based on** LFT results (Table 7) ~~are to be obtained within 28 days prior to ALN-TTRSC02 dosing and results are to be reviewed prior to each dose of ALN-TTRSC02~~ **collected at the previous dosing visit (up to 14 weeks prior to dosing); in all cases the most recently available LFTs should be used**. ~~Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.~~ **All laboratory samples should be sent to the central laboratory; an exception is for situations related to the COVID-19 pandemic if central laboratory collection is not possible, then a local laboratory may be used. These local laboratory results must be sent to the site for review by the Investigator and entry into the clinical database.**
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 6.
3. For any ALT or AST elevation >3× ULN:
    a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days. **If a central laboratory result is not possible due to the COVID-19 pandemic, a local laboratory may be used for monitoring in consultation with the Medical Monitor; all local laboratory results should be sent to the clinical site for entry into the clinical database.**
    b. Perform assessments per Table 6 and Table 8.
    c. If an alternative cause is found, provide appropriate care.

Sections also reflecting this change:

- Table 1, Table 2, Table 3 Schedules of Assessments
- Section 6.5.6, Clinical Laboratory Assessments

Purpose: Made the following visit to performance of efficacy assessments at Month 9:

- *Confirmed that all efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits).*
- *Specified that on situations in which a Month 9 efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the medical monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 efficacy assessment. After consultation with the medical monitor, Month 9 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15).*

The primary change occurs in Section 6 (Study Assessments),

Added text:

All efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits). In situations in which a Month 9 efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the medical monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 efficacy assessment. After consultation with the medical monitor, Month 9 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15).

Sections also reflecting this change:

- Synopsis
- Table 1 Schedule of Assessments
- Section 3.1 Summary of Study Design

Purpose: After Week 12, TTR/Vitamin A sample collections between ALN-TTRSC02 dosing visits have been removed for all patients.

The primary changes occur in Table 1 and Table 2

The following TTR/Vitamin A assessments have been eliminated for all patients:

- Table 1: No longer required at Week 18 and Week 30
- Table 2: No longer required at Week 42, Week 54, and Week 66

Purpose: Reduced the frequency of select assessments or combined assessments from different visits to align with doing visits in order to limit the number of times a patient needs to visit the site/interact with home healthcare professionals. The following changes have been made in this regard:

- *Reduced the number of visits at which symptom-directed physical examinations are conducted to reduce patient burden and issues related to inability of home healthcare professionals to conduct these visits outside the clinic.*
- *Eliminated the previous requirement that patients in the ALN-TTRSC02 cohort have assessments of vital signs and weight at visits that were originally included to correspond to timepoints necessary to support dosing in the patisiran cohort.*
- *Moved selected time points for collection of exploratory analysis samples so they coincide with assessments done at ALN-TTRSC02 dosing visits.*
- *Added guidance that PK sample collection timepoints at 6 and 24 hours after dosing are optional when samples are being collected outside the clinic (eg, the patient's home).*

The primary changes occur in the following sections:
Table 1, Table 2, Table 3, schedules of assessments:

- Split physical examination assessments from assessments of vital signs and weight as they will now have a separate schedule. The following changes in the schedules of symptom-directed physical examinations have been made for all patients:
  - Table 1: No longer required at Week 3, Week 6, Week 9, Week 15, Week 18, Week 21, Week 27, Week 30, Week 33
  - Table 2: No longer required at Week 39, Week 42, Week 45, Week 51, Week 54, Week 57, Week 63, Week 66, Week 69, Week 75, Week 78

- Vital signs and weight assessments are no longer being required for patients in the ALN-TTRSC02 cohort outside of their dosing visits:
  - Table 1: No longer required at Week 3, Week 6, Week 9, Week 15, Week 18, Week 21, Week 27, Week 30, Week 33; Still required at Visit 3, Week 12, and Week 24
  - Table 2: No longer required at Week 39, Week 42, Week 45, Week 51, Week 54, Week 57, Week 63, Week 66, Week 69, Week 75, Week 78.
- Selected samples for exploratory analysis for all patients shifted to coincide with assessments done at ALN-TTRSC02 dosing visits:
  - Table 1: Shifted sample collection from Week 18 to Week 24.
  - Table 2: Shifted sample collection from Week 57 to Week 60.

Pharmacokinetic Time Points (Table 4 [ALN-TTRSC02] and Table 5 [Patisiran]):

- Added the following footnote: PK sample collection timepoints at 6 and 24 hours after dosing are optional when samples are being collected outside the clinic (eg, the patient's home).

Purpose: Changed the secondary endpoint related to comparison of TTR percent reduction in the ALN-TTRSC02 arm compared to patisiran through 9 months to 18 months.

The primary change occurs in Section 7.2.5.2 (Secondary Endpoints)

Revised text (relevant text only):

Revised bullet in hierarchical order: TTR percent reduction through ~~9~~**18** months

The TTR percent reduction through Month ~~9~~**18** will be derived as the average trough TTR percent reduction from Month 6 to ~~9~~**18**which is the steady state period for both ALN-TTRSC02 and patisiran. A Hodges-Lehmann method stratified by previous TTR stabilizer use (yes vs no) will be used to estimate the 95% CI for the median difference between the ALN-TTRSC02 and patisiran groups in this study. Non-inferiority will be declared if the lower limit of the 95% CI for the treatment difference is greater than –10%. A sensitivity analysis will be conducted to compare the TTR percent reduction between the ALN-TTRSC02 group from this study and the pooled patisiran groups from this Phase 3 study and the APOLLO study.

Sections also reflecting this change:

- Synopsis

Purpose: Added collection of information related to the impact of the COVID 19 pandemic on patient participation in the study for each patient.

The primary change occurs in newly added Section 6.5.8, COVID-19 Data Collection

Added text:

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

Sections also reflecting this change:

- Section 7.2

Purpose: Updated study administration text.

The primary change occurs in Section 8.1.1, Informed Consent and Medical Records Release Form and Section 8.1.2, Ethical Review

8.1.1. Informed Consent and Medical Records Release Form *(relevant changed text only)*

Added text:

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

8.1.2. Ethical Review *(relevant changed text only)*

Added text:

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study **(except those that support the need to remove an apparent immediate hazard to the patient)**.

2.2. Changes Not Related to Urgent Safety Measures to be Implemented After Regulatory Authority and Ethics Committee Approval

Purpose: The secondary endpoint all-cause hospitalization and death events over 18 months in patients with cardiac involvement was removed.

The primary change occurs in Section 2 (Objectives and Endpoints)

Objectives	Endpoints
Secondary	
• To determine the efficacy of ALN-TTRSC02 on gait speed, nutritional status, and disability • To characterize the effect of ALN-TTRSC02 on serum TTR levels • To evaluate patient mortality and hospitalization • To determine the efficacy of ALN-TTRSC02 on improvement in neurologic impairment and on quality of life	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – Timed 10-meter walk test (10-MWT); – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R-ODS) • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran arm • Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study ~~• Composite events of all-cause deaths and/or all-cause hospitalizations in patients with cardiac involvement (over 18 months) compared to patients with cardiac involvement in the placebo arm of the APOLLO study~~

Objectives	Endpoints
	• Change at Month 18 compared to baseline in mNIS+7 in ALN-TTRSC02-treated patients • Change at Month 18 compared to baseline in Norfolk QoL-DN total score in ALN-TTRSC02-treated patients

Sections also reflecting this change:

- Synopsis
- Section 7.2.5.2 (Secondary Endpoints)

3. REFERENCES

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, (20/03/2020; updated 27/03/2020; updated 28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards (03/2020; updated 16/04/2020). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic

ALN-TTRSC02-002 PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES DATED 17 JULY 2020

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

1. RATIONALE FOR PROTOCOL AMENDMENT

The COVID-19 pandemic has led to a shift in healthcare from the clinic to home settings world-wide and has required adjustments to ensure patient safety and study integrity which were implemented in a previous protocol amendment (Amendment 2 dated 06 May 2020). To date, the risk mitigation steps introduced with this prior amendment have allowed dosing to continue as scheduled for the majority of ALN-TTRSC02 patients, while maintaining appropriate safety monitoring and minimizing missed efficacy assessments. However, the ongoing COVID-19 pandemic presents risks in some regions for disruption of treatment, potentially impacting key efficacy assessments, until a vaccine or effective treatment is widely available. This amendment includes revisions to the study endpoints for the primary purpose of mitigating any potential impact from the pandemic on key efficacy assessments. This amendment also includes analysis of efficacy endpoints at Month 18 as secondary endpoints in the statistical hierarchy to allow more complete characterization of the treatment effect of ALN-TTRSC02. Collectively, these changes will ensure the adequate evaluation of the effects of ALN-TTRSCO2 on neurological impairment, quality of life, gait speed, nutritional status and disability, while minimizing potential confounding effects of the COVID-19 pandemic.

As the primary analysis will be conducted at Month 9, it should be noted that as of the time of this amendment, the majority (approximately 67%) of patients have not yet completed the Month 9 efficacy visit. The Sponsor has remained blinded to efficacy data in accordance with the data integrity plan and thus has made the changes without any knowledge of these data. Therefore, the changes to the co-primary endpoint and select secondary endpoints are not considered to impact study integrity.

The changes to the endpoints are outlined below and a detailed summary of changes is provided in Section 2.

Changes to the Primary Analysis at Month 9 to Mitigate Risks related to the Pandemic

Quality of life (Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QoL-DN]), nutritional status (modified body mass index [mBMI]), and disability (Rasch-built Overall Disability Scale [R-ODS]) are efficacy measures that are important for establishing the benefit of ALN-TTRSC02 in patients with hereditary ATTR amyloidosis with polyneuropathy. The pandemic has the potential to affect components of these assessments in multiple ways, including changes in anxiety and stress from the pandemic, the potential for loss of employment, and disruptions in physical activity and social interactions due to social distancing and the closure of public gathering places related to the pandemic.

While it is difficult to predict the precise impact of the pandemic, changes to endpoints at Month 9 have been introduced to mitigate the potential risk of these external factors confounding interpretation of the true treatment effect of ALN-TTRSC02:

- The co-primary endpoint of change from baseline in Norfolk QoL-DN total score at Month 9 has been changed to the first key secondary endpoint in the hierarchical testing order. Modified NIS+7 will now be the sole primary endpoint at Month 9.

  While Norfolk QoL-DN involves neuropathy-specific measures, it also includes questions about general physical and emotional health, both of which may be impacted by the COVID-19 pandemic in a manner that is difficult to precisely estimate. The change to key secondary endpoint has been made to mitigate the risk of any potential confounding impact of the pandemic. Establishing the efficacy of ALN-TTRSC02 on the patient's perception of neuropathy impairment with the Norfolk-QoL remains a critical objective of the study; having this measure as a key secondary endpoint will support the clinical relevance of observed changes in the primary endpoint of modified NIS+7. Modified NIS+7 is a well-established and reproducible measure of neuropathy progression that may be less susceptible to external factors associated with the pandemic and thus will remain as the primary endpoint at Month 9.

- The secondary endpoints of mBMI and R-ODS at Month 9 have been changed from secondary to exploratory endpoints.

  R-ODS captures activity and social participation limitations and provides an overall picture of disability. Modified BMI provides an assessment of nutritional status. Both of these assessments may also be impacted by pandemic related stressors, missed doses and/or impact on lifestyle. Accordingly, these two endpoints have been changed from secondary to exploratory endpoints at Month 9. With this amendment, these endpoints will be formally tested at Month 18, when we expect they will be less subject to impact from the pandemic, as described below.

Expanded Analysis at Month 18 to Further Characterize Treatment Effect Over Time

- The following efficacy endpoints have been added to the testing hierarchy at Month 18 for change from baseline parameters compared to the placebo arm of Study ALN-TTR02-004 (APOLLO; patisiran): mNIS+7, Norfolk QoL-DN total score, timed 10-meter walk test (10-MWT), mBMI, and R-ODS.

  The addition of these endpoints at Month 18 is consistent with the timepoint used for analysis of the primary endpoint in the APOLLO study. The expanded analysis at Month 18 will allow for more complete characterization of the treatment effect of ALN-TTRSC02 over time and the potential for sustained improvements in neurologic impairment, quality of life, gait speed, disability and nutrition.

Additional Changes to Endpoints

- Removed change at Month 18 compared to baseline in mNIS+7 and Norfolk QoL-DN total score in ALN-TTRSC02-treated patients. The additional endpoint analyses added at Month 18 have replaced the need for this analysis.

- Removed the secondary endpoint of composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study; removed adjudication of the reasons for hospitalizations. Deaths due to COVID-19 and changes in health care utilization related to COVID-19 may confound interpretation of these data. Adjudication of the reasons for hospitalizations was considered no longer necessary.
- Added percent reduction in serum TTR compared to baseline as an exploratory endpoint.

Additional Changes and Clarifications

- Added a clarification that for submission of the marketing authorization to the European Union, formal hypothesis testing will be conducted at Month 18, with mNIS+7 compared to the placebo arm of the APOLLO study at Month 18 considered the primary endpoint. Details will be specified in the statistical analysis plan (SAP).
- Added a definition of the Per-Protocol Population.
- Similar to the clarification at Month 9 for efficacy assessments in the previous amendment (Amendment 2 dated 06 May 2020), a specification was added that when a Month 18 efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18 efficacy assessment. After consultation with the Medical Monitor, Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 24).
- Added clarification that if a dose is delayed (up to 8-weeks for ALN-TTRSC02 or 7 days for patisiran), study assessments associated with the originally scheduled dose may also be delayed to coincide with the delayed dose.
- Added clarification that the delay of Month 18 efficacy assessments will not affect the timepoint for patients on patisiran to switch to ALN-TTRSC02 at Week 84.
- Removed the requirement that assessors who perform efficacy assessments at Central Assessment Sites will be different from site personnel who monitor administration of study drug and the well-being of the patient during the study. This change was made as involvement of site personnel in patient management is not expected to impact efficacy assessment evaluations and the requirement placed an undue burden on sites, especially amid COVID-19 restrictions at the sites.
- Added a clarification that postural blood pressure will be measured as described in the Study Manual.

The following changes are not detailed: administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. PROTOCOL AMENDMENT 3 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 3 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: The following changes were made to the endpoints for the study:

- *The co-primary endpoint of change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score at Month 9 compared to the placebo arm of the APOLLO study has been changed to the first key secondary endpoint in the hierarchical testing order.*
- *Added mNIS+7, Norfolk QoL-DN total score, timed 10-meter walk test (10 MWT) at Month 18 in addition to analyses already specified for Month 9 to ensure the treatment effect of vutrisiran is completely characterized at Month 18.*
- *Rasch-built Overall Disability Scale (R-ODS) and modified body mass index (mBMI) changed from Month 9 to Month 18; the Month 9 assessments of these parameters were moved to exploratory endpoints. These changes have been made to mitigate the potential for missed doses due to COVID-19, as well as the physical and mental impact of the pandemic, to affect the analyses of these endpoints at Month 9.*
- *Removed change at Month 18 compared to baseline in mNIS+7 and Norfolk QoL DN total score in ALN-TTRSC02-treated patients.*
- *Removed the secondary endpoint of composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study; removed adjudication of the reasons for hospitalizations.*
- *Added percent reduction in serum TTR compared to baseline as an exploratory endpoint.*
- *Added a clarification that for submission of the marketing authorization to the European Union, formal hypothesis testing will be conducted at Month 18, with mNIS+7 compared to the placebo arm of the APOLLO study at Month 18 considered the primary endpoint.*

The primary change occurs in Section 2, Objectives and Endpoints

Revised text:

The ~~co-~~primary, and most secondary and exploratory efficacy endpoints are in comparison to the placebo arm of the Phase 3 pivotal patisiran study (ALN-TTR02-004, also referred to as the APOLLO study) as specified in the statistical analysis section of **this**

protocol ~~the HELIOS-A protocol. The primary analysis will be conducted at Month 9. An additional analysis of all efficacy endpoints will be conducted at Month 18.~~

Objectives	Endpoints
Primary	
• To determine the efficacy of ALN-TTRSC02 in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment ~~and on quality of life~~	~~Co-Primary:~~ • Change from baseline in the Modified Neurologic Impairment Score +7 (mNIS+7) compared to the placebo arm of the APOLLO study **at Month 9** • ~~Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score compared to the placebo arm of the APOLLO study~~
Secondary	
• To determine the efficacy of ALN-TTRSC02 on **quality of life,** gait speed, **neurologic impairment,** nutritional status, and disability • To ~~characterize~~ **demonstrate** the ~~effect~~ **noninferiority** of ALN-TTRSC02 ~~on~~ **compared to patisiran with respect to** serum TTR levels • ~~To evaluate patient mortality and hospitalization~~ • ~~To determine the efficacy of ALN-TTRSC02 on improvement in neurologic impairment and on quality of life~~	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study: – **Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score at Month 9;** – Timed 10-meter walk test (10-MWT) **at Month 9;** – **mNIS+7 at Month 18;** – **Norfolk QoL-DN total score at Month 18;** – **10-MWT at Month 18;** – Modified body mass index (mBMI) **at Month 18;**

Objectives	Endpoints
	– Rasch-built Overall Disability Scale (R-ODS) at Month 18 • Percent reduction in serum TTR levels in the ALN-TTRSC02 arm compared to the within-study patisiran arm **through Month 18** • ~~Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo arm of the APOLLO study~~ • ~~Change at Month 18 compared to baseline in mNIS+7 in ALN-TTRSC02-treated patients~~ • ~~Change at Month 18 compared to baseline in Norfolk QoL-DN total score in ALN-TTRSC02-treated patients~~
Exploratory	
• To determine the effect of ALN-TTRSC02 on: – **Disability and nutritional status;** – Manifestations of cardiac amyloid involvement; – Other assessment of neurologic impairment; – Other assessments of quality of life; – Disease stage; – Performance of daily activities • To characterize the pharmacodynamic (PD) effect of ALN-TTRSC02 and	• Change from baseline in the following parameters compared to the placebo arm of the APOLLO study **at Month 9**: – **R-ODS;** – **mBMI** • **Change from baseline over time:** – N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters, Troponin I and T levels, New York Heart Association (NYHA) class; – Neurologic Impairment Score (NIS); – EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the

Objectives	Endpoints
patisiran on **serum TTR and** vitamin A levels • To characterize plasma pharmacokinetics (PK) of ALN-TTRSC02 and patisiran • To assess presence of antidrug antibodies (ADA) to ALN-TTRSC02 and patisiran	EuroQoL-Visual Analog Scale (EQ-VAS); – Familial Amyloidotic Polyneuropathy (FAP) stage and Polyneuropathy Disability (PND) score; – Karnofsky Performance Status (KPS) • Change from baseline in technetium scintigraphy cardiac parameters **at Month 18** • Percent reduction in serum **TTR and** vitamin A levels **over time** • PK profile of ALN-TTRSC02 and patisiran • Incidence and titers of ADA to ALN-TTRSC02 and patisiran
Safety	
• To determine the safety and tolerability of ALN-TTRSC02 in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

For submission of the marketing authorization to the European Union, formal hypothesis testing will be conducted at Month 18, with mNIS+7 compared to the placebo arm of the APOLLO study at Month 18 considered the primary endpoint. Details will be specified in the statistical analysis plan (SAP).

Section(s) also reflecting these changes:

- Synopsis
- Section 3.1, Summary of Study Design
- Section 3.8, Adjudication Committee
- Section 6.2.7, Deaths and Hospitalizations

- Section 7.1, Determination of Sample Size
- Section 7.2.3, Handling of Missing Data
- Section 7.2.5.1, Primary Endpoint
- Section 7.2.5.2, Secondary Endpoints

Purpose: Added a definition of the Per-Protocol Population.

The primary change occurs in Section 7.2.1, Populations to be Analyzed

Added text: **TTR Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment associated with adequate treatment compliance between Month 6 and Month 18. Specific details will be provided in the SAP.**

Purpose: Added a specification that when a Month 18 efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 18 efficacy assessment.

The primary change occurs in Section 6, Study Assessments:

Revised text: All efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits). In situations in which a Month 9 **or Month 18** efficacy visit is unable to be completed due to the COVID-19 pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 **or Month 18** efficacy assessment. After consultation with the Medical Monitor, Month 9 **or Month 18** efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15 **or Study Month 24**).

Section(s) also reflecting this change:

- Section 3.1, Summary of Study Design

Purpose: Added clarification that if a dose is delayed (up to 8-weeks for ALN-TTRSC02 or 7 days for patisiran), study assessments associated with the originally scheduled dose may also be delayed to coincide with the delayed dose.

The primary change occurs in Section 5.2.2.1, ALN-TTRSC02

Revised text: Missed Doses of ALN-TTRSC02

If a patient does not receive a dose of ALN-TTRSC02 within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered with up to an 8-week delay (to be considered a delayed dose). Thereafter, the dose will be considered missed and not administered. If a dose is administered with a delay, the next dose will resume following the original schedule. In cases in which a dose is delayed in this manner for issues related to the COVID-19 pandemic, the Medical Monitor should be informed as soon as possible, but prior consultation is not required. In all cases, the dose should be administered as close as possible to the scheduled timepoint. **If a dose is delayed, all assessments associated with the originally scheduled dose may also be delayed to coincide with the delayed dose.**

Section(s) also reflecting this change:

- Section 5.2.2.2, Patisiran

Purpose: Added clarification that the delay of Month 18 efficacy assessments will not affect the timepoint for patients on patisiran to switch to ALN-TTRSC02 at Week 84.

The primary change occurs in Section 5.2.2.3, Switching from Patisiran to ALN-TTRSC02 After Month 18

Added text: On Week 84, patients in the patisiran arm will be switched to ALN-TTRSC02 treatment and will receive the first ALN-TTRSC02 dose. The last dose of patisiran will be at Week 81, and patients should receive treatment with ALN-TTRSC02 3 weeks later on Week 84 and thereafter q3M (12 weeks ±7 days) for the remainder of the study. **If a patient receiving patisiran is unable to complete the Month 18 efficacy visit at the study center due to COVID-19 (Section 3.1) before Week 84, they may transition to treatment with ALN-TTRSC02 at Week 84 or later.**

Purpose: Removed the requirement that assessors who perform efficacy assessments at Central Assessment Sites will be different from site personnel who monitor administration of study drug and the well-being of the patient during the study.

The primary change occurs in Section 6, STUDY ASSESSMENTS

Deleted text: Central Assessment Sites (CAS) can perform all efficacy assessments and perform the same assessments as at a PCS (as stated above). Efficacy assessments (NIS, mNIS+7, HRdb, 10-MWT, FAP and PND, KPS, echocardiogram) in this study may require special training as described further in Section 6.2; therefore, all patients must be sent to a CAS to collect these efficacy assessments during screening and predose baseline assessments, Month 9, Month 18, and during the Treatment Extension period at Month 27 and Month 36. ~~Assessors who will perform efficacy assessments at a CAS will be different from site personnel who monitor the administration of study drug during the study and monitor the well-being of the patient during the study. This is instituted to minimize the influence patient management and AEs may have on efficacy assessment evaluation(s).~~

Purpose: Added a clarification that postural blood pressure will be measured as described in the Study Manual.

The primary change occurs in Section 6.2.1.1, Modified Neurological Impairment Score +7 (mNIS+7)

Revised text: Postural blood pressure ~~is~~ **will be** measured to assess autonomic function **as described in the Study Manual**. ~~Postural blood pressure is measured sitting down and standing up.~~ Points are assigned based on the change in blood pressure with standing.

ALN-TTRSC02-002 PROTOCOL AMENDMENT 4
SUMMARY OF CHANGES DATED 19 FEBRUARY 2021

HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)

1. RATIONALE FOR PROTOCOL AMENDMENT

[redacted]

- [redacted]
- [redacted]
- [redacted]

Additional updates

- Specified that for study visits done outside the clinic, such as at home, physical examinations may be deferred to the next in clinic visit
- Revised overdose reporting instructions
- Updated pregnancy reporting to be any time during study conduct

The following changes are not detailed: administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, cross references, and formatting.

2. PROTOCOL AMENDMENT 4 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 4 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Addition of a Randomized Treatment Extension (RTE) Period [redacted]

The primary change occurs in Section: Section 3.1, Summary of Study Design

Revised text:

This is a global Phase 3 randomized, open-label study designed to evaluate efficacy, safety, and PK/PD of ALN-TTRSC02 in adult patients with hATTR amyloidosis. Patients will be randomized 3:1 to ALN-TTRSC02 or patisiran, a reference comparator. Randomization will be stratified by TTR genotype (V30M vs. non-V30M) and baseline NIS score (<50 vs ≥50).

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, and an 18-month **RTE Period in lieu of the Legacy Treatment Extension Period**. A Follow-up Period of up to 1 year will occur after the last dose of study drug (Figure 2).

18-Month Treatment Period

After the Screening period at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of ALN-TTRSC02 administered as a SC injection q3M or patisiran administered as an IV infusion q3w; patients in the patisiran arm will also receive premedications prior to each dose (see Section 5.2.2.2). During the 18-month Treatment Period, patients will undergo assessments for efficacy and/or safety (as outlined in the Schedule of Assessments), with key efficacy assessments being performed prior to first dose, at Month 9 (primary efficacy analysis timepoint) and at Month 18; samples for TTR assessment will be collected more frequently throughout the 18-month Treatment Period.

All efficacy visits must be conducted at the clinic (Month 9, Month 18, ~~Month 27, Month 36,~~ and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness to access the study center or their ability to have received their scheduled doses of study drug, the Medical Monitor should be consulted as soon as possible to determine the appropriate timing of the Month 9 or Month 18 efficacy assessments as applicable. After consultation with the Medical Monitor, the Month 9 or Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Month 15 or Month 24, respectively).

Dosing may be allowed outside of the study center (eg, the patient's home) under certain circumstances as specified in Section 5.2.2.1 and Section 5.2.2.2. In addition, routine assessments and collection of relevant safety information may be collected outside the study center as specified at the beginning of Section 6.

The placebo arm of the APOLLO study will be used as an external control for the primary, most secondary, and most exploratory efficacy analysis. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

In order to allow for a robust cross study comparison, attempts will be made to minimize differences between the HELIOS-A and APOLLO study populations. As such, baseline disease characteristics will be monitored and may result in enrollment limitations based on certain characteristics (eg, genotype) to ensure comparability. Decisions around enrollment adjustments will be made by staff without access to primary efficacy results.

Randomized Treatment Extension (RTE) Period

Follow-up Period

During the Follow-up Period, all patients on ALN-TTRSC02 will undergo safety assessments quarterly until serum TTR levels return to ≥80% of baseline (for up to 1 year after the last dose of study drug), or until the patient starts a TTR lowering regimen as a part of clinical care, whichever comes first; all patients will be followed for a minimum of 3 months. Female patients of child-bearing potential **who discontinue ALN-TTRSC02** will be followed until serum TTR levels return to ≥80% of baseline.

Section(s) also reflecting these changes:

- Synopsis
- Synopsis Footnote to Table 2, revisions to Table 3; and addition of Table 4
- Study Design Figure 1 and added Figure 2
- Section 1.5, Study Design Rationale
- Section 1.6, Dose Rationale
- Section 1.7, Benefit-Risk Assessment

- Section 3.1, Summary of Study Design
- Section 3.2, Duration of Treatment
- Section 3.3, Duration of Study
- Section 3.3.1, Definition of End of Study for an Individual Patient
- Section 3.5, Method of Assigning Patients to Treatment Groups
- Section 4.3.1, Discontinuation of Study Drug or Declining Procedural Assessments
- Section 4.3.2.1, Patient or Legal Guardian Stops Participation in the Study
- Section 5.2.1, Description (Study Drug)
- Section 5.2.2.1, ALN-TTRSC02 (Dose and Administration)
- Section 5.2.2.3, Switching from Patisiran to ALN-TTRSC02 After Month 18
- Section 5.2.4, Preparation, Handling, and Storage
- Section 6 (and subsections within), Study Assessments
- Section 7.2, Statistical Methodology
- Section 7.2.5, Efficacy Analyses

Purpose: To define the collection times for PK blood samples during the Treatment Extension Period

The primary change occurs in Section: Synopsis, Table 5

Added text:

Study Day	Protocol Time (hh:mm)	PK Blood (Plasma)
Day 1 and Day 253±3 days	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
	06:00 (±1 hr) after dosing	X
	24:00 (±2 hr) after dosing	X
Day 85 and Day 169 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
Day 337, Day 421, and Day 505 (±3 days)	Predose (within 60 minutes before dosing)	X
	03:00 (±1 hr) after dosing	X
[redacted]	[redacted]	[redacted]
Early Drug Discontinuation Visit	Collect any time within the visit window	X
Modified Efficacy Visits for Patients Who Discontinue Treatment before Month 18 (Part A or Part B)	Collect any time within the visit window	X

Purpose: Vutrisiran does not have a drug-drug interaction with hormonal contraception.

The primary change occurs in Section 5.6.1: Contraception

Revised text:

- Established use of oral (except for low dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation. ~~Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).~~

Section(s) also reflecting this change:

Not applicable

Purpose: To allow flexibility due to the COVID-19 pandemic.

The primary change occurs in Section 6.5.3: Physical Examination

Revised text:

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. **In situations where the patient has a home visit, symptom-directed physical examinations may be deferred until the next in-clinic visit.**

Section(s) also reflecting this change:

Not applicable

Purpose: Clarifications to pregnancy reporting and overdose reporting instructions.

The primary change occurs in Section 6.5.7.7 Pregnancy Reporting and Section 6.5.7.8: Overdose Reporting, respectively

Revised text:

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, **or through their last visit in the study (whichever is later)**, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy.

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. **When an overdose is suspected, the Investigator should inform the Medical Monitor.** ~~The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.~~

~~All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.~~

Section(s) also reflecting this change: Not applicable